Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

EXT2 (exostoses (multiple) 2)

Judith VMG Bovée

Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands (JVMGB)

Published in Atlas Database: March 2002

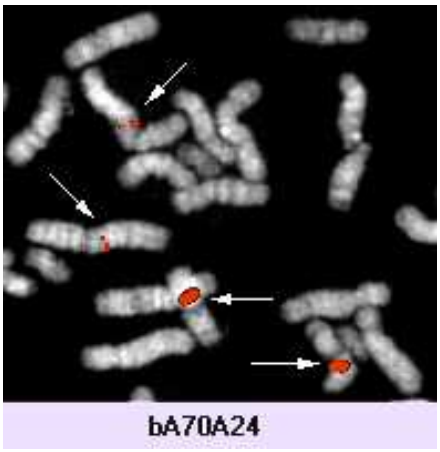
Online updated version : http://AtlasGeneticsOncology.org/Genes/EXT2ID213.html
DOI: 10.4267/2042/37861

This article is an update of: Bovée JVMG. EXT2. Atlas Genet Cytogenet Oncol Haematol.2000;4(1):5-6.

Identity

HGNC (Hugo): EXT2

Location: 11p11-p12



EXT2 (11p12) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

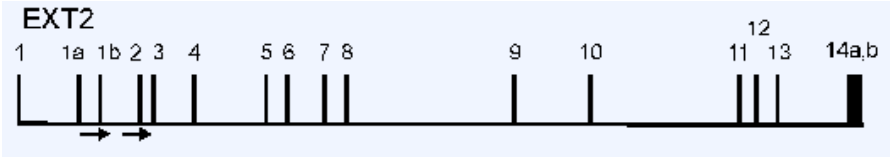
DNA/RNA

Description

Sixteen exons across the EXT2 locus were identified, two of which (1a and 1b) are alternatively spliced; spans approximately 108 kb of genomic DNA.

Transcription

3.5 and 3.7 kb.



Protein

Description

718 amino acids; 82.2 kDa.

Expression

mRNA is ubiquitously expressed. In mouse embryo's, a high level of expression of Ext2 mRNA has been found in developing limb buds and expression was demonstrated to be confined to the proliferating and prehypertrophic chondrocytes of the growth plate.

Localisation

Endoplasmic reticulum.

Function

A tumour suppressor function is suggested; exostosin-2 (EXT2) is an endoplasmic reticulum localized type II transmembrane glycoprotein which together with exostosin-1 (EXT1) forms a Golgi-localized hetero-oligomeric complex that catalyzes heparan sulphate (HS) polymerization.

It is thus hypothesized that EXT controls HSPG synthesis and display at the cell surface, which in turn is involved in FGF and IHh/PTHrP signalling within the normal growth plate.

Homology

Human EXT1, EXTL1, EXTL2 and EXTL3, mouse Ext2.

Mutations

Germinal

Germline mutations in EXT2 are causative for hereditary multiple exostoses, a heterogeneous autosomal dominant disorder; mutations include nucleotide substitutions (57%), small deletions (19%) and small insertions (24%), 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 1-3% of the HME cases.

Cytogenetics

11p rearrangement was found in 1 sporadic osteochondroma (exostosis) using cytogenetic analysis; loss of heterozygosity at the EXT2 locus was absent in 14 osteochondromas.

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

Wu YQ, Heutink P, de Vries BB, Sandkuijl LA, van den Ouweland AM, Niermeijer MF, Galjaard H, Reyniers E, Willems PJ, Halley DJ. Assignment of a second locus for multiple exostoses to the pericentromeric region of chromosome 11. Hum Mol Genet. 1994 Jan;3(1):167-71

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

Wuyts W, Ramlakhan S, Van Hul W, Hecht JT, van den Ouweland AM, Raskind WH, Hofstede FC, Reyniers E, Wells DE, de Vries B. Refinement of the multiple exostoses locus (EXT2) to a 3-cM interval on chromosome 11. Am J Hum Genet. 1995 Aug;57(2):382-7

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

Clines GA, Ashley JA, Shah S, Lovett M. The structure of the human multiple exostoses 2 gene and characterization of homologs in mouse and Caenorhabditis elegans. Genome Res. 1997 Apr;7(4):359-67

Stickens D, Evans GA. Isolation and characterization of the murine homolog of the human EXT2 multiple exostoses gene. Biochem Mol Med. 1997 Jun;61(1):16-21

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

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

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

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

Stickens D, Brown D, Evans GA. EXT genes are differentially expressed in bone and cartilage during mouse embryogenesis. Dev Dyn. 2000 Jul;218(3):452-64

Wuyts W, Van Hul W. Molecular basis of multiple exostoses: mutations in the EXT1 and EXT2 genes. Hum Mutat. 2000;15(3):220-7

This article should be referenced as such:

Bovée JVMG. EXT2 (exostoses (multiple) 2). Atlas Genet Cytogenet Oncol Haematol. 2002; 6(3):185-186.