Hereditary Multiple Osteochondromas

Synonyms: Diaphyseal Aclasis, Hereditary Multiple Exostoses, Multiple Cartilaginous Exostoses

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Summary

Clinical characteristics

Hereditary multiple osteochondromas (HMO), previously called hereditary multiple exostoses (HME), is characterized by growths of multiple osteochondromas, benign cartilage-capped bone tumors that grow outward from the metaphyses of long bones. Osteochondromas can be associated with a reduction in skeletal growth, bony deformity, restricted joint motion, shortened stature, premature osteoarthrosis, and compression of peripheral nerves. The median age of diagnosis is three years; nearly all affected individuals are diagnosed by age 12 years. The risk for malignant degeneration to osteochondrosarcoma increases with age, although the lifetime risk for malignant degeneration is low (~2%-5%).

Diagnosis/testing

The diagnosis of HMO is established in a proband with characteristic radiographic findings of multiple osteochondromas and/or a heterozygous pathogenic variant in *EXT1* or *EXT2* identified on molecular genetic testing.

Management

Treatment of manifestations: Painful lesions in the absence of bone deformity are treated with surgical excision that includes the cartilage cap and overlying perichondrium to prevent recurrence; forearm deformity is treated with excision of the osteochondromas, corrective osteotomies, and ulnar-lengthening procedures; though uncomplicated resection of osteochondromas in growing children is frequently reported, there is a theoretic risk of growth abnormality resulting from resection of periphyseal osteochondromas; angular misalignment of the lower limbs may be treated with hemiepiphysiodeses (or osteotomies) at the distal femur, proximal tibia, or

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distal tibia; leg-length inequalities greater than 2.5 cm are often treated with epiphysiodesis (growth plate arrest) of the longer leg or lengthening of the involved leg; early treatment of ankle deformity may prevent or decrease later deterioration of function; sarcomatous degeneration is treated by surgical resection.

Surveillance: Monitoring of the size of exostoses in adults may aid in early identification of malignant degeneration, but no cost/benefit analyses are available to support routine surveillance; a single screening MRI of the spine in children with HMO has been recommended by some to identify spinal lesions that may cause pressure on the spinal cord and would warrant close clinical follow up with excision of lesions that cause spinal cord impingement and/or symptoms. To date, there are no prospective studies to show a benefit of systematic screening MRI in asymptomatic individuals.

Genetic counseling

HMO is inherited in an autosomal dominant manner. Penetrance is approximately 96% in females and 100% in males. In 10% of affected individuals HMO is the result of a *de novo* pathogenic variant. Offspring of an affected individual are at a 50% risk of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible if the pathogenic variant in a family is known.

Diagnosis

No consensus clinical diagnostic criteria for hereditary multiple osteochondromas (HMO) have been published.

Suggestive Findings

Hereditary multiple osteochondromas (HMO) **should be suspected** in individuals with the following radiographic features and family history:

- Multiple osteochondromas (cartilage-capped bony growths) arising from the area of the growth plate in the juxtaphyseal region of long bones or from the surface of flat bones (e.g., the scapula)
  - The key radiographic and anatomic feature of an osteochondroma is the uninterrupted flow of cortex and medullary bone from the host bone into the osteochondroma.
  - Osteochondromas possess the equivalent of a growth plate that ossifies and closes with the onset of skeletal maturity.
  - Approximately 70% of affected individuals have a clinically apparent osteochondroma about the knee, suggesting that radiographs of the knees to detect non-palpable osteochondromas may be a sensitive way to detect mildly affected individuals.
- Family history consistent with autosomal dominant inheritance (~10% of affected individuals have no family history of multiple osteochondromas.)

Note regarding terminology: Osteochondromas were previously called exostoses; however, the term "exostosis" is no longer used to describe the lesions in HMO because the term "osteochondroma" specifies that these lesions are cartilaginous processes that ossify and not simply outgrowths of bone. The updated terminology has been adopted by the World Health Organization (WHO).

