

Gene Section

Mini Review

EXT1 (exostoses (multiple) 1)

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Identity

Location : 8q24.11

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.

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