Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

SFRP4 (Secreted Frizzled-Related Protein 4)

Kendra S Carmon, David S Loose

University of Texas Health Science Center Houston, Houston, TX 77030, USA (KSC, DSL)

Published in Atlas Database: April 2009

Online updated version: http://AtlasGeneticsOncology.org/Genes/SFRP4ID42277ch7p14.html
DOI: 10.4267/2042/44714

Identity

Other names: FRP-4; sFRP-4; FRPHE; MGC26498; LOC6424

HGNC (Hugo): SFRP4

Location: 7p14.1

Local order: According to NCBI, SFRP4 is telomeric to EPDR1 (7p14.1) ependymin related protein 1 (zebrafish) and STARD3NL (7p14-p13) StAR-related lipid transfer domain containing 3 N-terminal like and centromeric to TXNDC3 (7p14.1) thioredoxin domain containing 3 (spermatozoa) and GPR141 (7p14.1) G protein-coupled receptor 141.

DNA/RNA

Description

The SFRP4 gene spans 10.99 kb on the short arm of chromosome 7 and is transcribed from the minus strand in the centromere-to-telomere orientation. The gene is encoded by six exons with the trans-lation initiation codon in the first exon.

Transcription

The SFRP4 mRNA transcript is 2974 bp, 1041 bp are coding sequence. Ensembl data predicts a second transcript from the SFRP4 gene, lacking the 81 bp exon 2, although this has not been demons-trated.

Protein

Description

SFRP4 protein is comprised of 346 amino acids with a predicted molecular weight of 39.9 kDa and an actual molecular weight of approximately 50-55 kDa.
SFRP4 belongs to a family of five SFRPs; these proteins fold into two independent domains. The N-terminus contains a secretion signal peptide followed by a ~120 amino acid cysteine-rich domain (CRD). The CRD is 30-50% identical to the extracellular putative Wnt-binding domain of frizzled (Fzd) receptors and is characterized by the presence of ten cysteine residues at conserved positions.

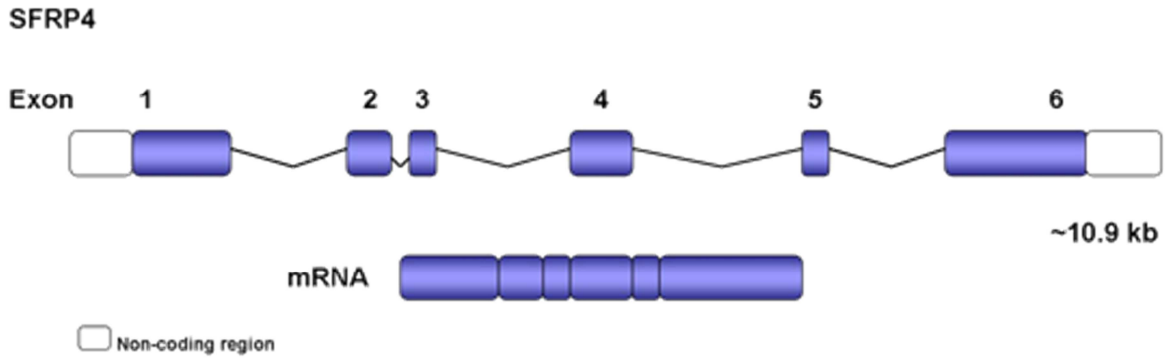


Diagram illustrates SFRP4 gene that contains a total of six exons.

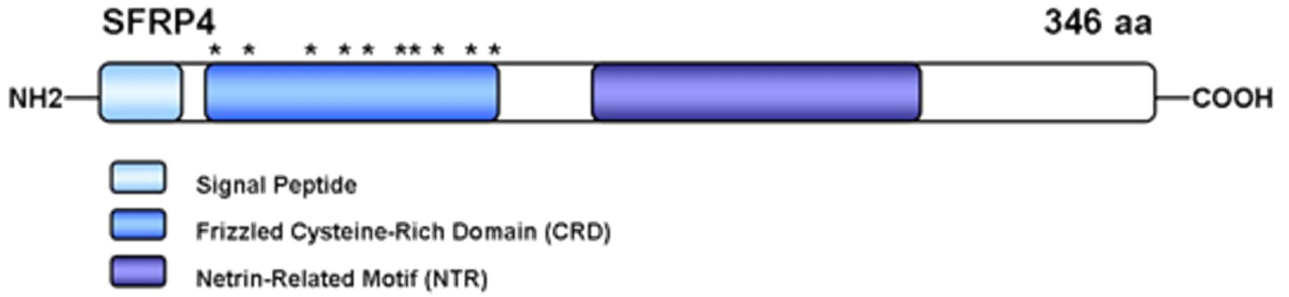


Diagram illustrates the full length SFRP4 protein which contains a signal peptide sequence of 20-30 amino acids, a cysteine-rich domain (CRD) of approximately 120 amino acids, and a netrin-related motif (NTR) domain. Conserved cysteines of the CRD are indicated by *.