Establishing the Diagnosis

The clinical diagnosis of HMO can be **established** in a proband with characteristic clinical features (see Suggestive Findings). If clinical features are inconclusive, a molecular diagnosis can be established in a proband by the identification of a heterozygous pathogenic variant in *EXT1* or *EXT2* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, 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 HMO 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 in whom the diagnosis of HMO has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of HMO, molecular genetic testing approaches can include use of a **multigene panel** or **serial single-gene testing**:

- **A multigene panel** that includes *EXT1*, *EXT2*, and other genes of interest if the clinical diagnosis is doubtful (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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Serial single-gene testing.** Sequence analysis of *EXT1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant in *EXT1* is detected, perform sequence analysis of *EXT2*. If no variant is detected, the next step is to perform gene-targeted deletion/duplication analysis of *EXT1* and *EXT2* to detect exon and whole-gene deletions or duplications, which account for approximately 10%-20% of pathogenic variants detected.

Option 2

When the diagnosis of HMO is doubtful 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. Exome array may be recommended to detect deletions/duplications.

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 Hereditary Multiple Osteochondromas

Gene [1, 2]	Proportion of Hereditary Multiple Osteochondromas Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
EXT1	65%-70% [6, 7, 8]	88%-93% [6, 8]	7%-12% [6, 7]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Hereditary Multiple Osteochondromas Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
EXT2	30%-35% [6, 7, 8]	>90% [6, 8]	<10% [6, 7]
Unknown	10%-13% [9]	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]; Pedrini et al [2011]; W Wuyts, personal communication
7. Whole-gene, partial-gene, and single-exon deletions have been described but there are no recurrent break points [Jennes et al 2009, Jennes et al 2011, Li et al 2019].
8. Fusco et al [2019]
9. It is suspected that simplex cases of HMO harbor a somatic *EXT1* or *EXT2* pathogenic variant not detected by standard protocols performed on DNA isolated from whole blood samples due to limits of detection [Szuhai et al 2011].

Clinical Characteristics

Clinical Description

To date, more than 1,000 individuals with a pathogenic variant in *EXT1 or EXT2* have been identified [Pedrini et al 2011, Fusco et al 2019] (see Leiden Open Variation Database: *EXT1* and *EXT2*). The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Hereditary Multiple Osteochondromas (HMO)

Feature	% of Persons with Feature	Comment
Osteochondromas	100%	More lesions in persons w/*EXT1*-HMO than in those w/*EXT2*-HMO [1]
Angular deformities of forearms or legs	30%-60% [2]	
Leg length discrepancy	10%-15% [3]	
Shortened stature	• 67% <50th centile • 46% of *EXT1*-HMO <10th centile	More pronounced in persons w/*EXT1*-HMO than *EXT2*-HMO [4]
Chondrosarcoma	2%-5% [5]	Predominantly localized to pelvis, scapula, proximal femur, & humerus

1. Pedrini et al [2011], Clement & Porter [2014b], Fusco et al [2019]
2. Schmale et al [1994], Clement & Porter [2013], Li et al [2017]
3. Schmale et al [1994]
4. Li et al [2017]
5. Fei et al [2018], Jurik et al [2020]

The number of osteochondromas, number and location of involved bones, and degree of deformity vary. Osteochondromas grow in size and gradually ossify during skeletal development and stop growing with skeletal maturity, after which no new osteochondromas develop. The proportion of individuals with hereditary multiple osteochondromas (HMO) who have clinical findings increases from approximately 5% at birth to 96% at age 12 years [Legeai-Mallet et al 1997]. The median age at diagnosis is three years. Males tend to be more severely affected than females [Pedrini et al 2011]. Although pain is a common complaint, most individuals with HMO lead active, healthy lives.

The number of osteochondromas that develop in an affected person varies widely even within families. Involvement is usually symmetric. Most commonly involved bones are the femur (30%), radius and ulna (13%), tibia (20%), and fibula (13%). Hand deformity resulting from shortened metacarpals is common. Abnormal bone remodeling may result in shortening and bowing with widened metaphyses [Porter et al 2004]. Anatomic distribution and number of osteochondromas depends on genotype and sex of the affected person [Clement & Porter 2014b].

Abnormal growth and development of the forearm and leg in untreated individuals with HMO is common, including both proportionate and disproportionate shortening of the two bones of the forearm or leg, producing shortened and angulated limbs, respectively. In a study of 46 kindreds in Washington State, 39% of individuals had a deformity of the forearm, 10% had an inequality in limb length, 8% had an angular deformity of the knee, and 2% had a deformity of the ankle [Schmale et al 1994]. Angular deformities (bowing) of the forearm and/or ankle are the most clinically significant orthopedic issues [Shin et al 2006].

