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Gene Section
Review

WIF1 (WNT inhibitory factor 1)

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Identity

Other names: WIF-1

HGNC (Hugo): WIF1

Location: 12q14.3

DNA/RNA

Description

The human WIF1 gene is located on the chromosome 12q14.2 from 65444404 bp to 65515346 bp (from pter). It is oriented on the minus strand and comprises 10 exons spanning 71007 bp of genomic DNA.
The first and the 10th exons are partially composed by untranslated regions.

Transcription

The mRNA produced is 2304 bp long.
The promoter region of WIF1 has been cloned and studied by Reguart et al. and its structure is shown in Figure 2B (Reguart et al., 2004).
Regulatory elements in the WIF1 promoter comprise a TATA box and binding sites of the transcription factors: Engrailed, E2F, GLI-Kruppel, NF-κB, and MYC, as visualized in Figure 2B.
The CpG island located upstream of the WIF1 transcriptional start site is prone to aberrant methylation in various tumor types.
Hypermethylation of this region has been found to be responsible for WIF1 downregulation, suggestive of tumor suppressor properties in different cancer types.

Pseudogene

No pseudogene known so far.

Protein

Description

WIF1 is a protein of 379 aminoacids, composed of a signal peptide for extracellular secretion, a WIF domain, five EGF repeats and a hydrophilic C terminus (Figure 3).
The WIF domain is responsible for the binding with some of the WNT ligands (3a, 4, 5a, 7a, 9a, 11) and to olfactomedin 1, a protein involved in neuronal differentiation (Hsieh et al., 1999).

Expression

In development WIF1 starts to be produced during somitogenesis and maintains its expression in adults mainly in the lung, heart, and at the cartilage-mesenchyme interface (data derived from Xenopus, zebrafish and mouse).

Localisation

WIF1 is an extracellular secreted protein.

Figure 1. WIF1 genomic context.

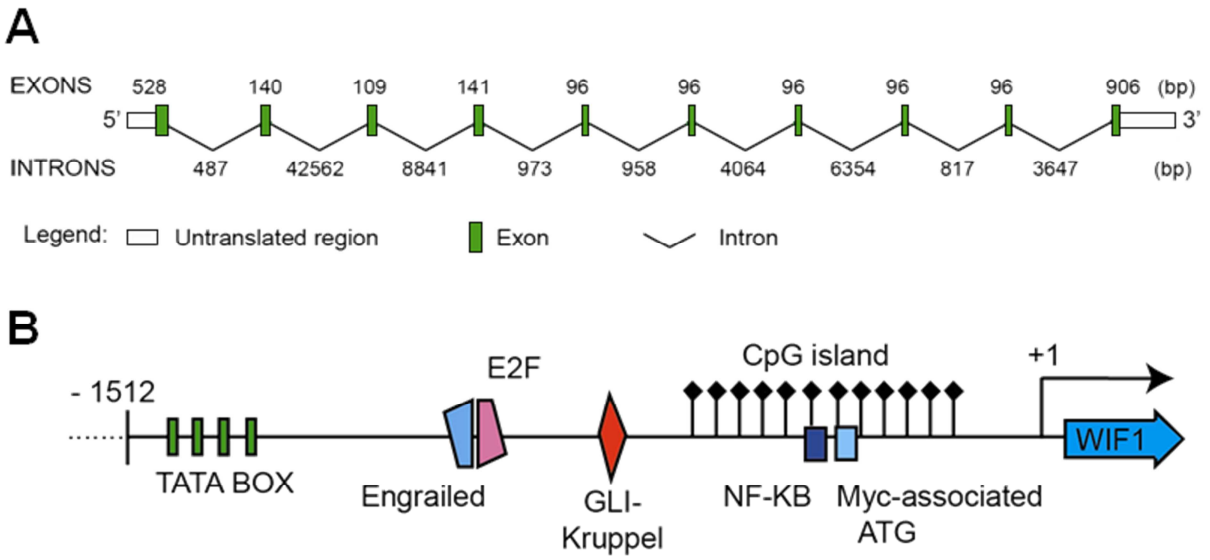

Figure 2. A) WIF1 gene structure. Transcription unit 71007 bp, mRNA 2304 bp. **B)** Structure of human WIF1 promoter.

