GENEReviews

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Multiple Epiphyseal Dysplasia, Dominant

[*Includes: Multiple Epiphyseal Dysplasia 1 (EDM1); Multiple Epiphyseal Dysplasia 2 (EDM2); Multiple Epiphyseal Dysplasia 3 (EDM3); Multiple Epiphyseal Dysplasia 5 (EDM5); Multiple Epiphyseal Dysplasia, COL9A1 Related*]

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Summary

Disease characteristics. Autosomal dominant multiple epiphyseal dysplasia (MED) presents early in childhood, usually with pain in the hips and/or knees after exercise. Affected children complain of fatigue during long walking. Waddling gait may be present. Adult height is either in the lower range of normal or mildly shortened. The limbs are relatively short in comparison to the trunk. Pain and joint deformity progress, resulting in early-onset osteoarthritis, particularly of the large weight-bearing joints.

Diagnosis/testing. The diagnosis of dominant MED is based upon the clinical and radiographic findings in the proband and other family members. In the initial stage of the disorder, often before the onset of clinical symptoms, delayed ossification of the epiphyses of the long tubular bones is found on radiographs. With the appearance of the epiphyses, the ossification centers are small with irregular contours, usually most pronounced in the hips and/or knees. The tubular bones may be mildly shortened. By definition, the spine is normal, although Schmorl bodies and irregular vertebral end plates may be observed. Mutations in five genes cause dominant MED: *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3*. However, in approximately 10%-20% of all samples analyzed, a mutation cannot be identified in any of the five genes above, suggesting that mutations in other as-yet unidentified genes are also involved in the pathogenesis of dominant MED.

Management. *Treatment of manifestations:* for pain control, a combination of analgesics and physiotherapy including hydrotherapy; referral to a rheumatologist or pain specialist as needed; consider realignment osteotomy and/or acetabular osteotomy to limit joint destruction and development of osteoarthritis; consider total joint arthroplasty if the degenerative hip changes cause too much pain/dysfunction; psychosocial support re 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.

Genetic counseling. Dominant MED is inherited in an autosomal dominant manner. Many individuals with dominant MED have inherited the mutant allele from one parent. The prevalence of new gene mutations is not known. Each child of an individual with dominant MED has a 50% chance of inheriting the mutation. Prenatal diagnosis is possible in pregnancies at risk if the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of autosomal dominant multiple epiphyseal dysplasia (MED) is based upon the clinical and radiographic presentation in the proband and other family members.

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.

Molecular Genetic Testing

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

Genes. Mutations in five genes have been shown to cause autosomal dominant MED [Unger & Hecht 2001, Briggs & Chapman 2002]:

- *COMP*
- *COL9A1*
- *COL9A2*

- *COL9A3*
- *MATN3*

Other loci

- Mutations remain undetected in approximately 10%-20% of individuals with MED, suggesting that mutations in as-yet unidentified genes are also involved in the pathogenesis of MED.
- In some families genetic linkage studies have excluded linkage to the five known loci.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis
- Preimplantation genetic diagnosis

Clinical testing

- **Sequence analysis.** Sequence analysis of select exons and splice junctions should be capable of detecting the vast majority of mutations located within the coding region of these genes.

  Note: (1) Sequence analysis does not detect large deletions (such as those spanning intron-exon boundaries [Mabuchi et al 2003]. (2) Polymorphisms located within introns may disrupt the annealing of primers during PCR, resulting in the amplification of only one allele.

  COMP. Mutations in *COMP* are located in the exons encoding the type III repeats (exons 8-14) and C-terminal domain (exons 15-19) [reviewed in Unger & Hecht 2001, Briggs & Chapman 2002]. A recent study by Kennedy, Jackson, Ramsden et al (2005) demonstrated that approximately 70% of MED-causing mutations in *COMP* reside in exons 10, 11, and 13.

  COL9A1, COL9A2, COL9A3. Sequence analysis of the relevant exons and flanking intronic sequence includes: *COL9A1* (exons 8-10), *COL9A2* (exons 2-4), *COL9A3* (exons 2-4). Mutations in *COL9A2* and *COL9A3* are found in the splice donor and/or acceptor sequences of exon 3, while a single mutation has been found in the splice acceptor sequence of exon 9 of *COL9A1*.