Hip dysplasia frequently results from osteochondromas of the proximal femur and from coxa valga. Decreased center-edge angles and increased uncovering of the femoral heads may lead to early thigh pain and abductor weakness and late arthritis [Makhdom et al 2014, Wang et al 2015]. Femoral-acetabular impingement may also arise from proximal femoral osteochondromas, limiting hip motion [Viala et al 2012, Higuchi et al 2016, Duque Orozco et al 2018].

It has been stated that 40% of individuals with HMO have "shortened stature." Although interference with the linear growth of the long bones of the leg often results in reduction of predicted adult height, the height of most adults with *EXT2* pathogenic variants and many with *EXT1* pathogenic variants falls within the normal range [Porter et al 2004]. Shortened stature is more pronounced in persons with *EXT1* pathogenic variants [Pedrini et al 2011, Clement et al 2012, Li et al 2017]. Height has been found to be directly proportional to leg length, and in a number of individuals with *EXT1-* and *EXT2*-HMO, height is below the 10th centile [Li et al 2017]. Multivariate analysis determined that the presence of a distal femoral osteochondroma was an independent predictor of knee deformity, diminished knee joint range of motion, and short stature [Clement & Porter 2014a].

Note: "Shortened stature" is used to indicate that although stature is often shorter than predicted based on the heights of unaffected parents and sibs, it is usually within the normal range.

Osteochondromas typically arise in the juxtaphyseal region of long bones and from the surface of flat bones (pelvis, scapula). An osteochondroma may be sessile or pedunculated. Sessile osteochondromas have a broad-based attachment to the cortex. The pedunculated variants have a pedicle arising from the cortex that is usually directed away from the adjacent growth plate. The pedunculated form is more likely to irritate overlying soft tissue, such as tendons, and compress peripheral nerves or vessels. The marrow and cancellous bone of the host bone are continuous with the osteochondroma.

Symptoms may also arise secondary to mass effect. Compression or stretching of peripheral nerves usually causes pain but may also cause sensory or motor deficits [Göçmen et al 2014, Onan et al 2014, Payne et al 2016]. Spinal cord compression and myelopathy from cervical osteochondromas have been reported [Aldea et al 2006, Giudicissi-Filho et al 2006, Pandya et al 2006, Ashraf et al 2013, Veeravagu et al 2017, Akhaddar et al 2018, Gigi et al 2019, Montgomery et al 2019], as has dysphagia from a cervical osteochondroma [Gulati et al 2013].

Bilateral inferior cervical osteochondromas have been found to produce neurogenic and vascular thoracic outlet syndrome [Abdolrazaghi et al 2018]. Syringomyelia and tethered cord/fibrolipoma in individuals undergoing screening spine exams without evidence of spinal osteochondromas have also been described [Legare et al 2016]. Mechanical blocks to motion may result from large osteochondromas impinging on the adjacent bone of a joint. Overlying muscles and tendons may be irritated or entrapped, resulting in pain and loss of motion [Andrews et al 2019]. Nerves and vessels may be displaced from their normal anatomic course, complicating attempts at surgical removal of osteochondromas. Rarely, urinary or intestinal obstruction results from large pelvic osteochondromas. Thoracic osteochondromas have been reported to lead to diaphragmatic rupture [Abdullah et al 2006], pneumothorax [Chawla et al 2013, Imai et al 2014, Dumazet et al 2018], hemothorax [Yoon et al 2015, Lin et al 2017], coronary artery compression [Rodrigues et al 2015], and severe chest pain [Kanthasamy et al 2020]. Osteochondromas have led to pseudoaneurysms [Oljaca et al 2019, Iqbal et al 2020] that can mimic sarcoma. Biopsy of a misdiagnosed pseudoaneurysm can have life-threatening consequences [Iqbal et al 2020].

