

## Hereditary multiple exostoses (HME)

### Identity

Other names  
EXT  
diaphyseal aclasis

**Inheritance** autosomal dominant disorder, genetically heterogeneous; males are more often affected, possibly partly due to an incomplete penetrance in females; approximately 62% of the patients have a positive family history

### Clinics

**Phenotype and clinics** presence of multiple osteochondromas (osteocartilaginous exostosis), bony protrusions covered by a cartilaginous cap on the outer surface of bone, resulting in a variety of orthopaedic deformities such as disproportionate short stature and bowing of the forearm;  
osteochondromas are the most common benign bone tumours, representing approximately 50% of all primary benign tumours of bone; they gradually develop and increase in size in the first decade of life; the stratified zones of chondrocytes that are normally found in the growth plate can still be recognised on the interface of cartilage and bone in osteochondroma; consequently, osteochondromas cease growing as the growth plates close during puberty;  
the majority of osteochondromas is asymptomatic and is located in bones that developed from cartilage, especially the long bones in the extremities

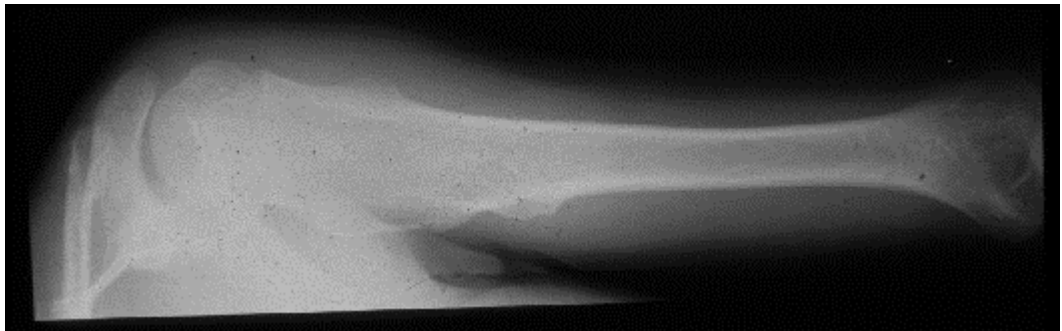


Figure 1: X-ray of the upper arm of a patient coming from a family with hereditary multiple exostoses (HME), demonstrating multiple osteochondromas (exostoses)

**Neoplastic risk** malignant transformation is low in solitary osteochondromas (<1%) but is estimated to occur in 1-3% of cases of hereditary multiple exostoses

**Treatment** osteochondromas can be surgically removed for cosmetic or functional

reasons

## Cytogenetics

Cytogenetics of cancer clonal karyotypic abnormalities in the cartilaginous cap of osteochondroma involving 8q22-24.1 were found in ten out of 30 sporadic and in 1 out of 13 hereditary osteochondromas, supporting a neoplastic origin; this was confirmed since aneuploidy was found in 4 out of 10 osteochondromas and LOH was almost exclusively found at the EXT1 locus in 5 out of 14 osteochondromas; no somatic EXT1 cDNA alterations were found in sporadic osteochondromas

## Genes involved and Proteins

Note HME is a genetically heterogeneous disorder for which at present, two genes, [EXT1](#) and [EXT2](#) located respectively on 8q24 and 11p11-p12, have been isolated; the EXT1 gene was reported to show linkage in 44%-66% of the HME families, whereas EXT2 would be involved in 27%; additional linkage to chromosome 19p has been found, suggesting the existence of an EXT3 -gene, although loss of heterozygosity studies could not confirm this;

two patients with multiple osteochondromas demonstrated a germline mutation in EXT1 combined with loss of the remaining wild type allele in three osteochondromas, confirming the tumour suppressor function of the EXT genes and indicating that in cartilaginous cells of the growth plate inactivation of both copies of the EXT1-gene is required for osteochondroma formation in hereditary cases

**Gene Name** [EXT1](#)

**Location** 8q24

### Protein

**Function** a tumour suppressor function is suggested for the EXT genes, which was confirmed by the combination of EXT1 germline mutations with loss of the remaining wildtype allele in osteochondroma;

