

# Cancer Prone Disease Section

## Mini Review

## Hereditary multiple exostoses (HME)

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### Identity

**Alias:** 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 is asymptomatic and is located in bones that developed from cartilage, especially the long bones in the extremities.

#### *Neoplastic risk*

Malignant transformation is low in solitary osteochondromas (<1%) but is estimated to occur in 1-5% of cases of hereditary multiple exostoses.

#### *Treatment*

Osteochondromas can be surgically removed for cosmetic or functional reasons.

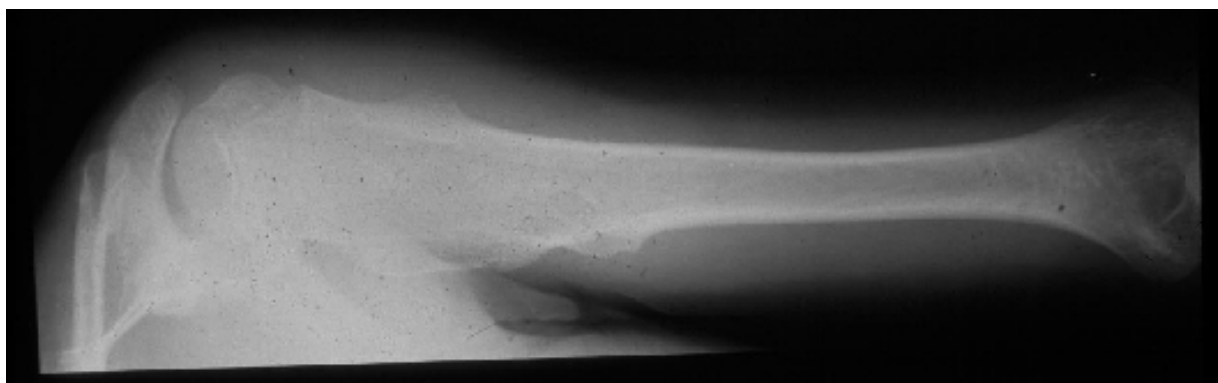


Figure 1: X-ray of the upper arm of a patient coming from a family with hereditary multiple exostoses (HME), demonstrating multiple osteochondromas (exostoses).

## 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

### EXT1 and EXT2

#### Location

8q24 and 11p11-p12.

#### 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.

#### 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; the EXT gene products were shown to be involved in heparan sulphate biosynthesis.

#### Mutations

Germline: Germline mutations of EXT1 and EXT2 in HME patients have been studied extensively in Caucasian as well as Asian populations.

Somatic: No somatic mutations were found in the EXT1 and EXT2 gene in 34 sporadic and hereditary osteochondromas and chondrosarcomas tested.

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