The most serious complication of HMO is sarcomatous degeneration of an osteochondroma. Axial sites, such as the pelvis, scapula, ribs, and spine, are more commonly the location of degeneration of osteochondromas to chondrosarcoma [Porter et al 2004]. Rapid growth and increasing pain, especially in a physically mature person, are signs of sarcomatous transformation, a potentially life-threatening condition:

- A bulky cartilage cap (best visualized with MRI or CT) thicker than 2.0 to 3.0 cm is highly suggestive of chondrosarcoma [Shah et al 2007, Bernard et al 2010].
- After skeletal maturity, increased radionucleotide uptake on serial technetium bone scans may also be evidence of malignancy.
- High metabolic activity in the cartilage as evidenced by uptake of gadolinum on T_2-weighted MRI may also be indicative of malignancy [De Beuckeleer et al 1996].
- FDG-PET imaging may be useful in the workup for malignant transformation in HMO. An SUV_{max} of 2 has been reported as the cutoff above which chondrosarcomatous degeneration of an osteochondroma has likely occurred, although lesions with an SUV_{max} as low as 1.3 have been found in grade I chondrosarcoma [Aoki et al 1999, Feldman et al 2005, Purandare et al 2019].

The incidence of malignant degeneration to chondrosarcoma, or less commonly to other sarcomas, is estimated at 2%-5%. In a large cohort of 529 affected individuals, the rate of malignant transformation was calculated to be 5% [Pedrini et al 2011]. A survey of an international heterogeneous cohort of 757 individuals with HMO revealed 21 (2.7%) with malignant degeneration, with pelvis and scapula the most common sites of malignant change from benign osteochondromas [Czajka & DiCaprio 2015].

Malignant degeneration can occur during childhood or adolescence, but the risk increases with age. Based on a study of HMO in Washington State (USA), it was estimated that HMO may increase the risk of developing a chondrosarcoma by a factor of 1,000 to 2,500 over the risk for individuals without HMO.

Phenotype Correlations by Gene

Most studies have identified a higher burden of disease in persons with *EXT1* pathogenic variants than in those with *EXT2* pathogenic variants, including greater number of exostoses, skeletal deformity, and shorter stature [Porter et al 2004, Pedrini et al 2011, Li et al 2017]. Pedrini et al [2011] suggested a clinical classification system based on the presence or absence of deformities and functional limitations (adapted in Mordenti et al [2013]). In 529 individuals with multiple osteochondromas (MO) a more severe MO phenotype was found to be associated with pathogenic variants in *EXT1* and male sex. The risk for chondrosarcoma may also be higher in individuals with an *EXT1* pathogenic variant [Porter et al 2004], although this was not found in all studies [Pedrini et al 2011].

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *EXT1 or EXT2* have been identified.

Penetrance

The penetrance is estimated to be 96% in females and 100% in males [Schmale et al 1994]. Most published instances of reduced penetrance have occurred in females. However, comprehensive skeletal radiographs have not been performed in most of these instances.

Nomenclature

"Multiple osteocartilaginous exostoses" was used to convey the observation that the growths are composed primarily of cartilage in the child and ossify as skeletal maturity is reached.

In the United States, the terms "exostosis" and "hereditary multiple exostoses" have been used to denote the growths and the disorder, but the World Health Organization (WHO) has selected the nomenclature "osteochondromas" for exostoses and "multiple osteochondromas" for the disorder [Bovée & Hogendoorn 2002]. These latter terms are preferable as they more precisely describe the lesions as cartilaginous in origin. However, "hereditary multiple exostoses" (HME) and "multiple hereditary exostoses" (MHE) are still frequently used as abbreviations for this disorder, and the genes are named exostosin-1 (*EXT1*) and exostosin-2 (*EXT2*).

Prevalence

The reported prevalence of HMO ranges from as high as one in 100 in a small population in Guam to approximately one in 100,000 in European populations [Krooth et al 1961, Hennekam 1991]. The prevalence has been estimated to be at least one in 50,000 in Washington State [Schmale et al 1994].

Genetically Related (Allelic) Disorders

EXT1 or *EXT2* **pathogenic variants.** No phenotypes other than those discussed in this *GeneReview* are associated with pathogenic variants in *EXT1* or *EXT2*.