  MATN3. With one exception, all MED-causing mutations in *MATN3* are missense mutations found within exon 2, which encodes the single A-domain of matrilin-3. The vast majority of these mutations affect conserved residues within the six beta-strands that comprise the single beta-sheet of the A-domain. Recently, however, several mutations have been found in the alpha-helix regions of the A-domain, suggesting that MED-causing mutations in *MATN3* are more widespread than previously thought [Chapman et al 2001, Jackson et al 2004, Mabuchi et al 2004, Cotterill et al 2005, Itoh et al 2006]. The single exception is a missense mutation identified in exon 1 (p.Arg70His) [Maeda et al 2005]; however, this mutation is within five residues of the A-domain and may well play a role in its structure and/or function.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Multiple Epiphyseal Dysplasia, Dominant

Test Method	Mutations Detected	Proportion of Dominant MED Attributed to Mutations in this Gene [1]	Mutation Detection Frequency [2]	Test Availability
Sequence analysis	*COMP* sequence variants (exons 8-19)	~80% [1]	>80%	Clinical Testing
	COL9A1 sequence variants	<5%		Clinical Testing
	COL9A2 sequence variants [3]			Clinical Testing
	COL9A3 sequence variants [4]			Clinical Testing
	MATN3 sequence variants [5]	<10%		Clinical Testing

1. The frequency of MED-causing mutations in these genes is not well established. Previous studies have suggested detection frequencies of 10%-36% for *COMP* [Jakkula et al 2005; Kennedy, Jackson, Ramsden et al 2005], 10% for *MATN3*, and 5% for the type IX collagen genes [Briggs & Chapman 2002, Jackson et al 2004]. However, in a recent study by the European Skeletal Dysplasia Network (ESDN), the detection rate for MED-causing mutations in *COMP* increased to 81% when a strict clinical-radiographic review was undertaken before molecular genetic testing was performed [Zankl et al 2007].

2. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

3. All mutations identified cluster in the splice donor site of exon 3

4. All mutations identified in the splice acceptor and or donor site of exon 3

5. All mutations identified cluster in exon 2

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

Testing Strategy

Ideally a comprehensive clinical and radiographic review of the proband should precede molecular genetic testing. By confirming the clinical diagnosis of MED, the mutation detection rate can be significantly increased [Zankl et al 2007].

For autosomal dominant MED, genes are best tested in the following order, which reflects the relative contribution of each gene to the overall of MED:

- *COMP* (~80%)
- *MATN3* (~10%)
- *COL9A1*, *COL9A2*, and *COL9A3* (<5%)

Based on molecular findings [Kennedy, Jackson, Ramsden et al 2005; Zankl et al 2007] the following testing regime has been recommended by the European Skeletal Dysplasia Network and Maeda et al (2005):

- Level 1: *COMP* (exons 10-15) and *MATN3* (exon 2)
- Level 2: *COMP* (exons 8 & 9 and 16-19)
- Level 3: *COL9A1* (exon 8), COL9A2 and COL9A3 (exon 3)

  Note: Amplimers should include splice donor and acceptor sites.

It is important to note that in some situations, autosomal dominant MED may not be distinguishable from autosomal recessive forms of MED; therefore, it may be appropriate to test *SCLA26A2* after testing *COMP*.

Genetically Related (Allelic) Disorders

COMP

Pseudoachondroplasia (PSACH). Pseudoachondroplasia shares clinical and radiographic abnormalities with dominant MED. However, individuals with pseudoachondroplasia have short-limb dwarfism with spondyloepimetaphyseal involvement on radiographs. Unlike MED, PSACH is not known to be genetically heterogeneous and appears to result exclusively from *COMP* mutations. 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 ("miniepiphyses"), irregularly shaped carpal and tarsal bones, and short tubular bones with small and fragmented epiphyses and metaphyseal irregularities.

COL9A2, COL9A3

Lumbar/intervertebral disk disease (IDD). IDD is one of the most common musculoskeletal disorders in the world. Specific alleles in the *COL9A2* and *COL9A3* genes have been shown to confer susceptibility to IDD (typically associated with sciatica) within the Finnish population [Annunen et al 1999, Paassilta et al 2001].