Figure 3. WIF1 protein domains.

Function

WIF1 is a secreted WNT inhibitor that works by sequestering soluble Wnt proteins. It prevents the interaction between WNT morphogens and their specific receptors (Figure 4). WIF1 has been shown to bind to agonists of both, the canonical and the non-canonical WNT pathway. In contrast to other inhibitors like DKKs that can inhibit only the β-catenin dependent pathway, WIF1 can block the activation of both the canonical and the non-canonical WNT signaling pathway (Kawano and Kypta, 2003). Recently has been shown by Malinauskas et al. that WIF1 has a modular mechanism of inhibition. The WIF domain is responsible for the binding of WNT1 with WNT ligands and the five EGF-like domains seems to be partially involved in the extracellular localization of WIF1. The essential formation of gradients of WNT morphogens during development is mediated by interaction of the EGF-like domains and some glycosaminoglycans, namely heparin and heparan sulfate (Malinauskas et al., 2011).

Homology

The WIF1 gene is conserved in
- P. troglodytes (WIF1)
- C. lupus (WIF1)
- M. musculus (WIF1)
- R. norvegicus (WIF1)
- G. gallus (WIF1)
- D. rerio (WIF1)
- D. melanogaster (shf)

Mutations

Note

WIF1 is rarely mutated in human cancer.

Somatic

According to COSMIC (Catalogue of Somatic Mutations in Cancer) only 6 samples over 1103 sequenced human cancer specimens show mutations that lead to amminoacid missense substitution.

Genomic deletions of the region where WIF1 is located have instead been reported for 10% of glioblastoma samples (Lambiv et al., 2011).

Implicated in

Cervical cancer

Note

WIF1 is downregulated by promoter hypermethylation in 87.5% of primary cervical cancer.

Peritumoral WIF1 gene transfer induces apoptosis and inhibits growth and invasion (Ramachandran et al., 2011).

Glioblastoma

Note

WIF1 silencing is mediated by both deletion (7/69, 10%) and promoter hypermethylation (29/110, 26%).

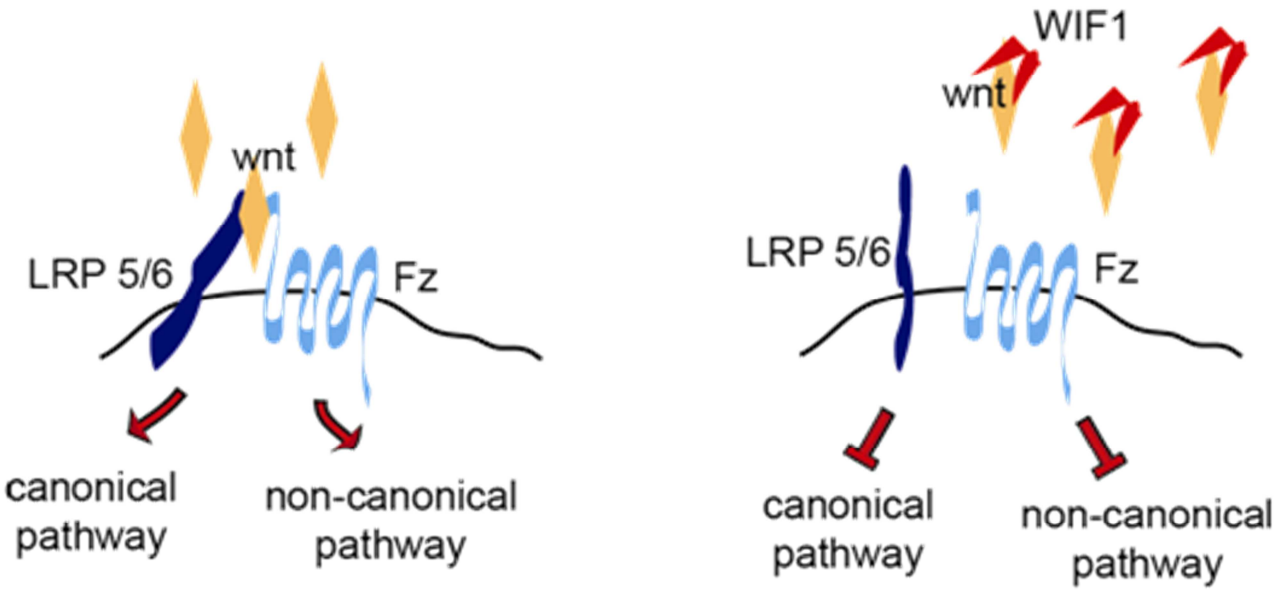

Figure 4. WIF1 inhibition mechanism.