Contiguous gene deletion syndromes. Langer-Giedion syndrome, involving deletion of *EXT1* and *TRPS1* (see Trichorhinophalangeal Syndrome), and Potocki-Shaffer syndrome, involving deletion of *EXT2* and *ALX4*, include multiple osteochondromas as one characteristic and should be considered in the differential diagnosis of hereditary multiple osteochondromas.

Differential Diagnosis

Solitary osteochrondroma. Skeletal surveys suggest that a solitary osteochondroma, a common benign bone tumor, can be found in 1%-2% of the population. Solitary osteochondromas demonstrate growth patterns similar to those of multiple osteochondromas. Conditions that may be confused with a solitary osteochondroma include juxtacortical osteosarcoma, soft tissue osteosarcoma, and heterotopic ossification. Plain radiographs or CT are often helpful in distinguishing these lesions from osteochondromas. Typically, none of these conditions displays the continuity of cancellous and cortical bone from the host bone to the lesion characteristic of hereditary multiple osteochondromas (HMO).

Inherited conditions in which multiple osteochondromas occur are summarized in Table 3.

Table 3. Inherited Conditions with Multiple Osteochondromas in the Differential Diagnosis of Hereditary Multiple Osteochondromas

Gene / Genetic Mechanism	Disorder	MOI	Distinguishing Features of Differential Diagnosis Disorder
Contiguous deletion syndrome involving *ALX4*, *EXT2*, & *PHF21A* [1]	Potocki-Shaffer syndrome (proximal 11p deletion syndrome) (OMIM 601224)	AD	• Parietal foramina & ossification defects of the skull (See Enlarged Parietal Foramina.) • Craniofacial abnormalities, syndactyly, & ID in some affected persons
Contiguous deletion syndrome involving *EXT1*, *RAD21*, & *TRPS1*	Trichorhinophalangeal syndrome II (Langer-Giedion syndrome)	AD	• ID • Characteristic craniofacial & digital anomalies
PTPN11	Metachondromatosis (OMIM 156250)	AD	• Assoc w/both osteochondromas & intraosseous enchondromas • Tumors occur predominantly in digits, point toward nearby joint, & do not cause shortening or bowing of long bone, joint deformity, or subluxation.

AD = autosomal dominant; ID = intellectual disability; MOI = mode of inheritance
1. Deletion events invariably remove *ALX4* and the adjacent gene, *EXT2*. *PHF21A*, which is variably deleted, is highly likely to account for the intellectual disability and facial dysmorphism.

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Hereditary Multiple Osteochondromas

System/Concern	Evaluation	Comment
Musculoskeletal	• Detailed history of symptoms from osteochondromas • Physical exam to document location of osteochondromas, functional limitations, & deformity (shortness of stature, forearm bowing & shortening, knee & ankle angular deformities)	Some suggest entire spinal canal or total body non-contrast MRI as a one-time screening test to document extent & location of involvement [Roach et al 2009, Akhaddar et al 2018]. MRI is preferred to CT in those w/ inherited predisposition to malignancy. In general, decisions re surgical interventions are based on pain & functional impairment. The efficacy of screening in asymptomatic persons w/HMO has not been demonstrated & guidelines are not established. [1]
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of HMO to facilitate medical & personal decision making

HMO = hereditary multiple osteochondromas; MOI = mode of inheritance
1. Although spinal osteochrondomas are common in HMO and can cause neurologic impairment, intervention is reserved for symptomatic cases and in almost all cases there was complete recovery [Roach et al 2009, Akhaddar et al 2018, Jackson et al 2019].
2. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Hereditary Multiple Osteochondromas

