Multiple osteochondromas (MO)

Christianne MA Reijnders, Judith VMG Bovée

Dept of Pathology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands (CMAR, JVMGB)

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Identity

Alias
Hereditary multiple exostosis (HME)
Multiple hereditary exostoses (MHE)
Diaphyseal aclasis
Multiple hereditary osteochondromatosis
Multiple cartilaginous exostoses

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
MO is characterized by the presence of multiple osteochondromas (osteocartilaginous exostosis), i.e. bony protrusions covered by a cartilaginous cap on the outer surface of bone. This results 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. Patients with a 1 mutation have a more severe phenotype than patients with an 2 mutation.

Neoplastic risk
Malignant transformation is low in solitary osteochondromas (<1%) but is estimated to occur in 0.5-5% of cases of multiple osteochondromas (MO).

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 multiple 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 1 locus in 5 out of 14 osteochondromas. Aberrations of chromosome 1p (1p13-p22) were found in five of seven osteochondromas.

Genes involved and proteins

Note
MO is a genetically heterogeneous disorder for which at present, two genes, 1 and 2 located respectively on 8q24 and 11p11-p12, have been isolated. The EXT1 gene was reported to show linkage in 44%-66% of the MO families, whereas EXT2 would be involved in 27%. Additional linkage to chromosome 19p has been found, suggesting the existence of an 3 -gene, although loss of heterozygosity studies could not confirm this and the
gene has not been identified so far. Two patients with MO demonstrated a germline mutation in 1 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. Homozygous deletions of EXT1 identified in seven out of eight non-hereditary osteochondromas further support the two hit model. However, loss of the remaining wildtype allele can be demonstrated in only a subset of osteochondromas in MO patients.

**EXT1 (exostosin-1)**

**Location**

8q24

**DNA/RNA**

Description: The 1 gene is composed of 11 exons, and the 2 gene consists of 16 exons.

**Protein**

Expression: Both 1 and 2 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.

Function: A tumour suppressor function is suggested for the genes. The gene products, exostosin-1 (1) 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 are syndecan, glypican, perlecan and isoforms of CD44. HSPGs are required for high-affinity binding of fibroblast growth factor to its receptor. Furthermore, studies in Drosophila have shown that EXT (tout-velu, Ttv) is required for the diffusion of the morphogens: Hedgehog (Hh, human homologues Indian Hedgehog (IHh) and Sonic Hedgehog (SHh), decapentaplegic (dpp, human homologues TGF-beta and BMP) and wingless (human homologue Wnt). It was therefore hypothesized that EXT mutations affect IHh / PTHLH, TGF-beta/BMP and Wnt signaling pathways within the normal growth plate. Indeed, altered levels of the EXT1 and EXT2 protein and of their putative downstream effectors (IHh/PTHrP, TGF-beta/BMP and Wnt signalling pathways) were demonstrated in both sporadic and hereditary osteochondroma. In addition, due to impaired EXT1/EXT2 function the HSPGs appear to be retained in the Golgi apparatus and cytoplasm of the tumour cell, instead of being transported to the cell surface and/or extra cellular matrix where they normally exert their function. Moreover, EXT mutations were described to induce cytoskeletal abnormalities (altered actin distribution) in osteochondroma chondrocytes.

**Mutations**

Germinal: Germline mutations of 1 and 2 in MO patients have been studied extensively in Caucasian as well as Asian populations.

Somatic: One sporadic osteochondroma was described to harbour a deletion of one 1 gene combined with an inactivating mutation in the other 1 gene. No somatic mutations were found in the EXT1 and EXT2 gene in 34 sporadic and hereditary osteochondromas and secondary peripheral chondrosarcomas tested.

**EXT2 (exostosin-2)**

**Location**

11p11-p12

**References**


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Reijnders CMA, Bovée JVMG
Bovée JV, van den Broek LJ, Cleton-Jansen AM, Hogendoorn PC, Bovée JV. Decreased Indian Hedgehog signalling. J Pathol. 2007 Mar;211(4):399-409
Bovée JV, Multiple osteochondromas. Orphanet J Rare Dis. 2008 Feb 13:3-3

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