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Gene Section
Review

FZD5 (frizzled class receptor 5)

Ilaria Esposito

Department of Health Sciences, University of Milan, via A. Di Rudinò, 8 20142, Milan (Italy);ilaria.esposito1@studenti.unimi.it

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Abstract

The Wnt signalling pathways are ways of signalling that transduce signals into cells through cell surface receptors; they are three different type of pathways and all of these are activated by binding a Wnt-protein ligand to a Frizzled family receptor. Frizzled is a family of G-protein coupled receptor proteins that works as receptor in the Wnt signalling pathway; when activated, Frizzled works activating the Dishevelled protein inside the cell, to transduce the signal. Frizzled-5 (FZD5) is part of this family and it is encoded by the FZD5 gene (located on the chr2, 2q33.3). Like all Frizzled members, FZD5 has an amino-terminal cysteine-rich domain (CRD) which allows the Wnt binding, seven-transmembrane domains and a cytoplasmic tail containing the PDZ domain binding motif at the carboxy-terminus. FZD5 shows an important role in development and it seems to be overexpressed in several types of cancer. FZD5 preferably binds WNT3A, WNT5A, WNT7A and WNT10B, activating both canonical and non-canonical pathways.

Keywords
Wnt signalling pathway, FZD5, Frizzled, Coloboma

Identity

Other names: C2orf31, HFZ5, Fz-5, DKFZP434E2135, FzE5

HGNC (Hugo): FZD5

Location: 2q33.3

Location (base pair)
Starts at 207762586 and ends at 207769419 from pter (according to hg38-Dec_2013).

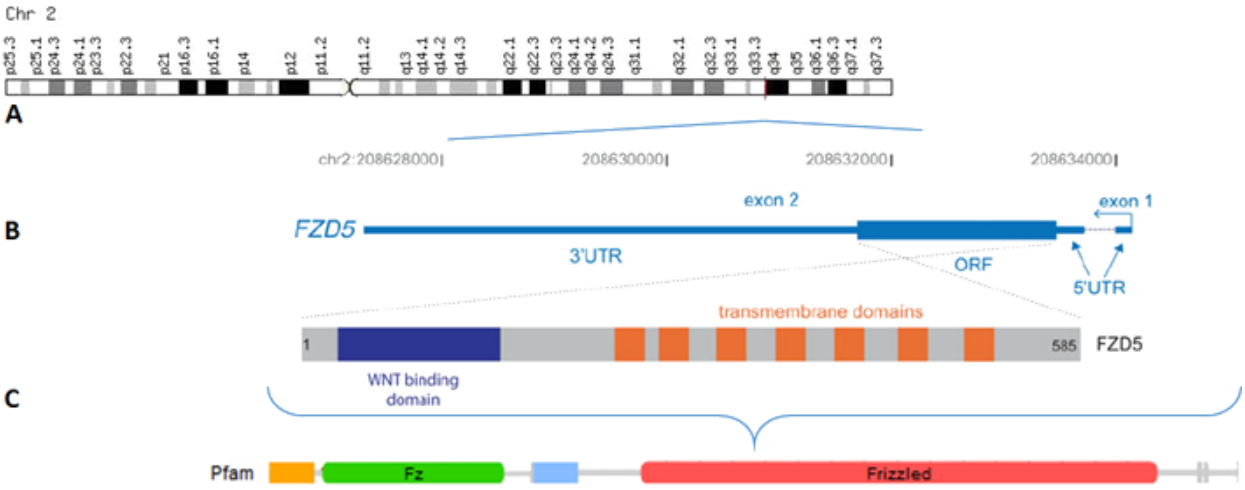


Figure 1: A) Location of FZD5 gene on chr2. B) Schematic representation of FZD5 gene, with exons 1 and 2. C) Protein structure and the subdivision into various domains.

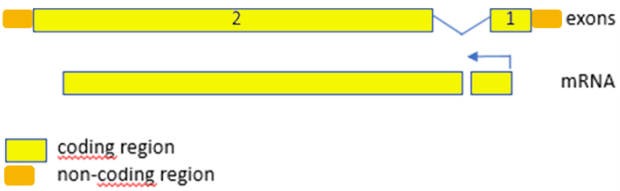


Figure 2: Schematic representation of FZD5 gene.