Manifestation/ Concern	Treatment	Considerations/Other
Asymptomatic osteochondromas	Require no therapy in absence of clinical problems	Though uncomplicated resection of osteochondromas in growing children is frequently reported, [1] it is asooc w/a theoretic risk of growth abnormality.
Painful osteochondromas w/o bony deformity	Simple surgical excision may slow growth disturbance & improve cosmesis.	Must incl cartilage cap & overlying perichondrium to avoid recurrence
Angular deformities of forearm	• May incl excision of osteochondromas, corrective osteotomies, &/or ulnar lengthening procedures to improve pronation, supination, & forearm alignment [2] • Adults w/untreated forearm deformities describe few functional limitations.	Waiting to resect osteochondromas until they have migrated away from the physis would ↓ risk of injury to physis, & could ↓ risk of recurrence of lesions, [3] but many studies suggest that early (age <10 yrs) treatment of forearm deformities via resection of distal osteochondromas may ↓ proportionate shortening & bowing of forearm [4] as well as ankle deformity. [5]
Angular misalignment of lower limbs	May be treated w/hemiepiphysiodeses (or osteotomies) at distal femur, proximal tibia, or distal tibia [6]	
Leg-length inequalities	Discrepancy >2.5 cm is often treated w/ epiphysiodesis (growth plate arrest) of longer leg.	
Tibio-talar tilt	Early surgical treatment may prevent or ↓ incidence of late deterioration of ankle function. [7]	Long-term follow-up studies are needed.
Sarcomatous degeneration	Surgical resection	Adjuvant radiotherapy & chemotherapy are controversial for secondary chondrosarcoma but often used w/secondary osteosarcoma.

1. Shin et al [2006], Ishikawa et al [2007]
2. Matsubara et al [2006], Shin et al [2006], Ishikawa et al [2007], Watts et al [2007]
3. Chin et al [2000], Shin et al [2006], Beutel et al [2014]
4. Masada et al [1989], Ishikawa et al [2007], Tonogai et al [2015], Kelly & James [2016], Iba et al [2018], Ahmed [2019], Li et al [2019]
5. Chin et al [2000]
6. Ofiram et al [2008], Boero et al [2011], Rupprecht et al [2011], Tompkins et al [2012], Driscoll et al [2013], Rupprecht et al [2015], Chu et al [2016], van Oosterbos et al [2016], Kang et al [2017]
7. Noonan et al [2002]

Surveillance

Table 6. Recommended Surveillance for Individuals with Hereditary Multiple Osteochondromas

System/Concern	Evaluation	Frequency/Comment
Osteochondromas involving pelvis or scapula	X-rays, CT, MRI, positron emission tomography, &/or technicium-99 radionuclide imaging to monitor growth of osteochondromas may aid in early identification of malignant degeneration.	In adults, optimal screening intervals have not been determined, nor has a prospective study shown efficacy. However, as osteochondromas in these locations have the highest likelihood of malignant degeneration, imaging of those w/pelvic or scapular lesions every 2-3 yrs seems reasonable. [1]

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency/Comment
Osteochondromas involving spine	Spine MRI to identify spinal lesions that may cause pressure on spinal cord [1]	Consider in children w/close clinical follow up for any osteochondromas in canal, encroaching lesions, & those causing symptoms that may merit excision. [2]

1. It is not known whether the benefits outweigh the risks of irradiation and the potential for false positive results that lead to unnecessary interventions. Fei et al [2018] estimated that it would take 3.9 years of screening to identify a single case of malignant change if all individuals with HMO were screened. To screen asymptomatic individuals, total body non-contrast MRI is preferable. This technique detects even small lesions and avoids gadolinium [Staal et al 2016, Jurik et al 2020].

2. There is insufficient data to support routine interval spine surveillance in asymptomatic individuals, as surgical interventions are reserved for those with intractable pain or functional impairment [Roach et al 2009].

Evaluation of Relatives at Risk

Asymptomatic, predictive testing is not warranted because the clinical diagnosis is evident at an early age and because no precipitants, protective strategies, or specific nonsurgical interventions are known.

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

Therapies Under Investigation

A clinical trial of the RARγ agonist palovarotene for patients younger than age 14 years with HMO was paused in January 2020, based on results of a futility analysis.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

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

The disorder hereditary multiple osteochondromas (HMO) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 90% of individuals with HMO have an affected parent.

- Approximately 10% of individuals diagnosed with HMO have the disorder as the result of a *de novo* pathogenic variant.

- If the proband is the only family member known to have HMO, recommendations for the evaluation of the parents of the proband include physical examination, radiographs, and/or molecular genetic testing (if the causative pathogenic variant has been identified in the proband).

- If the proband has a known *EXT1* or *EXT2* 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.* Parental somatic and germline mosaicism have been reported in HMO [Szuhai et al 2011].

