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Hereditary Multiple Osteochondromas

[*Diaphyseal Aclasis, Multiple Cartilaginous Exostoses, Hereditary Multiple Exostoses. Includes: Hereditary Multiple Osteochondromatosis, Type I; Hereditary Multiple Osteochondromatosis, Type II*]

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Summary

Disease characteristics. The disorder 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 of malignant degeneration is low (~1%).

Diagnosis/testing. The diagnosis of HMO is based on clinical and/or radiographic findings of multiple exostoses in one or more members of a family. The two genes known to be associated with HMO are *EXT1* and *EXT2*; a third locus is possible. A combination of sequence analysis and deletion analysis of the entire coding regions of both *EXT1* and *EXT2* detects mutations in 70%-95% of affected individuals.

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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 exostoses, corrective osteotomies, and ulnar-lengthening procedures; leg-length inequalities greater than one inch are 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.

Genetic counseling. HMO is inherited in an autosomal dominant manner. Penetrance is approximately 96%. Ten percent of affected individuals have HMO as the result of a *de novo* mutation. Offspring of an affected individual have a 50% risk of inheriting the disease-causing mutation. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation in a family is known.

Diagnosis

Clinical Diagnosis

Hereditary multiple osteochondromas (HMO) is diagnosed clinically in individuals with the following:

- 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 such as 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.

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

  Note: 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

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. Two genes are known to be associated with HMO:

- ***EXT1*.** Approximately 56%-78% of HMO
- ***EXT2*.** Approximately 21%-44% of HMO

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Note: Some questions remain regarding the relative proportion of disease related to mutations in these two genes. (1) Because *EXT1* was identified first, more publications describe molecular genetic testing for *EXT1* than for *EXT2*. (2) Although *EXT1*-related HMO was reported to be less frequent in ethnic Chinese (30%) [Xu et al 1999], confirmation of this observation is required because a mutation was identified in fewer than half of the individuals studied. (3) In most studies, *EXT1* mutations are more frequently found than *EXT2* mutations [Dobson-Stone et al 2000, Francannet et al 2001, Wuyts et al 2002, Porter et al 2004, White et al 2004]. *EXT1* accounted for 66%-78% of the mutations identified in 151 affected individuals in two clinical settings [Wuyts 2005, personal communication; Bale 2005, personal communication].

Other loci. One group has suggested that a third gene, *EXT3,* maps to chromosome 19 [Le Merrer et al 1994]; this linkage association has not been corroborated and may represent a false positive linkage result.

Clinical testing

- **Sequence analysis.** Sequence analysis of the entire coding regions of both *EXT1* and *EXT2* detects mutations in 70%-85% of affected individuals [Philippe et al 1997; Raskind et al 1998; Wuyts et al 1998; Porter et al 2004; White et al 2004; Jennes et al 2008; Bale 2005, personal communication].
- **Mutation scanning of entire gene**. Optimized denaturing high-performance liquid chromatography (DHPLC) protocols for analysis of the entire coding regions of both *EXT1* and *EXT2* have been described and result in detection frequencies of *EXT1* and *EXT2* mutations comparable to those associated with sequence analysis [Wuyts et al 2005, Signori et al 2007]
- **Deletion/duplication analysis.** Incorporating methods such as multiplex ligation-dependent probe amplification (MLPA) to detect exonic, multiexonic, and whole-gene deletions may increase the detection rate to as much as 85%-95% [White et al 2004, Signori et al 2007, Jennes et al 2008].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Hereditary Multiple Osteochondromas

Gene Symbol	Proportion of HMO Attributed to Mutations in This Gene	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method [1]	Test Availability
EXT1	56%-78%	Sequence analysis/ mutation scanning	Sequence variants	88%-93%	Clinical Testing
		FISH [2]	Large deletions	0%- 8%	
		Deletion/duplication analysis [3]	Exonic, multiexonic, and whole-gene deletions	7%-10%	
EXT2	21%-44%	Sequence analysis/ mutation scanning	Sequence variants	90%-100%	Clinical Testing
		FISH [2]	Large deletions	<1%	
		Deletion/duplication analysis [3]	Exonic, multiexonic, and whole-gene deletions	0%-8%	

1. Mutation detection frequency reflects a combined approach of sequence analysis and MLPA for both EXT1 and EXT2 [White et al 2004, Signori et al 2007, Jennes et al 2008].

2. FISH analysis alone can detect only large deletions and therefore cannot detect the single exon deletions that cause HMO.

