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Cancer Prone Disease Section

Mini Review

Multiple osteochondromas (MO)

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Identity

Alias

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

Crandall BF, Field LL, Sparkes RS, Spence MA. Hereditary multiple exostoses. Report of a family. Clin Orthop Relat Res. 1984 Nov;(190):217-9

Cook A, Raskind W, Blanton SH, Pauli RM, Gregg RG, Francomano CA, Puffenberger E, Conrad EU, Schmale G, Schellenberg G. Genetic heterogeneity in families with hereditary multiple exostoses. Am J Hum Genet. 1993 Jul;53(1):71-9

Le Merrer M, Legeai-Mallet L, Jeannin PM, Horsthemke B, Schinzel A, Plauchu H, Toutain A, Achard F, Munnich A, Maroteaux P. A gene for hereditary multiple exostoses maps to chromosome 19p. Hum Mol Genet. 1994 May;3(5):717-22

Ahn J, Lüdecke HJ, Lindow S, Horton WA, Lee B, Wagner MJ, Horsthemke B, Wells DE. Cloning of the putative tumour suppressor gene for hereditary multiple exostoses (EXT1). Nat Genet. 1995 Oct;11(2):137-43

Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. Am J Med Genet. 1995 Jan 2;55(1):43-6

Stickens D, Clines G, Burbee D, Ramos P, Thomas S, Hogue D, Hecht JT, Lovett M, Evans GA. The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes. Nat Genet. 1996 Sep;14(1):25-32

Wuyts W, Van Hul W, Wauters J, Nemtsova M, Reyniers E, Van Hul EV, De Boulle K, de Vries BB, Hendrickx J, Herrygers I, Bossuyt P, Balemans W, Fransen E, Vits L, Coucke P, Nowak NJ, Shows TB, Mallet L, van den Ouweland AM, McGaughran J, Halley DJ, Willems PJ. Positional cloning of a gene involved in hereditary multiple exostoses. Hum Mol Genet. 1996 Oct;5(10):1547-57

Hecht JT, Hogue D, Wang Y, Blanton SH, Wagner M, Strong LC, Raskind W, Hansen MF, Wells D. Hereditary multiple exostoses (EXT): mutational studies of familial EXT1 cases and EXT-associated malignancies. Am J Hum Genet. 1997 Jan;60(1):80-6

Legeai-Mallet L, Margaritte-Jeannin P, Lemdani M, Le Merrer M, Plauchu H, Maroteaux P, Munnich A, Clerget-Darpoux F. An extension of the admixture test for the study of genetic heterogeneity in hereditary multiple exostoses. Hum Genet. 1997 Mar;99(3):298-302

Legeai-Mallet L, Munnich A, Maroteaux P, Le Merrer M. Incomplete penetrance and expressivity skewing in hereditary multiple exostoses. Clin Genet. 1997 Jul;52(1):12-6

Philippe C, Porter DE, Emerton ME, Wells DE, Simpson AH, Monaco AP. Mutation screening of the EXT1 and EXT2 genes in patients with hereditary multiple exostoses. Am J Hum Genet. 1997 Sep;61(3):520-8

Bellaiche Y, The I, Perrimon N. Tout-velu is a Drosophila homologue of the putative tumour suppressor EXT-1 and is needed for Hh diffusion. Nature. 1998 Jul 2;394(6688):85-8

Raskind WH, Conrad EU 3rd, Matsushita M, Wijsman EM, Wells DE, Chapman N, Sandell LJ, Wagner M, Houck J. Evaluation of locus heterogeneity and EXT1 mutations in 34 families with hereditary multiple exostoses. Hum Mutat. 1998;11(3):231-9

Wuyts W, Van Hul W, De Boulle K, Hendrickx J, Bakker E, Vanhoenacker F, Mollica F, Lüdecke HJ, Sayli BS, Pazzaglia UE, Mortier G, Hamel B, Conrad EU, Matsushita M, Raskind WH, Willems PJ. Mutations in the EXT1 and EXT2 genes in hereditary multiple exostoses. Am J Hum Genet. 1998 Feb;62(2):346-54

Bovée JV, Cleton-Jansen AM, Wuyts W, Caethoven G, Taminiau AH, Bakker E, Van Hul W, Cornelisse CJ, Hogendoorn PC. EXT-mutation analysis and loss of heterozygosity in sporadic and hereditary osteochondromas and secondary chondrosarcomas. Am J Hum Genet. 1999 Sep;65(3):689-98

Park KJ, Shin KH, Ku JL, Cho TJ, Lee SH, Choi IH, Phillipe C, Monaco AP, Porter DE, Park JG. Germline mutations in the EXT1 and EXT2 genes in Korean patients with hereditary multiple exostoses. J Hum Genet. 1999;44(4):230-4

Xu L, Xia J, Jiang H, Zhou J, Li H, Wang D, Pan Q, Long Z, Fan C, Deng HX. Mutation analysis of hereditary multiple exostoses in the Chinese. Hum Genet. 1999 Jul-Aug;105(1-2):45-50

Bernard MA, Hogue DA, Cole WG, Sanford T, Snuggs MB, Montufar-Solis D, Duke PJ, Carson DD, Scott A, Van Winkle WB, Hecht JT. Cytoskeletal abnormalities in chondrocytes with EXT1 and EXT2 mutations. J Bone Miner Res. 2000 Mar;15(3):442-50