Both EXT1 and EXT2 mRNA is ubiquitously expressed. A high level of expression of Ext1 and Ext2 mRNA has been found in developing limb buds of mouse embryos and expression was demonstrated to be confined to the proliferating and prehypertrophic chondrocytes of the growth plate. The gene products, exostosin-1 (EXT1) and exostosin-2 (EXT2), are endoplasmic reticulum localized type II transmembrane glycoproteins which form a Golgi-localized hetero-oligomeric complex that catalyzes heparan sulphate (HS) polymerization. Heparan sulphate proteoglycans (HSPG) are large macromolecules composed of heparan sulphate glycosaminoglycan chains linked to a protein core. Four HSPG families have been identified: syndecan, glypican, perlecan and isoforms of CD44. HSPGs are required for high-affinity binding of fibroblast growth factor to its receptor. Furthermore, an EXT1 homologue in Drosophila (tout-velu. Ttv) has been shown to be required

for diffusion of an important segment polarity protein called Hedgehog (Hh), a homologue of mammalian Indian Hedgehog (Ihh). It was therefore hypothesized that EXT mutations affect FGF and Ihh signalling within the normal growth plate. Indeed, diminished levels of the EXT1 and EXT2 protein and of their putative downstream effectors (Ihh/PTHrP and FGF signalling pathway) were demonstrated in both sporadic and hereditary osteochondroma chondrocytes. Moreover, EXT mutations were described to induce cytoskeletal abnormalities (altered actin distribution) in osteochondroma chondrocytes.

## Mutations

- Germinal** germline mutations of EXT1 and EXT2 in HME patients have been studied extensively in Caucasian as well as Asian populations
- Somatic** One sporadic osteochondroma was described to harbour a deletion of one EXT1 gene combined with an inactivating mutation in the other EXT1 gene. No somatic mutations were found in the EXT1 and EXT2 gene in 34 sporadic and hereditary osteochondromas and [chondrosarcomas](#) tested

## Gene Name

[EXT2](#)

Location 11p11-p12

## External links

[Orphanet](#) [Symphalangism brachydactyly craniosynostosis](#)

## Bibliography

### **Hereditary multiple exostoses; report of a family.**

Crandall BF, Field LL, Sparkes RS, Spence MA.  
Clin Orthop 1983; 190: 217-219.

### **Genetic heterogeneity in families with hereditary multiple exostoses.**

Cook A, Raskind W, Blanton SH, Pauli RM, Gregg RG, Francomano CA, Puffenberger E, Conrad EU, Schmale G, Schellenberg G, et al.  
Am J Hum Genet 1993; 53: 71-79.

### **A gene for hereditary multiple exostoses maps to chromosome 19p.**

Le Merrer M, Legeai-Mallet L, Jeannin PM, Horsthemke B, Schinzel A, Plauchu H, Toutain A, Achard F, Munnich A, Maroteaux P.  
Hum Mol Genet 1994; 3: 717-722.

### **Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (EXT1).**

Ahn J, Ludecke H, Lindow S, Horton WA, Lee B, Wagner MJ, Horsthemke B, Wells DE.  
Nature Gen 1995; 11: 137-143.

**Natural history study of hereditary multiple exostoses.**

Wicklund LC, Pauli RM, Johnston D, Hecht JT.  
Am J Med Genet 1995; 55: 43-46.

**The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes.**

Stickens D, Clines G, Burbee D, Ramos P, Thomas S, Hogue D, Hecht JT, Lovett M, Evans GA.  
Nature Genet 1996; 14: 25-32.

**Positional cloning of a gene involved in hereditary multiple exostoses.**

Wuyts W, Van Hul W, Wauters J, Nemtsova M, Reyniers E, Van Hul E, De Boulle K, De Vries BBA, Hendrickx J, Herrygers I, et al.  
Hum Mol Genet 1996; 5: 1547-1557.

**Hereditary multiple exostoses (EXT): mutational studies of familial EXT1 cases and EXT-associated malignancies**

Hecht JT, Hogue D, Wang Y, Blanton SH, Wagner M, Strong LC, Raskind W, Hansen MF, Wells D.  
Am J Hum Genet 1997; 60: 80-86.

**An extension of the admixture test for the study of genetic heterogeneity in hereditary multiple exostoses.**

Legeai-Mallet L, Margaritte-Jeannin P, Lemdani M, Le Merrer M, Plauchu H, Maroteaux P, Munnich A, Clerget-Darpoux F.  
Hum Genet 1997; 99: 298-302.