These cysteines form a pattern of disulfide bridges. The C-terminal portion of the SFRP protein is characterized by segments of positively charged residues that appear to confer heparin-binding properties in at least two SFRPs (SFRP1 and SFRP3) and contains a netrin-related motif (NTR) with six cysteine residues that most likely form three disulfide bridges. NTR domains with similar features are found in a wide range of unrelated proteins, including Netrin-1, tissue inhibitors of metallo-proteinases (TIMPs), complement proteins and type I procollagen C-proteinase enhancer proteins (PCOLCEs). The six conserved cysteines in the NTR of SFRP4 share a similar spacing to SFRP3, whereas those of the SFRP1/SFRP2/SFRP5 subgroup are distinctively different, indicating a disparity in disulfide bond formation. Uniquely, SFRP4 contains two additional cysteine residues. The overall function of the NTR is unknown, yet there is some evidence that the NTR may also play a role in Wnt binding. This implies that multiple Wnt binding sites may exist on SFRP molecules and/or that SFRPs exhibit differential affinities for Wnt ligands according to the different SFRP conformational and post-translational modifications.

Expression

SFRP4 is expressed in various normal tissues including endometrium (specifically stromal cells with higher expression during proliferative phase of menstrual cycle), ovary, kidney, heart, brain, mammary gland, cervix, pancreas, stomach, colon, lung, skeletal muscle, testis, eye, bone, prostate, and liver.

Localisation

Secreted from cell; extracellular matrix; bound to plasma membrane.

Function

Since SFRPs share a similar CRD with the Fzd family of receptors; it is believed that SFRPs may act as soluble modulators that compete with Fzd to bind the Wnt ligands, thereby altering the Wnt signal. Individual SFRPs also have distinct binding specificity for distinct Wnt ligands. Reports have demonstrated that SFRP4 binds Wnt7a and there is conflicting data for SFRP4 binding to Wnt3a. SFRP4 expression is regulated by estrogen and progesterone and may act as a regulator of adult uterine morphology and function. SFRP4 has been shown to increase apoptosis during ovulation. Transgenic studies have found that SFRP4 decreases bone formation and inhibits osteoblast proliferation by attenuating canonical/beta-catenin-Wnt signaling. SFRP4 reportedly exhibits phospha-turic effects by specifically inhibiting sodium-dependent phosphate uptake.

Homology

Of the five human SFRPs (SFRP1, SFRP2, SFRP3, SFRP4, SFRP5), SFRP4 shares most significant homology with SFRP3.

Mutations

Note

It was reported that the T allele of the SFRP4 gene polymorphism ARG262 (CGC to CGT) of exon4 is associated with decreased bone mineral density in post-menopausal Japanese women.

Implicated in

Endometrial Carcinoma

Note

SFRP4 was more frequently down-regulated in (microsatellite instability). MSI cancers as compared with (microsatellite stable) MSS endo-metrioid endometrial cancers. Expression of SFRP4 is decreased in both low-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma.

