Hereditary multiple exostoses (HME)
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Identity
Alias: 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.

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.

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**

Location: 8q24

**EXT2**

Location: 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. 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 (toll-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.

**References**


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