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Gene Section
Mini Review

EXT1 (exostoses (multiple) 1)

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Identity

HGNC (Hugo): EXT1

Location: 8q24.11-q24.13

Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

11 exons, spans approximately 350 kb of genomic DNA.

Transcription

3.4 kb.

Protein

Description

746 amino acids, 86.304 kDa.

Expression

mRNA is ubiquitously expressed (also in chondrocytes), highest level of expression in liver.

Localisation

Endoplasmic reticulum.

Function

A tumour suppressor function is suggested; EXT1 is an endoplasmic reticulum (ER) resident type II transmembrane glycoprotein whose expression in cells alters the synthesis and display of cell surface heparan sulfate, and EXT1 was suggested to be involved in chain polymerization of heparan sulphate; an EXT1 homologue in Drosophila melanogaster (tout-velu, Ttv) was demonstrated to be involved in heparan sulphate proteoglycan biosynthesis controlling diffusion of an important segment polarity protein called Hedgehog (Hh).

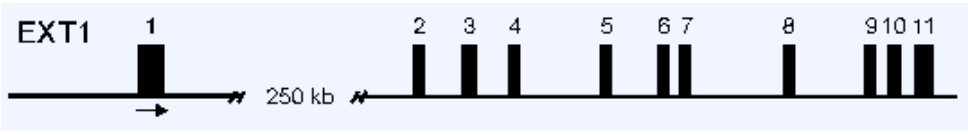
Homology

Human EXT2, EXTL1, EXTL2 and EXTL3, mouse Ext1, Drosophila tout velu.

Mutations

Germinal

Germline mutations in EXT1 are causative for hereditary multiple exostoses, a genetically heterogeneous autosomal dominant disorder; mutations include nucleotide substitutions (54%), small deletions (27%) and small insertions (16%), of which the majority is predicted to result in a truncated or non-functional protein.



Somatic

No somatic mutations were found in 34 sporadic and hereditary osteochondromas and secondary peripheral chondrosarcomas tested.

Implicated in

Hereditary multiple exostoses

Prognosis

The main complication in hereditary multiple exostoses is malignant transformation of an osteochondroma (exostosis) into chondrosarcoma, which is estimated to occur in 1-5% of the HME cases.

Cytogenetics

Clonal aberrations were found at band 8q24.1 in sporadic and hereditary osteochondromas using cytogenetic analysis; loss of heterozygosity was almost exclusively found at the EXT1 locus in 5 out of 14 osteochondromas.

Oncogenesis

Two patients with multiple osteochondromas demonstrated a germline mutation combined with loss of the remaining wild type allele in three osteochondromas, supporting the Knudson's two hit model for tumour suppressor genes in osteochondroma development; these results indicate that in cartilaginous cells of the growth plate inactivation of both copies of the EXT1-gene is required for osteochondroma formation in hereditary cases.

References

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

Mertens F, Rydholm A, Kreicbergs A, Willén H, Jonsson K, Heim S, Mitelman F, Mandahl N. Loss of chromosome band 8q24 in sporadic osteocartilaginous exostoses. Genes Chromosomes Cancer. 1994 Jan;9(1):8-12

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

Hecht JT, Hogue D, Strong LC, Hansen MF, Blanton SH, Wagner M. Hereditary multiple exostosis and chondrosarcoma: linkage to chromosome II and loss of heterozygosity for EXT-linked markers on chromosomes II and 8. Am J Hum Genet. 1995 May;56(5):1125-31

Raskind WH, Conrad EU, Chansky H, Matsushita M. Loss of heterozygosity in chondrosarcomas for markers linked to hereditary multiple exostoses loci on chromosomes 8 and 11. Am J Hum Genet. 1995 May;56(5):1132-9

Lin X, Wells D. Isolation of the mouse cDNA homologous to the human EXT1 gene responsible for Hereditary Multiple Exostoses. DNA Seq. 1997;7(3-4):199-202

Lohmann DR, Buiting K, Lüdecke HJ, Horsthemke B. The murine Ext1 gene shows a high level of sequence similarity with its human homologue and is part of a conserved linkage group on chromosome 15. Cytogenet Cell Genet. 1997;76(3-4):164-6

Lüdecke HJ, Ahn J, Lin X, Hill A, Wagner MJ, Schomburg L, Horsthemke B, Wells DE. Genomic organization and promoter structure of the human EXT1 gene. Genomics. 1997 Mar 1;40(2):351-4

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

Bridge JA, Nelson M, Orndal C, Bhatia P, Neff JR. Clonal karyotypic abnormalities of the hereditary multiple exostoses chromosomal loci 8q24.1 (EXT1) and 11p11-12 (EXT2) in patients with sporadic and hereditary osteochondromas. Cancer. 1998 May 1;82(9):1657-63

Lin X, Gan L, Klein WH, Wells D. Expression and functional analysis of mouse EXT1, a homolog of the human multiple exostoses type 1 gene. Biochem Biophys Res Commun. 1998 Jul 30;248(3):738-43

Lind T, Tufaro F, McCormick C, Lindahl U, Lidholt K. The putative tumor suppressors EXT1 and EXT2 are glycosyltransferases required for the biosynthesis of heparan sulfate. J Biol Chem. 1998 Oct 9;273(41):26265-8

McCormick C, Leduc Y, Martindale D, Mattison K, Esford LE, Dyer AP, Tufaro F. The putative tumour suppressor EXT1 alters the expression of cell-surface heparan sulfate. Nat Genet. 1998 Jun;19(2):158-61

Bovée JV, Cleton-Jansen AM, Kuipers-Dijkshoorn NJ, van den Broek LJ, Taminiau AH, Cornelisse CJ, Hogendoorn PC. Loss of heterozygosity and DNA ploidy point to a diverging genetic mechanism in the origin of peripheral and central chondrosarcoma. Genes Chromosomes Cancer. 1999 Nov;26(3):237-46

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

Kitagawa H, Shimakawa H, Sugahara K. The tumor suppressor EXT-like gene EXTL2 encodes an alpha1, 4-N-acetylhexosaminyltransferase that transfers N-acetylgalactosamine and N-acetylglucosamine to the common glycosaminoglycan-protein linkage region. The key enzyme for the chain initiation of heparan sulfate. J Biol Chem. 1999 May 14;274(20):13933-7

McCormick C, Duncan G, Tufaro F. New perspectives on the molecular basis of hereditary bone tumours. Mol Med Today. 1999 Nov;5(11):481-6

Simmons AD, Musy MM, Lopes CS, Hwang LY, Yang YP, Lovett M. A direct interaction between EXT proteins and glycosyltransferases is defective in hereditary multiple exostoses. Hum Mol Genet. 1999 Nov;8(12):2155-64

The I, Bellaiche Y, Perrimon N. Hedgehog movement is regulated through tout velu-dependent synthesis of a heparan sulfate proteoglycan. Mol Cell. 1999 Oct;4(4):633-9

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