Malignant Pleural Mesothelioma

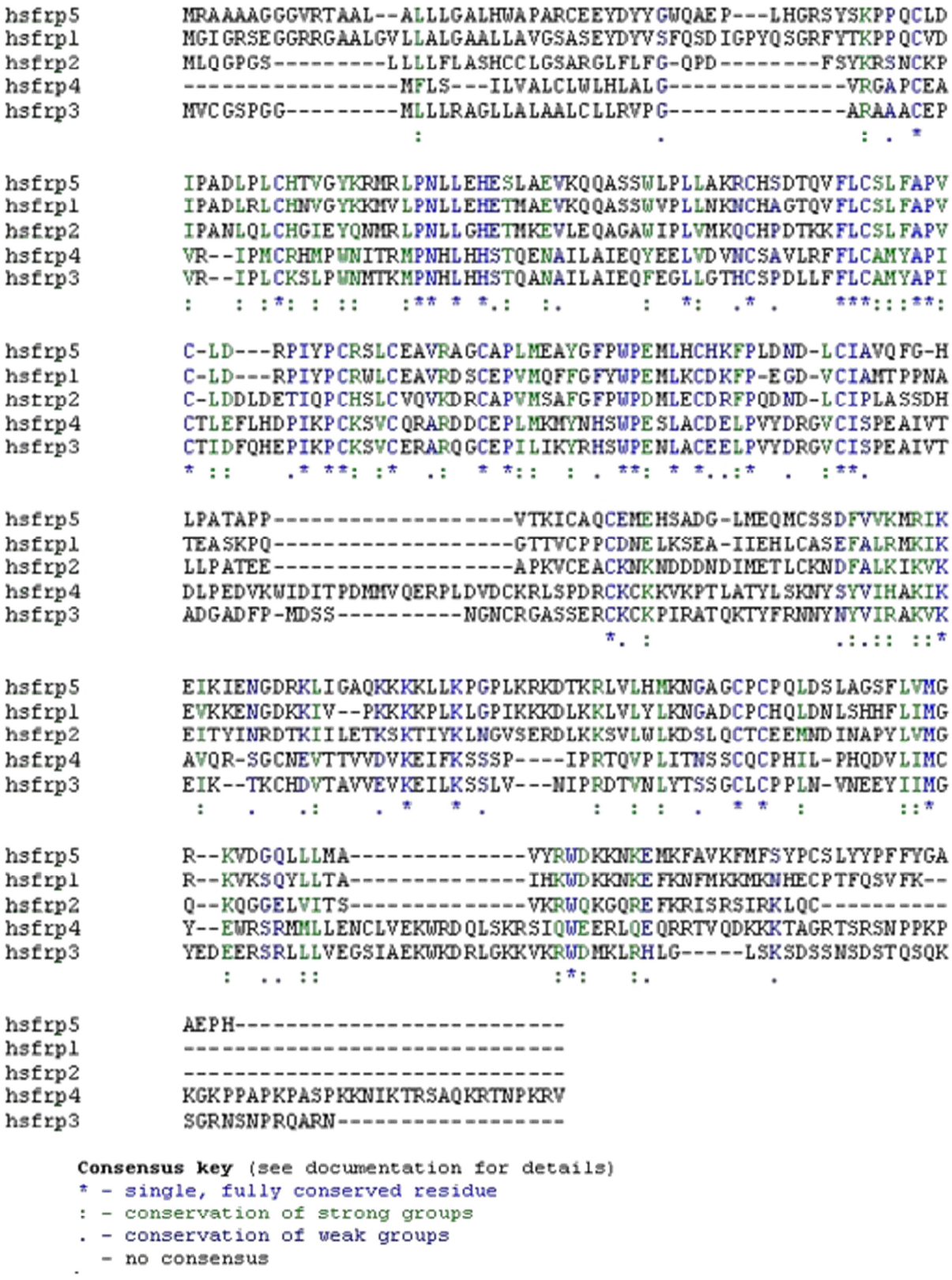
Note

SFRP4 promoter is frequently methylated in this cancer leading to inhibition of expression and is associated with abnormal growth; restoration of SFRP4 results in growth suppression and apoptosis in mesothelioma cell lines.

Tumor-induced osteomalacia

Note

Tumor-induced osteomalacia is a disorder in which there is an increase in renal phosphate excretion and a reduction in serum phosphate levels leading to hyperphosphaturia, hypophosphatemia and rickets.



CLUSTAL alignment of the 5 human SFRPs.

SFRP4 is highly expressed in such tumors and functions as a circulating phosphaturic factor that antagonizes renal Wnt-signaling.

Breast Cancer

Note

Studies have found evidence for SFRP4 overexpression in breast cancer.

Pancreatic Cancer

Note

SFRP4 found to be significantly hypermethylated in the tumors of cancer patients versus matched adjacent tissue controls.

Gastric Carcinoma

Note

The SFRP4 was highly methylated in gastric carcinoma samples with greater instance in H. pylori positive patients.

Prostate Cancer

Note

SFRP4 is overexpressed in prostate cancers and functions to inhibit cell proliferation and metastatic potential.

Prognosis

Increased expression of membranous SFRP4 is associated with a good prognosis in human localized androgen-dependent prostate cancer, suggesting a role for sFRP4 in early stage disease.

B-cell chronic lymphocytic leukemia

Note

SFRP4 was found to be frequently methylated and downregulated in CLL samples.

