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Gene Section
Mini Review

PTCH2 (patched homolog 2 (Drosophila))

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Identity

Hugo: PTCH2
Other names: PTC2; Patched 2; Patched homolog 2
Location: 1p34.1
Local order: Tel- PLK3 -LOC343521-LOC149478-PTCH2-EIF2B3-LOC728887-LOC128192 -Cen

DNA/RNA

Description

23 exons, approximately 20 kb of genomic sequence. The last exon is exon 22 due to the presence of exons 12A and 12B.

Transcription

Altrenative splice variants, skipping of exons 9 and 10 - maintenance of reading frame, skipping of exon 9 - maintenance of reading frame, skipping of exon 21- change of reading frame. Alternative 3' end - termination within intron 21.

Protein

Description

Putative 12 transmembrane protein, similar to PTCH1. Receptor of Hedgehog ligands but can not transduce signal activity as PTCH1 does.

Expression

Mainly testis and skin, generally weaker than PTCH1, gene expression dependent on Hedgehog signaling activation, as in PTCH1. However, in PTCH1 the up-regulation of gene expression due to signaling activation results in a negative feedback loop due to inhibition of the activity of the transmenbrane protein, Smoothened, but this does not appear to be the case for PTCH2.

Localisation

Cellular membranes.

Function

Receptor of Hedgehog ligands but lacks the strong capacity of PTCH1 to inhibit the signaling molecule Smoothened, which, through a series of intracellular events, activates the GLI family of transcription factors. Thus, while PTCH1 regulates Smoothened activity depending on Hedgehog ligand binding, PTCH2 is not. This is despite the fact that the three mammalian Hedgehog ligands Sonic, Desert and Indian Hedgehog have similar affinity for both PTCH1 and PTCH2. The expression of the PTCH2 receptor and the Desert Hedgehog ligand in the testis, as well as the requirement of Desert Hedgehog in testicular development has led to the proposal that PTCH2 may mediate the Desert Hedgehog effects in that tissue and could act as a tumor suppressor in germ cell tumors, as these are frequently deleted in 1p33-34. However, no PTCH2 mutations have been identified in such tumors and knock-out mouse models of PTCH2 have not revealed any testicular phenotype.

Homology

Homolog to PTCH1. Mouse, Chicken and Zebrafish have both PTCH homologs but Drosophila only one.

Mutations

Germinal

None described

Somatic

Only two cases reported:
- Medulloblastomas, 2 bp deletion in exon 8 - germline DNA not checked.
- Basal Cell Carcinoma, nucleotide change in intron 20, five bases from 5' splice junction.

Implicated in

Various cancers

Note: There are no genetic diseases or tumors where the role of PTCH2 has been clearly demonstrated by the unambiguous detection of PTCH2 mutations that disrupt the protein function.

The various suggestions of a possible role of PTCH2 in tumor development are generally circumstantial and are mostly based on chromosomal deletions that encompass the PTCH2 genomic region. The strongest evidence that PTCH2 hay have a role in tumor development comes from knock-out mouse model systems. Thus while Ptch2(-/-) mice have no obvious phenotype and do not develop tumors, if they are crossed with Ptch1 (+/-) heterozygotes, then the resulting Ptch2(-/-)Ptch1(+/-) mice developed at a higher incidence typical Ptch1(+/-) tumors such as medulloblastomas and rhabdomyosarcomas, suggesting genetic interactions between Ptch2 and Ptch1.

A possible role of PTCH2 in testicular development, acting as a Desert Hedgehog receptor has been suggested.

Overexpression of PTCH2 in basal cell carcinomas cannot compensate for mutated PTCH1 implying distinct roles of the two homologs. This can be rationalized by the very weak capacity of PTCH2 relative to PTCH1 in inhibiting the signaling molecule Smoothened. Additionally, based mostly on chromosomal deletion in the 1p32-34 region where the PTCH2 gene resides, a role in neurofibromas, pituitary tumors, medulloblastomas and meningiomas has been proposed. Also, PTCH2 is implicated in thymus, dental, prostate, ovary, and bone tissue development, as PTCH2 expression has been detected in these tissues.

In a mouse model, deletions of exons 5 to 17 in both Ptch2 alleles did not result in any obvious phenotype. However in the context of Ptch1+/- mice, this deletion of Ptch2 resulted in higher incidence and broader spectrum of tumor formation. In another mouse model of Ptch2, with a targeted insertion in exon 6 that would results in premature termination, the resulting homozygous mice were characterized with alopecia and epidermal hyperplasia.

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