3. Deletion/duplication testing refers to a variety of test methods used to identify exonic, multiexonic, and whole-gene deletions; they include MLPA, quantitative PCR, real-time PCR, and "heterozygosity testing."

Note:
(1) FISH probes that are commonly used for diagnosis of Langer-Giedion syndrome (also known as trichorhinophalangeal syndrome type II (TRPS2) (OMIM 150230) are not recommended for HMO diagnosis. Langer-Giedion syndrome is a contiguous gene deletion syndrome that includes *EXT1* as well as *TRPS1*, the gene for trichorhinophalangeal syndrome type I (TRPS1), and other genes responsible for mental retardation located near, but outside, the *EXT1* gene.
(2) FISH probes used for diagnosis of the contiguous gene deletion syndrome known as "Potocki-Shaffer syndrome" or "deletion proximal 11p deletion syndrome" (P11pDS; OMIM 601224) are not recommended for HMO diagnosis. P11pDS includes EXT2 and ALX4, the gene associated with enlarged parietal foramina/cranium bifidum type 2.

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

Testing Strategy

To confirm the diagnosis in a proband

1. Sequence *EXT1* first because *EXT1* mutations are more frequently detected than *EXT2* mutations.
2. If no mutation is detected in *EXT1* by sequence analysis, then *EXT2* should be sequenced.
3. If no mutation is identified in either *EXT1* or *EXT2* by sequence analysis, then both genes should be further analyzed for deletions by MLPA or quantitative PCR.

Prenatal diagnosis and preimplantation genetic diagnosis for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *EXT1* or *EXT2*.

However, two contiguous gene deletion syndromes include multiple osteochondromas as one characteristic:

- Langer-Giedion syndrome involving deletion of s *EXT1* and *TRPS1* at 8q24.11-q24.13 (see also Differential Diagnosis)
- Potocki-Shaffer syndrome, also known as proximal 11p deletion syndrome (P11pDS), involving deletion of *EXT2* and *ALX4* at 11p11.2 (see also Differential Diagnosis)

Clinical Description

Natural History

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. By adulthood, 75% of affected

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individuals have a clinically evident bony deformity. Males tend to be more severely affected than females. 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].

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.

Hip dysplasia may result 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 [Malagon 2001, Ofiram & Porat 2004].

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* mutations and many with *EXT1* mutations falls within the normal range [Porter et al 2004]. Shortened stature is more pronounced in persons with *EXT1* mutations [Porter et al 2004].

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 still 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 [Hattori et al 2006]. Spinal cord compression and myelopathy from cervical osteochondromas has been reported [Aldea et al 2006, Giudicissi-Filho et al 2006, Pandya et al 2006]. Mechanical blocks to motion may result from large osteochondromas impinging on the adjacent bone of a joint. Overlying muscles and tendons may be irritated, resulting in pain and loss of motion. 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].

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].

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- 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 T2 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 2.0 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].

The reported incidence of malignant degeneration to chondrosarcoma, or less commonly to other sarcomas, has ranged from 0.5% to 20%, with many reports strongly favoring the lower estimates [Legeai-Mallet et al 1997]. However, in certain families, the rates of malignant degeneration have been reported to be as high as 6% [Vujic et al 2004, Porter et al 2004].

Malignant degeneration can occur during childhood or adolescence, but the risk increases with age. The prevalence of chondrosarcoma in the general population is approximately one in 250,000 to one in 100,000; however, 5% of those with a chondrosarcoma have HMO. Based on a study of HMO in Washington state, it was estimated that HMO increases the risk of developing a chondrosarcoma by a factor of 1000 to 2500 over the risk for individuals without HMO.

Note: It is hard to estimate the actual risk because so many published studies are series from the surgical literature. In the approximately 20 studies over the last 25 years that included affected family members of probands (i.e., those who did not themselves present for medical treatment), the rates of sarcomatous degeneration averaged approximately 2%-4%. However, no longitudinal studies have addressed the issue of lifetime risks.

Genotype-Phenotype Correlations

Some studies have identified a higher burden of disease in persons with *EXT1* mutations than in those with *EXT2* mutations:

- See findings reported by Francannet et al [2001].
- In a study of 172 individuals from 78 families, Porter et al [2004] identified more severe disease in individuals with mutations in *EXT1* than in *EXT2* on the basis of shortened stature, skeletal deformity (shortened forearm or bowing, knee deformity), and function (elbow, forearm, and knee range of motion). The risk of chondrosarcoma may also be higher in individuals with an *EXT1* mutation [Porter et al 2004].
- Persons with *EXT1* mutations were found to have a greater number of exostoses, a greater incidence of limb malalignment with shorter limb segments and height, and more frequent pelvic and flat bone involvement than those with *EXT2* mutations [Alvarez et al 2006].