- The substitution of a glutamine at residue 326 for that of tryptophan (p.Glu326Trp) in the α2(IX) chain (Trp2 allele) is thought to account for 15% of the disease prevalence.
- The substitution of arginine at residue 103 for that of tryptophan (p.Arg103Trp) in the α3(IX) chain (Trp3 allele) has been calculated to confer a threefold increase in the risk of IDD.

MATN3

Spondyloepimetaphyseal dysplasia (SEMD); matrilin-3 related. Borochowitz et al (2004) described a consanguineous family with an autosomal recessive form of spondyloepimetaphyseal dysplasia. Affected individuals presented with disproportionate short stature, severe bowing of the lower limbs, and lumbar lordosis. All affected members of this family were homozygous for a p.Cys304Ser mutation in the first EGF-domain of matrilin-3.

Hand osteoarthritis and spinal disc degeneration. A p.Thr303Met substitution in the first EGF-domain of matrilin-3 has been implicated in the pathogenesis of hand osteoarthritis [Stefansson et al 2003] and spinal disc degeneration [Min et al 2006], but the precise mechanism of this mutation remains unresolved [Otten et al 2005].

Clinical Description

Natural History

Autosomal dominant multiple epiphyseal dysplasia (MED) was originally divided into a mild form called Ribbing disease and a more severe form known as Fairbank disease. 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 osteoarthritis.

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

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

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.

The natural history of 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 cases, the osteoarthritis is sufficiently severe to require joint replacement in early adult life.

Associated anomalies are absent. Intelligence is normal.

Genotype-Phenotype Correlations

Preliminary 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* mutations is characterized by significant involvement at the capital femoral epiphyses and irregular acetabuli [Unger et al 2001]. However, the recurrent p.Arg718Trp mutation in *COMP* appears to cause a mild form of the disorder, more consistent with MED caused by a type IX collagen gene mutation [Jakkula et al 2003].
- Type IX collagen defects result in more severe involvement of the knees and relative sparing of the hips.
- *MATN3* mutations result in knee abnormalities that are similar to those in individuals with *COL9A2* mutations; the hip abnormalities are more severe (although not as severe as those in individuals with *COMP* mutations) [Mortier et al 2001]. However, more intra- and interfamilial variability is evident in MED caused by *MATN3* mutations. A mutation 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, Makitie et al 2004].

It is important to note that striking intra- and interfamilial variability can be observed in MED caused by mutations in *MATN3* [Chapman et al 2001, Mortier et al 2001, Jackson et al 2004, Makitie et al 2004], in *COL9A3* [Bonnemann et al 2000, Nakashima et al 2005], and in some instances, in *COMP*. These findings make the establishment of strong genotype-phenotype correlations in dominant MED less likely in the long term.

Penetrance

There is some evidence for reduced penetrance in MED caused by *MATN3* mutations [Mortier et al 2001, Makitie et al 2004].

Anticipation

Anticipation is not observed.

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), which is a form of multiple diaphyseal sclerosis.

Prevalence

Studies undertaken to determine the birth prevalence of skeletal dysplasias suggest a prevalence of 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.

Differential Diagnosis

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

Three other disorders have features that overlap with those of autosomal dominant multiple epiphyseal dysplasia (MED).

Autosomal recessive MED (EDM4/rMED). Recessive multiple epiphyseal dysplasia is characterized by joint pain (usually in the hips and/or knees); deformities of hands, feet, and knees; and scoliosis. About 50% of affected individuals have some anomaly at birth, e.g., clubfoot, cleft palate, cystic ear swelling, or clinodactyly. Onset of pain is variable, but usually occurs in late childhood. Stature is usually within the normal range prior to puberty; in adulthood, stature is only slightly diminished, with the median height shifting from 50th to the tenth percentile; range is between 150 and 180 cm. Functional disability is mild or absent. EDM4/rMED is diagnosed on clinical and radiographic findings. Of particular note is double-layered patella (i.e., presence of a separate anterior and posterior ossification center) observed on lateral knee radiographs in about 60% of individuals with EDM4/rMED. This finding appears to be age related and may not be apparent in adults. Diagnosis can be confirmed by molecular genetic testing of the *SLC26A2 (DTDST*) gene [Superti-Furga et al 1999].