**Incomplete penetrance and expressivity skewing in hereditary multiple exostoses.**

Legeai-Mallet L, Munnich A, Maroteaux P, Le Merrer M.  
Clin Genet 1997; 52: 12-16.

**Mutation screening of the EXT1 and EXT2 genes in patients with hereditary multiple exostoses.**

Philippe C, Porter DE, Emerton ME, Wells DE, Simpson AHRW, Monaco AP.  
Am J Hum Genet 1997; 61: 520-528.

**Evaluation of locus heterogeneity and EXT1 mutations in 34 families with hereditary multiple exostoses.**

Raskind WH, Conrad EU, III, Matsushita M, Wijsman EM, Wells DE, Chapman N, Sandell LJ, Wagner M, Houck J.  
Hum Mutat 1998; 11: 231-239.

**Mutations in the EXT1 and EXT2 genes in hereditary multiple exostoses.**

Wuyts W, Van Hul W, De Boulle K, Hendrickx J, Bakker E, Vanhoenacker F, Mollica F, Ludecke H, Sitki Sayli B, Pazzaglia UE, et al.  
Am J Hum Genet 1998; 62: 346-354.

**EXT-mutation analysis and loss of heterozygosity in sporadic and hereditary osteochondromas and secondary chondrosarcomas.**

Bovee JVMG, Cleton-Jansen AM, Wuyts W, Caethoven G, Taminiau AHM, Bakker E, Van Hul W, Cornelisse CJ, Hogendoorn PCW.  
Am J Hum Genet 1999; 65: 689-698.

**Germline mutations in the EXT1 and EXT2 genes in Korean patients with hereditary multiple exostoses.**

Park KJ, Shin K, Ku J, Cho T, Lee SH, Choi IH, Phillipe C, Monaco AP, Porter DE, Park J  
J Hum Genet 1999; 44: 230-234.

**Mutation analysis of hereditary multiple exostoses in the Chinese.**

Xu L, Xia J, Jiang H, Zhou J, Li H, Wang D, Pan Q, Long Z, Fan C, Deng H.  
Hum Genet 1999; 105: 45-50.

**Cytoskeletal abnormalities in chondrocytes with EXT1 and EXT2 mutations.**

Bernard MA et al.  
J.Bone Miner.Res.2000; 15 (3): 442-450.

**Up-regulation of PTHrP and Bcl-2 expression characterizes the progression of osteochondroma towards peripheral chondrosarcoma and is a late event in central chondrosarcoma.**

Bovee JVMG et al.  
Lab.Invest.2000; 80: 1925-1933.

**EXT 1 gene mutation induces chondrocyte cytoskeletal abnormalities and defective collagen expression in the exostoses.**

Legeai-Mallet L et al.  
J.Bone Miner.Res.2000; 15 (8): 1489-1500.

**Clinical and radiographic analysis of osteochondromas and growth disturbance in hereditary multiple exostoses.**

Porter DE et al.  
J.Pediatr.Orthop.2000; 20 (2): 246-250.

**Diminished levels of the putative tumor suppressor proteins EXT1 and EXT2 in exostosis chondrocytes.**

Bernard MA et al.  
Cell Motil.Cytoskeleton 2001; 48 (2): 149-162.

[REVIEW articles](#)     *automatic search in PubMed*

[Last year publications](#)

automatic search in PubMed

**Contributor(s)**

<b>Written</b>	01-2000	Judith V.M.G. Bovee
<b>Updated</b>	03-2002	Judith V.M.G. Bovee

**Citation**

*This paper should be referenced as such :*

**Bovee JVMG** . Hereditary multiple exostoses (HME). Atlas Genet Cytogenet Oncol Haematol. January 2000 .

URL :

<http://www.infobiogen.fr/services/chromcancer/Tumors/HeredMultExostosID10061.html>

**Bovee JVMG** . Hereditary multiple exostoses (HME). Atlas Genet Cytogenet Oncol Haematol. March 2002 .

URL :

<http://www.infobiogen.fr/services/chromcancer/Tumors/HeredMultExostosID10061.html>

© Atlas of Genetics and Cytogenetics in Oncology and Haematology

---