WIF1 re-expression abolishes tumorigenicity of glioblastoma cell lines potentially by inducing senescence (Lambiv et al., 2011).

Primary non-small-cell lung carcinoma (NSCLC)

Note

WIF1 is frequently downregulated and this downregulation is correlated with WIF1 promoter hypermethylation (Mazieres et al., 2004).

Osteosarcoma

Note

Hypermethylation of the WIF1 promoter is found in the majority of osteosarcoma cell lines tested and it correlates with WIF1 mRNA downregulation (Rubin et al., 2010).

Hepatocellular carcinoma (HCC)

Note

WIF1 is frequently downregulated through promoter hypermethylation (Deng et al., 2010).

Mesothelioma

Note

WIF-1 promoter methylation was reported from 73.9% of mesothelioma tissues and in 100% of tested mesothelioma cell lines (Kohno et al., 2010).

Renal cell carcinoma (RCC)

Note

WIF-1 is downregulated by promoter methylation and when re-expressed induces apoptosis in RCC cells (Kawakami et al., 2009).

Bladder cancer

Note

Epigenetic inactivation of WIF1 in bladder cancer deregulates WNT pathway activation. WIF1 re-expression induces a G1-arrest via p27 and p21 accumulation (Tang et al., 2009; Urakami et al., 2006).

Esophageal adenocarcinoma (EAC)

Note

Epigenetic alteration of WIF1 is an early event in the carcinogenesis of EAC. It's suggested to be involved in the progression from Barrett's esophagus (BE) to EAC thus WIF1 hypermethylation is proposed to be used as a diagnostic and predictive marker for increased EAC risk in BE patients (Clément et al., 2008).

Gastrointestinal cancers

Note

WIF-1 expression has been reported to be downregulated in 80.0% of esophageal, 74.2% of gastric, 82.0% of colorectal, and 75% of pancreatic cancer tissues. WIF1 silencing, mediated by hypermethylation, is proposed to be an early event in colorectal carcinogenesis (Taniguchi et al., 2005).

Breast cancer

Note

67% of the investigated invasive breast adenocarcinoma (Stages II or III) shows aberrant WIF1 promoter methylation (Ai et al., 2006).

Salivary gland pleomorphic adenoma

Note

WIF1 is rearranged resulting in a HMGA2/WIF1 fusion transcript. In consequence of this fusion WIF1 that in normal salivary gland tissue is highly expressed becomes downregulated. On the contrary, HMGA2 that in normal tissue is not expressed is strongly upregulated (Queimado et al., 2007).

References

Hsieh JC, Kodjabachian L, Rebbert ML, Rattner A, Smallwood PM, Samos CH, Nusse R, Dawid IB, Nathans J. A new secreted protein that binds to Wnt proteins and inhibits their activities. Nature. 1999 Apr 1;398(6726):431-6

Kawano Y, Kypta R. Secreted antagonists of the Wnt signalling pathway. J Cell Sci. 2003 Jul 1;116(Pt 13):2627-34

Mazieres J, He B, You L, Xu Z, Lee AY, Mikami I, Reguart N, Rosell R, McCormick F, Jablons DM. Wnt inhibitory factor-1 is silenced by promoter hypermethylation in human lung cancer. Cancer Res. 2004 Jul 15;64(14):4717-20

Reguart N, He B, Xu Z, You L, Lee AY, Mazieres J, Mikami I, Batra S, Rosell R, McCormick F, Jablons DM. Cloning and characterization of the promoter of human Wnt inhibitory factor-1. Biochem Biophys Res Commun. 2004 Oct 8;323(1):229-34

Taniguchi H, Yamamoto H, Hirata T, Miyamoto N, Oki M, Nosho K, Adachi Y, Endo T, Imai K, Shinomura Y. Frequent epigenetic inactivation of Wnt inhibitory factor-1 in human gastrointestinal cancers. Oncogene. 2005 Nov 24;24(53):7946-52