Other studies note no difference in phenotype associated with mutations in *EXT1* versus *EXT2* [Jennes et al 2008].

Penetrance

The penetrance is estimated to be 96%. Most published instances of reduced penetrance have occurred in females. However, comprehensive skeletal radiographs have not been performed in most of these instances.

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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 and exostosin-2.

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].

Differential Diagnosis

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

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).

Three inherited conditions in which multiple osteochondromas occur:

- **Metachondromatosis** is inherited in an autosomal dominant manner. In contrast to HMO, metachondromatosis is characterized by both osteochondromas and intraosseous enchondromas. The osteochondromas of metachondromatosis occur predominantly in the digits and, unlike those of HMO, point toward the nearby joint and do not cause shortening or bowing of the long bone, joint deformity, or subluxation.
- **Langer-Giedion syndrome** (OMIM 150230) is a contiguous gene deletion syndrome involving *EXT1*. Affected individuals have mental retardation and characteristic craniofacial and digital anomalies. Skeletal abnormalities result from haploinsufficiency of *TRPS1*, the gene responsible for trichorhinophalangeal syndrome type I (TRSP1).
- **11p11 deletion syndrome** (formerly known as DEFECT 11 or Potocki-Shaffer syndrome) (OMIM 601224) [Wu et al 2000] is a contiguous gene deletion syndrome involving *EXT2* and *ALX4* (OMIM 168500). Deletion of *ALX4* results in parietal foramina and ossification defects of the skull (see Enlarged Parietal Foramina/ Cranium Bifidum). As-yet unidentified genes are responsible for the craniofacial abnormalities, syndactyly, and mental retardation seen in some cases [Mavrogiannis et al 2001, Romeike & Wuyts 2007].

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Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hereditary multiple osteochondromas (HMO), the following evaluations are recommended:

- Detailed history of symptoms from osteochondromas
- Physical examination to document location of osteochondromas, functional limitations, and deformity (shortness of stature, forearm bowing and shortening, knee and ankle angular deformities)

Treatment of Manifestations

Osteochondromas require no therapy in the absence of clinical problems.

Angular deformities, leg-length inequalities, and pain resulting from irritation of skin, tendons, or nerves often require surgery. Most individuals with HMO have at least one operative procedure and many have multiple procedures [Porter et al 2004]:

- Painful lesions without bony deformity can be treated with simple surgical excision. Excision of osteochondromas may also slow the growth disturbance and improve cosmesis and must include the cartilage cap and overlying perichondrium to avoid recurrence.
- Surgery for forearm deformity may involve excision of the osteochondromas, corrective osteotomies, and/or ulnar lengthening procedures that may improve pronation, supination, and forearm alignment [Matsubara et al 2006, Shin et al 2006, Ishikawa et al 2007, Watts et al 2007]; however, adults with HMO and untreated forearm deformities describe few functional limitations.
- Leg-length inequalities greater than 2.5 cm are often treated with epiphysiodesis (growth plate arrest) of the longer leg.
- Early surgical treatment of tibio talar tilt may prevent or decrease the incidence of late deterioration of ankle function, but long-term follow-up studies are needed [Noonan et al 2002].
- Surgical resection is the treatment for sarcomatous degeneration. Adjuvant radiotherapy and chemotherapy are controversial for secondary chondrosarcoma, but are often used in the setting of a secondary osteosarcoma.

Surveillance

Monitoring of the size of adult osteochondromas, in particular those involving the pelvis or scapula, may aid in early identification of malignant degeneration, but no cost/benefit analyses are available to support routine surveillance.

Radiography, CT scanning, MRI, positron emission tomography and technicium-99 radionuclide imaging can be used to evaluate centrally located osteochondromas, but it is not known whether the benefits outweigh the risks of irradiation and the potential for false positive results that lead to unnecessary interventions. In addition, optimal screening intervals have not been determined.

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Testing of Relatives at Risk

Presymptomatic 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

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

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% have a *de novo* mutation.
- Recommendations for the evaluation of parents of an individual with simplex HMO (i.e., a single occurrence in a family) include physical examination, radiographs, and/or molecular genetic testing if a mutation has been identified in the proband.

Note: Although 90% of individuals diagnosed with HMO have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members and/or decreased penetrance.

Sibs of a proband

- The risk to sibs depends on the genetic status of the parents.