Colorectal Carcinoma

Note

SFRP4 expression was shown to be up-regulated in colorectal cancer.

Esophageal Adenocarcinoma

Note

SFRP4 mRNA and protein expression were significantly decreased due to hypermethylation in esophageal adenocarcinoma and Barrett's esophagus patients.

References

Finch PW, He X, Kelley MJ, Uren A, Schaudies RP, Popescu NC, Rudikoff S, Aaronson SA, Varmus HE, Rubin JS. Purification and molecular cloning of a secreted, Frizzled-related antagonist of Wnt action. Proc Natl Acad Sci U S A. 1997 Jun 24;94(13):6770-5

Abu-Jawdeh G, Comella N, Tomita Y, Brown LF, Tognazzi K, Sokol SY, Kocher O. Differential expression of frpHE: a novel human stromal protein of the secreted frizzled gene family, during the endometrial cycle and malignancy. Lab Invest. 1999 Apr;79(4):439-47

Bafico A, Gazit A, Pramila T, Finch PW, Yaniv A, Aaronson SA. Interaction of frizzled related protein (FRP) with Wnt ligands and the frizzled receptor suggests alternative mechanisms for FRP inhibition of Wnt signaling. J Biol Chem. 1999 Jun 4;274(23):16180-7

Bányai L, Patthy L. The NTR module: domains of netrins, secreted frizzled related proteins, and type I procollagen C-proteinase enhancer protein are homologous with tissue inhibitors of metalloproteases. Protein Sci. 1999 Aug;8(8):1636-42

Dennis S, Aikawa M, Szeto W, d'Amore PA, Papkoff J. A secreted frizzled related protein, FrzA, selectively associates with Wnt-1 protein and regulates wnt-1 signaling. J Cell Sci. 1999 Nov;112 (Pt 21):3815-20

Uren A, Reichsman F, Anest V, Taylor WG, Muraiso K, Bottaro DP, Cumberledge S, Rubin JS. Secreted frizzled-related protein-1 binds directly to Wingless and is a biphasic modulator of Wnt signaling. J Biol Chem. 2000 Feb 11;275(6):4374-82

Dann CE, Hsieh JC, Rattner A, Sharma D, Nathans J, Leahy DJ. Insights into Wnt binding and signalling from the structures of two Frizzled cysteine-rich domains. Nature. 2001 Jul 5;412(6842):86-90

Roszmusz E, Patthy A, Trexler M, Patthy L. Localization of disulfide bonds in the frizzled module of Ror1 receptor tyrosine kinase. J Biol Chem. 2001 May 25;276(21):18485-90

Yamaguchi TP. Heads or tails: Wnts and anterior-posterior patterning. Curr Biol. 2001 Sep 4;11(17):R713-24

Chong JM, Uren A, Rubin JS, Speicher DW. Disulfide bond assignments of secreted Frizzled-related protein-1 provide insights about Frizzled homology and netrin modules. J Biol Chem. 2002 Feb 15;277(7):5134-44

Fujita M, Ogawa S, Fukuoka H, Tsukui T, Nemoto N, Tsutsumi O, Ouchi Y, Inoue S. Differential expression of secreted frizzled-related protein 4 in decidual cells during pregnancy. J Mol Endocrinol. 2002 Jun;28(3):213-23

Berndt T, Craig TA, Bowe AE, Vassiliadis J, Reczek D, Finnegan R, Jan De Beur SM, Schiavi SC, Kumar R. Secreted frizzled-related protein 4 is a potent tumor-derived phosphaturic agent. J Clin Invest. 2003 Sep;112(5):785-94

Drake JM, Friis RR, Dharmarajan AM. The role of sFRP4, a secreted frizzled-related protein, in ovulation. Apoptosis. 2003 Aug;8(4):389-97

Ace CI, Okulicz WC. Microarray profiling of progesterone-regulated endometrial genes during the rhesus monkey secretory phase. Reprod Biol Endocrinol. 2004 Jul 7;2:54

Fujita M, Urano T, Shiraki M, Momoeda M, Tsutsumi O, Hosoi T, Orimo H, Ouchi Y, Inoue S.. Association of a single nucleotide polymorphism in the secreted frizzled-related protein 4 (sFRP4) gene with bone mineral density. Ger. Geront. Int. 2004; 4 (3): 175-180.