Bilateral Perthes disease (BPD). Legg-Calve-Perthes disease (or Perthes disease) (OMIM 150600) is a form of juvenile osteonecrosis of the femoral head, caused by a disruption of the blood supply during endochondral ossification. Perthes disease usually affects males between the ages of three and 15 years. Up to 20% of individuals with Perthes disease have bilateral involvement. Several studies have identified differences between bilateral and unilateral Perthes disease, prominent among which is the greater severity of BPD. The radiographic changes observed in Perthes disease differ from those of MED, with more involvement of the metaphyses and femoral neck.

Beukes familial hip dysplasia (BFHD). An inherited skeletal disorder that shares many clinical and radiographic features with MED, BFHD was first identified in 47 individuals in six generations of an Afrikaner family in South Africa [Cilliers & Beighton 1990]. The International Nosology and Classification of Genetic Skeletal Disorders (2006 Revision) now recognize BFHD as a form of MED. Genetic linkage studies determined that the as-yet unidentified causative gene maps an 11-cM region on 4q35 [Roby et al 1999].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with multiple epiphyseal dysplasia (MED):

- Elicitation of pain history
- Assessment of joint mobility
- Radiographs to determine the extent and severity of joint involvement

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 indviduals, 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 [Hunter 1998a, 1998b].

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

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

Testing 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 for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

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

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

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Autosomal dominant multiple epiphyseal dysplasia (MED) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals with dominant MED have inherited the mutant allele from one parent.
- A proband with dominant MED may have the disorder as the result of a *de novo* gene mutation. The prevalence of *de novo* gene mutations is not known.
- When a diagnosis of MED is considered, it is sometimes worthwhile to evaluate both parents for signs of MED or early-onset osteoarthritis. If a disease-causing mutation has been identified in an affected family member, molecular genetic testing of the parents is available.

Sibs of a proband

- The risk to sibs depends on the genetic status of the proband's parents.
- If a parent is found to have dominant MED, the risk to each sib of the proband is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. However, a number of families in which one of the parents has germline mosaicism for a dominantly inherited mutation have been reported, resulting in a family history suggestive of autosomal recessive inheritance.

Offspring of a proband. Each child of an individual with dominant MED has a 50% chance of inheriting the mutation.

Other family members

- The risk to other family members depends upon the status of the proband's parents.
- If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

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 mutation have been reported, resulting in a family history suggestive of autosomal recessive inheritance.

Testing of at-risk individuals during childhood. The testing of asymptomatic at-risk individuals younger than age 18 years is controversial. This testing can be justified only if it is believed that knowledge of the disease status of the child will influence care of that 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* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

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

Prenatal Testing

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

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

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

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Molecular Genetics

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

Table A. Molecular Genetics of Multiple Epiphyseal Dysplasia, Dominant

Gene Symbol	Chromosomal Locus	Protein Name
COL9A1	6q13	Collagen alpha-1(IX) chain
COL9A2	1p33-p32.2	Collagen alpha-2(IX) chain
COL9A3	20q13.3	Collagen alpha-3(IX) chain
COMP	19p13.1	Cartilage oligomeric matrix protein
MATN3	2p24-p23	Matrilin-3

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

Table B. OMIM Entries for Multiple Epiphyseal Dysplasia, Dominant

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

Table C. Genomic Databases for Multiple Epiphyseal Dysplasia, Dominant

Gene Symbol	Entrez Gene	HGMD
COL9A1	1297 (MIM No. 120210)	COL9A1
COL9A2	1298 (MIM No. 120260)	COL9A2
COL9A3	1299 (MIM No. 120270)	COL9A3
COMP	1311 (MIM No. 600310)	COMP
MATN3	4148 (MIM No. 602109)	MATN3

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

Molecular Genetic Pathogenesis

The five genes *(COMP*, *COL9A1*, *COL9A2*, *COL9A3*, and *MATN3*) known to cause dominant MED code for three structural macromolecules of the cartilage extracellular matrix (cartilage oligomeric matrix protein, type IX collagen, and matrilin-3) [reviewed in Unger & Hecht 2001, Briggs & Chapman 2002]. These proteins have been shown to interact with each other and also with type II collagen 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].

Mutations in *COMP* exons encoding the type III repeats of *COMP* result in the misfolding of the protein and its retention in the rough endoplasmic reticulum (rER) of chondrocytes, which is thought to result in an unfolded protein/cell stress response and ultimately in increased cell apoptosis [Chen et al 2000, Maddox et al 2000, reviewed in Unger & Hecht 2001, Kleerekoper et al 2002].