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- Because most probands have a parent with the altered gene, the sibs of a proband with HMO usually have a 50% chance of inheriting the gene alteration; sibs who inherit the alteration have a 95% chance of manifesting symptoms.
- When the parents are clinically unaffected or the disease-causing mutation cannot be detected in the DNA of either parent, the risk to the sibs of a proband appears to be low. No instances of germline mosaicism have been reported, although it remains a possibility.

Offspring of a proband. The offspring have a 50% chance of inheriting the mutant allele.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is affected or has a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Consideration 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, parental mosaicism needs to be considered; possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly important when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

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 approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

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

Requests for prenatal testing for conditions that (like HMO) do not affect intellect or life span and for which some treatment exists are not common. Differences in perspective may exist among medical professionals and families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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Preimplantation genetic diagnosis (PGD) using embryonic cells is available to couples at 50% risk of having a child with HMO when the disease-causing mutation of *EXT1* or *EXT2* has been identified. Achievement of pregnancy is through assisted reproductive technology and requires coordination with specialists in fertility and endocrinology. For laboratories offering PGD, see Testing.

Molecular Genetics

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

Table A. Molecular Genetics of Hereditary Multiple Osteochondromas

Gene Symbol	Chromosomal Locus	Protein Name
EXT1	8q24.11-q24.13	Exostosin-1
EXT2	11p12-p11	Exostosin-2

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 Hereditary Multiple Osteochondromas

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

Table C. Genomic Databases for Hereditary Multiple Osteochondromas

Gene Symbol	Entrez Gene	HGMD
EXT1	2131 (MIM No. 133700)	EXT1
EXT2	2132 (MIM No. 133701)	EXT2

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Both *EXT* gene products (*EXT1*, *EXT2*) are involved in the biosynthesis of heparan sulfate. *EXT1* and *EXT2* encode glycosyltransferases that interact as heterooligomeric complexes [McCormick et al 2000]. Pathologic 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]. Some evidence suggests that *EXT1* and *EXT2* may have tumor suppressor activity [Hecht et al 1997].

A two-hit mutation model was proposed for *EXT1* and *EXT2* in the formation of osteochondromas, based on the observation of loss of heterozygosity in chondrosarcomas [Hecht et al 1997, Philippe et al 1997] and the identification of homozygous *EXT1* deletions in solitary osteochondromas [Hameetman et al 2007]. The failure to identify mutations in both alleles of *EXT1* and/or *EXT2* or loss of heterozygosity in osteochondromas of individuals with hereditary multiple osteochondromas (HMO) may argue against this model [Hall et al 2002]. However, it is possible that the second somatic mutation may arise in a related gene such as the *EXT*-like genes *EXTL1*, *EXTL2*, or *EXTL3*, or other genes involved in the signaling cascade of chondrocyte proliferation [Hall et al 2002]. Epigenetic loss of *EXT1* activity through

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hypermethylation has been observed in leukemias and other cancers, further supporting a tumor suppressor role for this gene product [Ropero et al 2004].

The *EXTL* family of genes, related to *EXT1* and *EXT2* by sequence homology, currently consists of three members (Table 2). To date, no disorder has been attributed to mutation in any of these genes.

Table 2. *EXTL* Gene Family Related Genes

Gene	Locus	Reference	Comment
EXTL1	1p36.1	Wise et al [1997]	Not associated with any disease
EXTL2	1p12-p11	Wuyts et al [1997]	LOH in osteochondromas [Bovée et al 1999]
EXTL3	8p21	Van Hul et al [1998]	Mutations found in colorectal tumors [Arai et al 1999]

More recent work suggests that not only do *EXT1* and *EXT2* code for transmembrane glycoproteins that together form a heterooligomeric heparan sulfate polymerase, but that the protein product participates in cell signaling and chondrocyte proliferation and differentiation [McCormick et al 2000, Senay et al 2000, Bernard et al 2001, Hall et al 2002]. Study of heparan sulfate proteoglycan synthesis in *Drosophila* suggests that a parallel signaling pathway may exist in humans [Bellaiche et al 1998].

Theories of osteochondroma pathogenesis are many. A routine aberrancy in the perichondrial groove of Ranvier [Porter & Simpson 1999] may be the functional change, which when coupled with haploinsufficiency of *EXT1* or *EXT2* proteins provides the double hit necessary for development of an osteochondroma [Hall et al 2002]. For individuals with HMO, the haploinsufficiency is caused by a mutation present in all chondrocytes; for those with isolated osteochondromas, the mutation may originate in a chondrocyte residing in the abnormal region of the groove of Ranvier. The abnormality in the groove of Ranvier may not be a chance occurrence, but rather a result of a nest of abnormally signaling chondrocytes. Loss of normal signal for chondrocyte proliferation may also contribute to inadequate formation of osteoblasts from stem cells, resulting in a focal defect in the local bone collar and thereby allowing protuberant growth of a pedunculated osteochondroma [Jones & Morcuende 2003]. The pathologic process that restricts the development of osteochondromas to the physeal margin is still not completely understood.