Horvath LG, Henshall SM, Kench JG, Saunders DN, Lee CS, Golovsky D, Brenner PC, O'Neill GF, Kooner R, Stricker PD, Grygiel JJ, Sutherland RL. Membranous expression of secreted frizzled-related protein 4 predicts for good prognosis in localized prostate cancer and inhibits PC3 cellular proliferation in vitro. Clin Cancer Res. 2004 Jan 15;10(2):615-25

Hrzenjak A, Tippl M, Kremser ML, Strohmeier B, Guelly C, Neumeister D, Lax S, Moinfar F, Tabrizi AD, Isadi-Moud N, Zatloukal K, Denk H. Inverse correlation of secreted frizzled-related protein 4 and beta-catenin expression in endometrial stromal sarcomas. J Pathol. 2004 Sep;204(1):19-27

Lee AY, He B, You L, Dadfarmay S, Xu Z, Mazieres J, Mikami I, McCormick F, Jablons DM. Expression of the secreted frizzled-related protein gene family is downregulated in human mesothelioma. Oncogene. 2004 Aug 26;23(39):6672-6

He B, Lee AY, Dadfarmay S, You L, Xu Z, Reguart N, Mazieres J, Mikami I, McCormick F, Jablons DM. Secreted frizzled-related protein 4 is silenced by hypermethylation and induces apoptosis in beta-catenin-deficient human mesothelioma cells. Cancer Res. 2005 Feb 1;65(3):743-8

Risinger JI, Maxwell GL, Chandramouli GV, Aprelikova O, Litzi T, Umar A, Berchuck A, Barrett JC. Gene expression profiling of microsatellite unstable and microsatellite stable endometrial

cancers indicates distinct pathways of aberrant signaling. Cancer Res. 2005 Jun 15;65(12):5031-7

Zou H, Molina JR, Harrington JJ, Osborn NK, Klatt KK, Romero Y, Burgart LJ, Ahlquist DA. Aberrant methylation of secreted frizzled-related protein genes in esophageal adenocarcinoma and Barrett's esophagus. Int J Cancer. 2005 Sep 10;116(4):584-91

Berndt TJ, Bielesz B, Craig TA, Tebben PJ, Bacic D, Wagner CA, O'Brien S, Schiavi S, Biber J, Murer H, Kumar R. Secreted frizzled-related protein-4 reduces sodium-phosphate co-transporter abundance and activity in proximal tubule cells. Pflugers Arch. 2006 Jan;451(4):579-87

Feng Han Q, Zhao W, Bentel J, Shearwood AM, Zeps N, Joseph D, Iacopetta B, Dharmarajan A. Expression of sFRP-4 and beta-catenin in human colorectal carcinoma. Cancer Lett. 2006 Jan 8;231(1):129-37

Liu TH, Raval A, Chen SS, Matkovic JJ, Byrd JC, Plass C. CpG island methylation and expression of the secreted frizzled-related protein gene family in chronic lymphocytic leukemia. Cancer Res. 2006 Jan 15;66(2):653-8

Turashvili G, Bouchal J, Burkadze G, Kolar Z. Wnt signaling pathway in mammary gland development and carcinogenesis. Pathobiology. 2006;73(5):213-23

Wawrzak D, Métioui M, Willems E, Hendrickx M, de Genst E, Leyns L. Wnt3a binds to several sFRPs in the nanomolar range. Biochem Biophys Res Commun. 2007 Jun 15;357(4):1119-23

Bu XM, Zhao CH, Zhang N, Gao F, Lin S, Dai XW. Hypermethylation and aberrant expression of secreted frizzled-related protein genes in pancreatic cancer. World J Gastroenterol. 2008 Jun 7;14(21):3421-4

Carmon KS, Loose DS. Secreted frizzled-related protein 4 regulates two Wnt7a signaling pathways and inhibits proliferation in endometrial cancer cells. Mol Cancer Res. 2008 Jun;6(6):1017-28

Kang GH, Lee S, Cho NY, Gandamihardja T, Long TI, Weisenberger DJ, Campan M, Laird PW. DNA methylation profiles of gastric carcinoma characterized by quantitative DNA methylation analysis. Lab Invest. 2008 Feb;88(2):161-70

Nakanishi R, Akiyama H, Kimura H, Otsuki B, Shimizu M, Tsuboyama T, Nakamura T. Osteoblast-targeted expression of Sfrp4 in mice results in low bone mass. J Bone Miner Res. 2008 Feb;23(2):271-7

This article should be referenced as such:

Carmon KS, Loose DS. SFRP4 (Secreted Frizzled-Related Protein 4). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(3):296-300.