The effect of mutations in the exons encoding the C-terminal domain of *COMP* is not fully resolved, but these mutations are not thought to prevent the secretion of mutant COMP into the cartilage extracellular matrix, where it may act in a dominant-negative manner [Spitznagel et al 2004, Schmitz et al 2006].

The effect of *MATN3* mutations appears similar to the effect caused by type III *COMP* mutations and results in the retention of mutant matrilin-3 in the rER of chondrocytes [Cotterill et al 2005, Otten et al 2005]. This ultimately causes an unfolded protein/cell stress response that is likely to induce early apoptosis.

The pathologic effect of mutations in *COL9A1*, *COL9A2*, and *COL9A3* is not well understood and a number of mechanisms have been proposed for these mutations including the degradation of mRNA from the mutant allele [Holden et al 1999, Spayde et al 2000], an accumulation of abnormal type IX collagen α-chains in the rER of chondrocytes [Bonnemann et al 2000], and/or the degradation of abnormal α-chains [van Mourik et al 1998].

COMP

Normal allelic variants: The coding sequence of the *COMP* gene is organized into 19 exons spanning approximately 8.5 kb. The p.Asn386Asp allele has occasionally been seen in the heterozygous state in several unaffected individuals (allele frequency of 0.03) and is therefore likely to be a polymorphism.

Pathologic allelic variants: *COMP* gene mutations and MED (EDM1: OMIM 132400). All of the pathogenic mutations identified in *COMP*, which result in MED, are either missense mutations or small in-frame deletions and duplications found in the type III or C-terminal domains of COMP. To date, nearly 60 different missense mutations have been reported in these two domains. The majority of mutations are in the type III repeats (~85%) with the remainder in the C-terminal domain (~15%) [Kennedy, Jackson, Ramsden et al 2005; Kennedy, Jackson, Barker et al 2005]. The small in-frame deletions (p.Arg367_Gly368del and p.Asn386del) and duplication (p.Asp473dup) are both in the type III repeat region of *COMP*, while a single nucleotide deletion has been reported at codon 742 in the C-terminal domain. A number of C-terminal missense mutations have been identified including p.Asn555Lys, p.Asp605Asn, p.Ser681Cys, p.Arg718Pro, and the recurrent p.Arg718Trp [Kennedy, Jackson, Barker et al 2005], while two mutations (p.Thr585Arg and p.Thr585Met) have been shown to result in either mild PSACH or MED, confirming that the two disorders are related.

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 the fifth member of the thrombospondin protein family and a modular and multifunctional protein, comprising a coiled-coil oligomerization domain, four type II (EGF-like) repeats, eight type III (CaM-like) repeats, and 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 nonfibrillar (type IX) collagens and fibronectin [Di Cesare et al 2002].

Abnormal gene product: Missense mutations in *COMP* result in misfolding of the gene product, which in some cases results in its retention in the rER of chondrocytes [Unger & Hecht 2001].

Collagen IX genes

Normal allelic variants: The coding sequence of the *COL9A1* gene is organized into 38 exons spanning approximately 90 kb [Pihlajamaa et al 1998]; the coding sequence of the *COL9A2*

and *COL9A3* genes is organized into 32 exons spanning approximately 15 kb and 23 kb respectively [Paassilta et al 1999]. A number of non-pathogenic changes have been identified in the type IX collagen genes, including an in-frame deletion and several synonymous changes [Paassilta et al 1999, Loughlin et al 2002].

Pathologic allelic variants: Type IX collagen gene mutations and MED (EDM2: OMIM 600204; EDM3: OMIM 600969; EDM6). All type IX collagen gene mutations reported in MED are clustered in either the splice donor site of exon 3 of *COL9A2*, the splice acceptor site of exon 3 of *COL9A3*, or the splice acceptor site of exon 8 of *COL9A1*. The mutations in *COL9A2* and *COL9A3* result in the skipping of exon 3 during RNA splicing; the resulting 36-bp deletion in the mRNA from *COL9A2* and *COL9A3* gives rise to a 12-amino acid in-frame deletion from the α2(IX) or α3(IX) chains. The single mutation identified in the splice acceptor site of exon 8 of *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 from the α1(IX) chain. All of the deletions are located in a similar region of the COL3 domain of type IX collagen and the precise location of the mutations demonstrates the importance of this domain [reviewed in Unger & Hecht 2001, Briggs & Chapman 2002].