EXT1

Normal allelic variants. *EXT1* contains 11 exons spanning 250 kb.

Pathologic allelic variants. More than 100 different mutations have been described in *EXT1* [reviewed in Wells et al 1997; Wuyts & Van Hul 2000; Cheung et al 2001; Xiao et al 2001; Wuyts & Bale, personal communication]. These mutations are dispersed throughout the entire gene and most are predicted to result in premature termination of the gene product. Only a few of the mutations have been identified in more than one family. There are several relative hot spots for mutations. Exons 1 and 6 contain one and two polypyrimidine tracts, respectively, which are often sites of frameshift mutations. Missense mutations cluster in codons 339 and 340. Mutations in the carboxy-terminal region are relatively sparse. Whole-gene, partial-gene, and single-exon deletions have been described [White et al 2004; Wuyts 2007, personal communication].

Normal gene product. Exostosin-1 comprises 746 amino acids and is involved in heparan sulfate synthesis. It is a type II transmembrane glycoprotein that localizes to the endoplasmic reticulum [McCormick et al 2000]. Exostosin-1 and exostosin-2 form a heterooligomeric

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complex that accumulates in the Golgi apparatus and has substantially higher glycosyltransferase activity than exostosin-1 or exostosin-2 alone [McCormick et al 2000].

Abnormal gene product. Nonsense and splice-site mutations have also been observed. Most of the missense mutations detected occur in residues that are highly conserved evolutionarily and are thought to be crucial for the activity of the protein. The clinical significance of missense mutations affecting residues that are not as highly conserved is uncertain, as they may be rare normal variants.

EXT2

Normal allelic variants. *EXT2* contains 14 exons plus two alternative exons spanning 110 kb. Single-base polymorphisms that do not result in amino acid substitutions have been described and at least four nonsynonymous changes appear to be rare polymorphisms [Cheung et al 2001].

Pathologic allelic variants. More than 40 pathologic allelic variants have been found in *EXT2* [Wells et al 1997; Wuyts et al 1998; Wuyts & Van Hul 2000; Cheung et al 2001; Xiao et al 2001; Wuyts & Bale, personal communication]. The pathologic allelic variants are dispersed throughout *EXT2* and are of all types (missense, frameshift, in-frame deletion, nonsense, and splice site). Several missense mutations and in-frame deletions have been reported in *EXT2*. Some missense mutations occur in evolutionarily conserved residues, have been seen in more than one family with HMO, and are likely to be pathologic allelic variants. Very few pathologic allelic variants have been found in the carboxy-terminal region of the gene.

Normal gene product. The protein comprises 718 amino acids. Like exostosin-1, exostosin-2 is a type II transmembrane glycoprotein that localizes to the endoplasmic reticulum and is involved in heparan sulfate synthesis [McCormick et al 2000]. Exostosin-1 and exostosin-2 form a heterooligomeric complex that accumulates in the Golgi apparatus and has substantially higher glycosyltransferase activity than exostosin-1 or exostosin-2 alone [McCormick et al 2000].

Abnormal gene product. The frameshift, nonsense, and splice-site mutations are predicted to result in premature chain termination and loss of gene function.

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.

MHE and Me
14 Stony Brook Drive
Pine Island NY 10969
Phone: 845-258-6058
Email: mheandme@yahoo.com
www.mheandme.com

MHE Research Foundation
Phone: 877-486-1758

Email: sarahziegler@MHEResearchFoundation.org
www.MHEResearchfoundation.org

Musculoskeletal Imaging Teaching Files, Case 25
Radiographs typical of EXT
www.uhrad.com

The MHE Coalition
6783 York Road Apt 104
Parma Heights OH 44130-4596
Phone: 440-842-8817
Email: CheleZ1@aol.com
www.mhecoalition.org

References

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

Published Statements and Policies Regarding Genetic Testing

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

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Suggested Reading

Bovée JVMG (July 2008) Multiple osteochondromas (MO). Atlas of Genetics and Cytogenetics Oncology and Haematology. atlasgeneticsoncology.org.

Chapter Notes

Revision History

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