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- The family history of some individuals diagnosed with HMO may appear to be negative because of failure to recognize the disorder in family members and/or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Note: If the parent is the individual in whom the pathogenic variant first occurred, they may have somatic mosaicism for the variant and may be mildly/minimally affected.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known HMO-related 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 [Szuhai et al 2011].
- If the parents have not undergone molecular genetic testing but are clinically unaffected, sibs are still presumed to be at increased risk for HMO because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism [Szuhai et al 2011].

Offspring of a proband. Each child of an individual with HMO has a 50% chance of inheriting an HMO-causing pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

Family planning

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

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, 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 genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

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

Differences in perspective may exist among medical professionals and families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MHE Research Foundation**
  Phone: 917-848-7774
  Email: mhefuntasia@gmail.com
  www.mherf.org

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. Hereditary Multiple Osteochondromas: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EXT1	8q24.11	Exostosin-1	EXT1 gene database	EXT1	EXT1
EXT2	11p11.2	Exostosin-2	EXT2 gene homepage	EXT2	EXT2

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 Hereditary Multiple Osteochondromas (View All in OMIM)

133700	EXOSTOSES, MULTIPLE, TYPE I; EXT1
133701	EXOSTOSES, MULTIPLE, TYPE II; EXT2
608177	EXOSTOSIN GLYCOSYLTRANSFERASE 1; EXT1
608210	EXOSTOSIN GLYCOSYLTRANSFERASE 2; EXT2

Molecular Pathogenesis

Both *EXT* (*EXT1*, *EXT2*) gene products are involved in the biosynthesis of heparan sulfate. *EXT1* and *EXT2* encode glycosyltransferases that interact as heterooligomeric complexes [McCormick et al 2000]. Pathogenic variants in *EXT1* or *EXT2* cause cytoskeletal abnormalities that include actin accumulation, excessive bundling by alpha-actinin, and abnormal presence of muscle-specific alpha-actin [Bernard et al 2000].

Osteochondroma mouse models have shown that complete inactivation of both *Ext1* alleles in a small fraction of chondrocytes is sufficient for the development of osteochondromas and other skeletal defects associated with MHO and that osteochondromas are composed of a mixture of EXT$^{+/-}$ and EXT$^{-/-}$ cells [Jones et al 2010, Matsumoto et al 2010, Pacifici 2018]. Biallelic loss of EXT has been demonstrated in osteochondromas and the failure to identify pathogenic variants in both alleles of *EXT1* and/or *EXT2* or loss of heterozygosity in osteochondromas of individuals with hereditary multiple osteochondromas (HMO) in older studies [Hall et al 2002, Hameetman et al 2007, Zuntini et al 2010] may be caused by mosaicism, or may reflect the limitations of sensitivity of the detection test used.

Not only do *EXT1* and *EXT2* code for transmembrane glycoproteins that together form a heterooligomeric heparan sulfate polymerase; the protein product also participates in cell signaling and chondrocyte proliferation and differentiation [Pacifici 2018].

EXT1. Only a few pathogenic variants have been identified in more than one family. There are several relative hot spots for mutation. Exons 1 and 6 contain one and two polypyrimidine tracts, respectively, which are often sites of frameshift variants. Missense variants cluster in codons 339 and 340. Pathogenic variants in the region encoding the carboxy-terminal protein region are relatively sparse.

EXT2. Pathogenic variants are mainly located in the first eight exons and are primarily loss-of-function variants (frameshift, in-frame deletion, nonsense, and splice site).

Mechanism of disease causation. Loss of function

Table 7. Hereditary Multiple Osteochondromas: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Reference
EXT1	NM_000127.3 NP_000118.2	c.1018C>T	p.Arg340Cys	Jennes et al [2009], Fusco et al [2019]
		c.1019G>A	p.Arg340His	
		c.1469delT	p.Leu490ArgfsTer9	Jennes et al [2009]
		See footnote 2.		Jennes et al [2011], Szuhai et al [2011]
EXT2	NM_207122.2 NP_997005.1	c.67C>T	p.Arg23Ter	Jennes et al [2009]
		c.679G>A	p.Asp227Asn	
		c.1225delG	p.Ala409ProfsTer27	Santos et al [2018]
		See footnote 2.		Jennes et al [2011], Szuhai et al [2011]

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 in alphabetic order.

2. Exon, multiexon, and whole-gene deletions

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Chapter Notes

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