Ai L, Tao Q, Zhong S, Fields CR, Kim WJ, Lee MW, Cui Y, Brown KD, Robertson KD. Inactivation of Wnt inhibitory factor-1 (WIF1) expression by epigenetic silencing is a common event in breast cancer. Carcinogenesis. 2006 Jul;27(7):1341-8

Urakami S, Shiina H, Enokida H, Kawakami T, Tokizane T, Ogishima T, Tanaka Y, Li LC, Ribeiro-Filho LA, Terashima M, Kikuno N, Adachi H, Yoneda T, Kishi H, Shigeno K, Konety BR, Igawa M, Dahiya R. Epigenetic inactivation of Wnt inhibitory factor-1 plays an important role in bladder cancer through aberrant canonical Wnt/beta-catenin signaling pathway. Clin Cancer Res. 2006 Jan 15;12(2):383-91

Queimado L, Lopes CS, Reis AM. WIF1, an inhibitor of the Wnt pathway, is rearranged in salivary gland tumors. Genes Chromosomes Cancer. 2007 Mar;46(3):215-25

Clément G, Guilleret I, He B, Yagui-Beltrán A, Lin YC, You L, Xu Z, Shi Y, Okamoto J, Benhattar J, Jablons D. Epigenetic alteration of the Wnt inhibitory factor-1 promoter occurs early in the carcinogenesis of Barrett's esophagus. Cancer Sci. 2008 Jan;99(1):46-53

Kawakami K, Hirata H, Yamamura S, Kikuno N, Saini S, Majid S, Tanaka Y, Kawamoto K, Enokida H, Nakagawa M, Dahiya R. Functional significance of Wnt inhibitory factor-1 gene in kidney cancer. Cancer Res. 2009 Nov 15;69(22):8603-10

Tang Y, Simoneau AR, Liao WX, Yi G, Hope C, Liu F, Li S, Xie J, Holcombe RF, Jurnak FA, Mercola D, Hoang BH, Zi X. WIF1, a Wnt pathway inhibitor, regulates SKP2 and c-myc expression leading to G1 arrest and growth inhibition of human invasive urinary bladder cancer cells. Mol Cancer Ther. 2009 Feb;8(2):458-68

Deng Y, Yu B, Cheng Q, Jin J, You H, Ke R, Tang N, Shen Q, Shu H, Yao G, Zhang Z, Qin W. Epigenetic silencing of WIF-1 in hepatocellular carcinomas. J Cancer Res Clin Oncol. 2010 Aug;136(8):1161-7

Kohno H, Amatya VJ, Takeshima Y, Kushitani K, Hattori N, Kohno N, Inai K. Aberrant promoter methylation of WIF-1 and SFRP1, 2, 4 genes in mesothelioma. Oncol Rep. 2010 Aug;24(2):423-31

Rubin EM, Guo Y, Tu K, Xie J, Zi X, Hoang BH. Wnt inhibitory factor 1 decreases tumorigenesis and metastasis in osteosarcoma. Mol Cancer Ther. 2010 Mar;9(3):731-41

Lambiv WL, Vassallo I, Delorenzi M, Shay T, Diserens AC, Misra A, Feuerstein B, Murat A, Migliavacca E, Hamou MF, Sciuscio D, Burger R, Domany E, Stupp R, Hegi ME. The Wnt inhibitory factor 1 (WIF1) is targeted in glioblastoma and has a tumor suppressing function potentially by induction of senescence. Neuro Oncol. 2011 Jul;13(7):736-47

Malinauskas T, Aricescu AR, Lu W, Siebold C, Jones EY. Modular mechanism of Wnt signaling inhibition by Wnt inhibitory factor 1. Nat Struct Mol Biol. 2011 Jul 10;18(8):886-93

Ramachandran I, Thavathiru E, Ramalingam S, Natarajan G, Mills WK, Benbrook DM, Zuna R, Lightfoot S, Reis A, Anant S, Queimado L. Wnt inhibitory factor 1 induces apoptosis and inhibits cervical cancer growth, invasion and angiogenesis in vivo. Oncogene. 2012 May 31;31(22):2725-37

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