

Gene Section

Mini Review

FAM123B (family with sequence similarity 123B)

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Identity

Other names: WTX (Wilms Tumor on the X chromosome); AMER1 (APC Membrane Recruitment 1); FLJ39827; RP11-403E24.2

HGNC (Hugo): FAM123B

Location: Xq11.1

Local order: Cen-ARHGEF9-WTX-ASB12-Ter.

DNA/RNA

Description

2 or 3 exons spanning 18-21kb genomic DNA.

Transcription

FAM123B is predicted to generate an mRNA of 8.4kb. The WTX/FAM123B gene is transcribed as a 7.5kb mRNA; an alternatively spliced transcript 831nt shorter has been observed in human primary cell lines, generated by use of a splice donor and splice acceptor site both located within exon 2. Exon 1 is noncoding. The entire ORF of the 7.5kb mRNA is contained within a single exon.

Pseudogene

No known pseudogenes.

Protein

Description

Two isoforms (858-1135aa) due to alternative splicing. The 858aa WTX isoform 2 lacks amino acids 50-326 of the larger isoform.

Expression

Ubiquitous.

Localisation

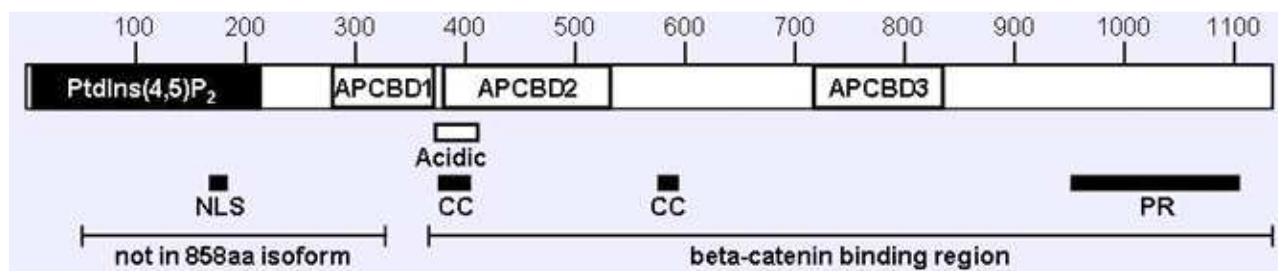
Plasma membrane (1135aa isoform), nucleus (858aa isoform).

Function

The N-terminus of the WTX protein has a predicted nuclear localization signal (NLS; residues 166-182), and 2 phosphatidylinositol(4,5)-biphosphate-binding domains (PtdIns(4,5)P₂; residues 2-142 and 143-209) that are involved in its localization to the plasma membrane. The WTX protein also has 3 adenomatous polyposis coli (APC) binding domains (APCBD1, residues 280-368; APCBD2, 380-531; and APCBD3, 717-834) that mediate its interaction with the armadillo (ARM) repeats of the tumor suppressor APC, as well as a beta-catenin binding site (located between residue 367 and the C-terminus), an acidic domain (residues 370-411), two coiled-coil domains (residues 374-403 and 574-593) and a proline-rich region (residues 951-1104).

The 858aa isoform is missing both PtdIns(4,5)P₂ binding domains and localizes to the nucleus in a punctate pattern. Interestingly, this shorter isoform lacks the predicted NLS, and the longer isoform that includes the predicted NLS localizes to the plasma membrane.

WTX forms a protein complex with beta-catenin, AXIN1, beta-transducin repeat-containing protein 2 (beta-TrCP2) and APC and negatively regulates the WNT signaling pathway by promoting the ubiquitination and degradation of beta-catenin.



The 1135 amino acid WTX protein. Black box, the two phosphatidylinositol(4,5)-biphosphate-binding domains (PtdIns(4,5)P₂). Open boxes, the three APC binding domains (APCBD1, APCBD2, APCBD3). Acidic, the acidic domain. NLS, the predicted nuclear localization signal. CC, coiled-coil domain. PR, proline-rich region. Horizontal lines indicate the 277aa not present in the 858aa WTX isoform 2 and the beta-catenin binding region.

WTX also plays a role in the recruitment of APC from microtubules to the plasma membrane and appears to be involved in the maintenance of intercellular junctions.

Homology

The amino terminus of WTX shows homology to FAM123A; 32% identical over 586aa. The regions with the highest percentage identity include the predicted NLS, the APCBD1 and APCBD2 binding domains, and the acidic domain.

Mutations

Note

Mutational analysis of the WTX gene in gastric, colorectal, and hepatocellular carcinomas and in acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) showed no deletion or truncating mutations of WTX. Missense mutations were found in 1/47 colorectal carcinomas and 1/60 normal karyotype AML cases. Various missense mutations (D233Y, K292N, E395D, R584G, Y599C, P880L, P884L, and I1003M) found in Wilms tumors were also in most cases found in normal tissues from the same patient. The missense mutations seen in the one colorectal carcinoma and one AML were tumor-specific. Although these are not currently known to be SNPs (dbSNP, build 129), they may not constitute functional mutations in WTX.

Inactivating mutations in WTX (deletions and truncating/frameshift mutations) appear to be negatively correlated in Wilms tumors with activating mutations in exon 3 of CTNNB1 (encoding beta-catenin), implicating the activation of the WNT signaling pathway in the formation of Wilms tumors since both inactivating mutations of WTX and activating mutations of CTNNB1 function to activate this signaling pathway.