Normal gene product: Type IX collagen 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; it comprises three collagenous (COL) domains separated by non-collagenous (NC) domains. The amino-terminal NC domain (NC4) is encoded entirely by the *COL9A1* gene. It is a heterotrimer [α1(IX)α2(IX)α3(IX)] of polypeptides derived from three distinct genes *(COL9A1*, *COL9A2*, and *COL9A3*). Type IX collagen comprises three collagenous (COL1-COL3) domains separated by four non-collagenous (NC1-NC4) domains and is closely associated with type II collagen fibrils, where it is thought to act as a molecular bridge between collagen fibrils and other cartilage matrix components.

Abnormal gene product: Exon skip mutations in *COL9A1*, *COL9A2*, and *COL9A3* result in the in-frame deletion of amino acids from the COL3 domain of type IX collagen, which may affect its ability to fold correctly or interact with other components of the cartilage extracellular matrix [reviewed in Unger & Hecht 2001, Briggs & Chapman 2002].

MATN3

Normal allelic variants: The coding sequence of the *MATN3* gene is organized into eight exons spanning approximately 21 kb. The p.Glu252Lys allele has occasionally been seen in the heterozygous state in several unaffected individuals (allele frequency of 0.025) and is therefore likely to be a polymorphism.

Pathologic allelic variants:

- Matrilin-3 mutations and MED (EDM5: OMIM 607078). Mutations in the single A-domain of matrilin-3 can result in dominant MED [Chapman et al 2001]. One of these mutations (p.Arg121Trp) has been identified in approximately 40% of MED families with a *MATN3* mutation, while other mutations (p.Ala123Lys, p.Val194Asp, p.Thr195Lys, p.Ala219Asp, p.Ile192Asn, p.Thr120Met, p.Tyr218Asn, p.Glu134Lys) are so far private to each family [Jackson et al 2004, Mabuchi et al 2004, Cotterill et al 2005]. While the majority of mutations lie within the β-sheet of the A-domain, a single mutation has been identified in the α-1 helix [Mabuchi et al 2004], suggesting that they may have a more widespread distribution than originally thought [Jackson et al 2004]. In addition, a mutation in *MATN3* (p.Ala218Pro) was

identified in a single family with bilateral microepiphyseal dysplasia (BMED) [Mostert et al 2003]; this disease is now recognized as a form of MED.

- Matrilin-3 mutations and SEMD (spondyloepimetaphyseal dysplasia, matrilin-3 related: OMIM 608728). Homozygosity for a *MATN3* mutation (p.Cys304Ser in the first EGF repeat) has been shown to cause a form of recessive SEMD, bowed-legs type [Borochowitz et al 2004].

Normal gene product: Matrilin-3 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, and a coiled-coil domain, which facilitates oligomerization. Specifically, matrilin-3 is a protein of 486 amino acids, which comprises primarily a vWFA domain, four EGF-like repeats, and a coiled-coil domain [Belluoccio et al 1998]. Matrilins have been found in collagen-dependent and -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 [Mann et al 2004].

Abnormal gene product: *MATN3* mutations appear to delay the folding of the A-domain, which elicits an unfolded protein response and results in the retention of mutant matrilin-3 in the rER [Cotterill et al 2005, Otten et al 2005].

Resources

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

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Fax: 503-846-1590
Email: info@lpaonline.org
www.lpaonline.org

Restricted Growth Association (RGA)
PO Box 4008
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United Kingdom
Phone: +44 (0) 01935 841 364
Email: office@restrictedgrowth.co.uk
www.restrictedgrowth.co.uk

European Skeletal Dysplasia Network
North West Genetics Knowledge Park (Nowgen)
The Nowgen Centre 29 Grafton Street
Manchester M13 9WU
United Kingdom
Phone: 0161 276 3202
Fax: 0161 276 4058

Email: info@esdn.org
www.esdn.org

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

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

Published Statements and Policies Regarding Genetic Testing

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

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Chapter Notes

Author Notes

European Skeletal Dysplasia Network (ESDN)

Revision History

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