Bovée JV, van den Broek LJ, Cleton-Jansen AM, Hogendoorn PC. Up-regulation of PTHrP and Bcl-2 expression characterizes the progression of osteochondroma towards peripheral chondrosarcoma and is a late event in central chondrosarcoma. Lab Invest. 2000 Dec;80(12):1925-34

Legeai-Mallet L, Rossi A, Benoist-Lasselin C, Piazza R,

Mallet JF, Delezoide AL, Munnich A, Bonaventure J, Zylberberg L. EXT 1 gene mutation induces chondrocyte cytoskeletal abnormalities and defective collagen expression in the exostoses. J Bone Miner Res. 2000 Aug;15(8):1489-500

Porter DE, Emerton ME, Villanueva-Lopez F, Simpson AH. Clinical and radiographic analysis of osteochondromas and growth disturbance in hereditary multiple exostoses. J Pediatr Orthop. 2000 Mar-Apr;20(2):246-50

Bernard MA, Hall CE, Hogue DA, Cole WG, Scott A, Snuggs MB, Clines GA, Lüdecke HJ, Lovett M, Van Winkle WB, Hecht JT. Diminished levels of the putative tumor suppressor proteins EXT1 and EXT2 in exostosis chondrocytes. Cell Motil Cytoskeleton. 2001 Feb;48(2):149-62

Bovée JV, Hogendoorn PC.. Multiple osteochondromas. In: World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone, Editors: Fletcher CD, Unni KK, Mertens F, IARC Press, Lyon, 2002, 360-362.

Feely MG, Boehm AK, Bridge RS, Krallman PA, Neff JR, Nelson M, Bridge JA. Cytogenetic and molecular cytogenetic evidence of recurrent 8q24.1 loss in osteochondroma. Cancer Genet Cytogenet. 2002 Sep;137(2):102-7

Hall CR, Cole WG, Haynes R, Hecht JT. Reevaluation of a genetic model for the development of exostosis in hereditary multiple exostosis. Am J Med Genet. 2002 Sep 15;112(1):1-5

Khurana J, Mertens F, Bovée JV.. Osteochondroma. In: World Health Organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone, Editors: Fletcher CD, Unni KK, Mertens F, IARC Press, Lyon, 2002, 234-236.

Sawyer JR, Thomas EL, Lukacs JL, Swanson CM, Ding Y, Parham DM, Thomas JR, Nicholas RW. Recurring breakpoints of 1p13 approximately p22 in osteochondroma. Cancer Genet Cytogenet. 2002 Oct 15;138(2):102-6

Bornemann DJ, Duncan JE, Staatz W, Selleck S, Warrior R. Abrogation of heparan sulfate synthesis in Drosophila disrupts the Wingless, Hedgehog and Decapentaplegic signaling pathways. Development. 2004 May;131(9):1927-38

Hameetman L, Bovée JV, Taminiau AH, Kroon, HM, Hogendoorn PC.. Multiple osteochondromas: clinicopathological and genetic spectrum and suggestions for clinical management. Hereditary Cancer in Clinical Practice (2004); 2 (4) 161-173.

Han C, Belenkaya TY, Khodoun M, Tauchi M, Lin X, Lin X. Distinct and collaborative roles of Drosophila EXT family proteins in morphogen signalling and gradient formation. Development. 2004 Apr;131(7):1563-75

Porter DE, Lonie L, Fraser M, Dobson-Stone C, Porter JR, Monaco AP, Simpson AH. Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype study. J Bone Joint Surg Br. 2004 Sep;86(7):1041-6

Alvarez C, Tredwell S, De Vera M, Hayden M. The genotype-phenotype correlation of hereditary multiple exostoses. Clin Genet. 2006 Aug;70(2):122-30

Hameetman L, Rozeman LB, Lombaerts M, Oosting J, Taminiau AH, Cleton-Jansen AM, Bovée JV, Hogendoorn PC. Peripheral chondrosarcoma progression is accompanied by decreased Indian Hedgehog signalling. J Pathol. 2006 Aug;209(4):501-11

Alvarez CM, De Vera MA, Heslip TR, Casey B. Evaluation of the anatomic burden of patients with hereditary multiple exostoses. Clin Orthop Relat Res. 2007 Sep;462:73-9

Hameetman L, David G, Yavas A, White SJ, Taminiau AH, Cleton-Jansen AM, Hogendoorn PC, Bovée JV. Decreased EXT expression and intracellular accumulation of heparan sulphate proteoglycan in osteochondromas and peripheral chondrosarcomas. J Pathol. 2007 Mar;211(4):399-409

Hameetman L, Szuhai K, Yavas A, Knijnenburg J, van Duin M, van Dekken H, Taminiau AH, Cleton-Jansen AM, Bovée JV, Hogendoorn PC. The role of EXT1 in nonhereditary osteochondroma: identification of homozygous deletions. J Natl Cancer Inst. 2007 Mar 7;99(5):396-406

Jäger M, Westhoff B, Portier S, Leube B, Hardt K, Royer-Pokora B, Gossheger G, Krauspe R. Clinical outcome and genotype in patients with hereditary multiple exostoses. J Orthop Res. 2007 Dec;25(12):1541-51

Bovée JV. Multiple osteochondromas. Orphanet J Rare Dis. 2008 Feb 13;3:3

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