Germinal

In osteopathia striata congenita with cranial stenosis (OSCS), deletions of the entire WTX gene and truncation mutations (nonsense mutations and deletion/insertion + frameshift mutations) have been observed. In cases with truncation mutations in which

the mutations affect nucleotides 285-1112 (encoding residues 50-326), the mutations reside within intron 2 of the shorter alternatively spliced transcript and do not affect the 858aa isoform. However, such mutations are lethal in males and demonstrate a typical clinical phenotype in females, suggesting that retention of the wild-type 858aa isoform of WTX cannot compensate in terms of regulation of the WNT signaling pathway for loss or truncation of the 1135aa isoform.

Somatic

In Wilms tumors, the most commonly observed mutation is the deletion of the entire WTX gene. Truncation mutations and missense mutations have also been observed.

Implicated in

Wilms tumor (nephroblastoma)

Prognosis

The overall five-year survival is approximately 90%. Prognosis for Wilms tumor is excellent for favorable histology tumors with treatment according to Children's Oncology Group (COG) or Société Internationale d'Oncologie Pédiatrique (SIOP) protocols. The prognosis is less good for Wilms tumors with anaplastic histology, particularly those with diffuse anaplasia for which the overall four-year survival is approximately 65%.

Cytogenetics

Balanced translocation t(X;18)(q11;p11) with WTX deletion; Xq11.1 deletions.

Oncogenesis

7-29% of Wilms tumors show deletions or mutations of WTX.

Osteopathia striata congenita with cranial sclerosis (OSCS) (MIM300373)

Note

The severity of the OSCS phenotype appears to be correlated, in cases with truncating mutations in WTX, with the location of the truncating mutation, with truncations C-terminal to the acidic domain (residues 370-411) associated with a less severe phenotype, at least in males.

Prognosis

Most males with OPCS die at or before birth. Females with OPCS show multiple defects including sclerosis of the long bones and skull, longitudinal striations of osteosclerosis in the long bones, macrocephaly, and cleft palate.

Cytogenetics

X-linked dominant inheritance.

Oncogenesis

OPCS individuals with germline mutations in WTX do not appear to be predisposed to Wilms tumor or other malignancies.

References

Grohmann A, Tanneberger K, Alzner A, Schneikert J, Behrens J. AMER1 regulates the distribution of the tumor suppressor APC between microtubules and the plasma membrane. *J Cell Sci.* 2007 Nov 1;120(Pt 21):3738-47

Han M, Rivera MN, Batten JM, Haber DA, Dal Cin P, Iafrate AJ. Wilms' tumor with an apparently balanced translocation t(X;18) resulting in deletion of the WTX gene. *Genes Chromosomes Cancer.* 2007 Oct;46(10):909-13

Major MB, Camp ND, Berndt JD, Yi X, Goldenberg SJ, Hubbert C, Biechele TL, Gingras AC, Zheng N, Maccoss MJ, Angers S, Moon RT. Wilms tumor suppressor WTX negatively regulates WNT/beta-catenin signaling. *Science.* 2007 May 18;316(5827):1043-6

Rivera MN, Kim WJ, Wells J, Driscoll DR, Brannigan BW, Han M, Kim JC, Feinberg AP, Gerald WL, Vargas SO, Chin L, Iafrate AJ, Bell DW, Haber DA. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. *Science.* 2007 Feb 2;315(5812):642-5

Chung NG, Kim MS, Chung YJ, Yoo NJ, Lee SH. Tumor suppressor WTX gene mutation is rare in acute leukemias. *Leuk Lymphoma.* 2008 Aug;49(8):1616-7

Owen C, Virappane P, Alikian M, Stasevich I, Summers K, Lillington D, Bonnet D, Burnett A, Mills K, Lister TA, Fitzgibbon J. WTX is rarely mutated in acute myeloid leukemia. *Haematologica.* 2008 Jun;93(6):947-8

Perotti D, Gamba B, Sardella M, Spreafico F, Terenziani M, Collini P, Pession A, Nantron M, Fossati-Bellani F, Radice P. Functional inactivation of the WTX gene is not a frequent event in Wilms' tumors. *Oncogene.* 2008 Jul 31;27(33):4625-32

Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. *Genes Chromosomes Cancer.* 2008 Jun;47(6):461-70

Fukuzawa R, Anaka MR, Weeks RJ, Morison IM, Reeve AE. Canonical WNT signalling determines lineage specificity in Wilms tumour. *Oncogene.* 2009 Feb 26;28(8):1063-75

Jenkins ZA, van Kogelenberg M, Morgan T, Jeffs A, Fukuzawa R, Pearl E, Thaller C, Hing AV, Porteous ME, Garcia-Miñaur S, Bohring A, Lacombe D, Stewart F, Fiskerstrand T, Bindoff L, Berland S, Adès LC, Tchan M, David A, Wilson LC, Hennekam RC, Donnai D, Mansour S, Cormier-Daire V, Robertson SP. Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. *Nat Genet.* 2009 Jan;41(1):95-100

Yoo NJ, Kim S, Lee SH. Mutational analysis of WTX gene in Wnt/ beta-catenin pathway in gastric, colorectal, and hepatocellular carcinomas. *Dig Dis Sci.* 2009 May;54(5):1011-4

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