DNA/RNA

The FZD5 gene (6978 bp) contains a total of 2 exons and the FZD5 transcript is 6708 bp.

Description

Genomic size: 6978 bp. Exons count: 2, only one of which is coding. This gene has 1 transcript (splice variant), 66 orthologues, 12 paralogues.

Transcription

1 transcript variant has been found for this gene (font. www.ensembl.org). FZD5-201 ENST00000295417.3: mRNA 6708 bp, protein 585 aa.

Protein

Description

FZD5 protein, comprised of 585 aa with a mass of 64 kDa, is part of the frizzled gene family, 7-transmembrane domain proteins, which includes 10 members (FZD1 to FZD10). The FZD1-10 are bound and activated by the WNT family of lipoglycoproteins, inducing a network of signalling pathways: the WNT-FZD signalling system has a prevalent role in physiology during adulthood and dysfunction of this signalling leads to diseases, such as cancer and neurological and bone disorders. Wnt signals are transduced through at least three different pathways, including the canonical Wnt/β-catenin pathway, the Wnt/Ca^{2+} pathway, and the non-canonical planar cell polarity (PCP). The exclusive involvement of FZD5 in one of these three pathways is unclear, although some cases have been reported that WNT5A activate the canonical pathway in the presence of overexpressed FZD5 (He et al., 1997) and that WNT7A interacts with FZD5 to activate CTNNB1 (β-catenin)/canonical signalling (Carmon and Loose, 2008); however other evidences report that FZD5 can been associated with non-canonical Wnt signalling (Bischoff et al., 2015).

The secondary structure of FZD5 protein is composed by a large domain, the FZ domain, and two motifs, the Lys-Thr-X-X-X-Trp motif, and the PDZ-binding motif. The FZ domain (from aa 28 to aa 150) is an intracellular domain of about 120 amino acids, located close to the N-terminal end, first identified in the alpha-1 chain of mouse type XVIII collagen (Rehn and Pihlajaniemi, 1995).

The FZ domain, also known as CRD (cysteine rich domain) contains 10 conserved cysteines, and its crystal structure shows predominance of α -helix with disulphide bonds. Its presence is widely demonstrated to be involved in Wnt signalling (Povelones et al., 2005). The C-terminal cytoplasmic Lys-Thr-X-X-X-Trp motif (from aa 525 to aa 530) is located two amino acids after the seventh TM and frizzled receptors with point mutations into this motif lose their capacity to activate Wnt/β-catenin signalling (Umbhauer et al., 2000).

The PDZ domain (from aa 583 to aa 585) is a structural domain found in the signalling proteins and it plays a role in transport, ion channel signalling and transduction system, that typically recognize the extreme C-terminal end of the target proteins (Lee and Zheng, 2010).

Expression

Ishikawa et al. (2001) first isolated and characterized this novel mouse frizzled gene Fzd5. Its mRNA was expressed in the yolk sac, eyes and lung bud at 9.5 days post coitum, demonstrating its essential role in development.

In Xenopus embryos, after determining synergistic interactions between Wnts and frizzleds, misexpression, disruption or depletion of these components of Wnt pathway can inhibit the dorsal axis formation: these results suggest that the frizzled proteins work as receptors for Wnt ligands. To confirm that, Ishikawa et al. presents the evidence that the homozygous Fzd5 knockout mice are embryonically lethal, due to the defects they develop in the yolk sac vasculogenesis. Fzd5 is expressed in the developing retina in zebrafish, Xenopus Laevis, chick and mouse.

Later, human FZD5 was mapped on chromosome 2q33.3-q34 (Saitoh et al., 2001) and one of its ligand, WNT7A, activate Wnt/β-catenin signalling pathway and cell motility/invasion in metastatic melanoma, endometrial and ovarian cancer cell lines (Carmon and Loose, 2008, Ueno et al., 2013).

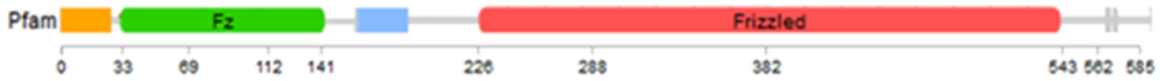


Figure 3: Schematic illustration of domains of FZD5 protein.

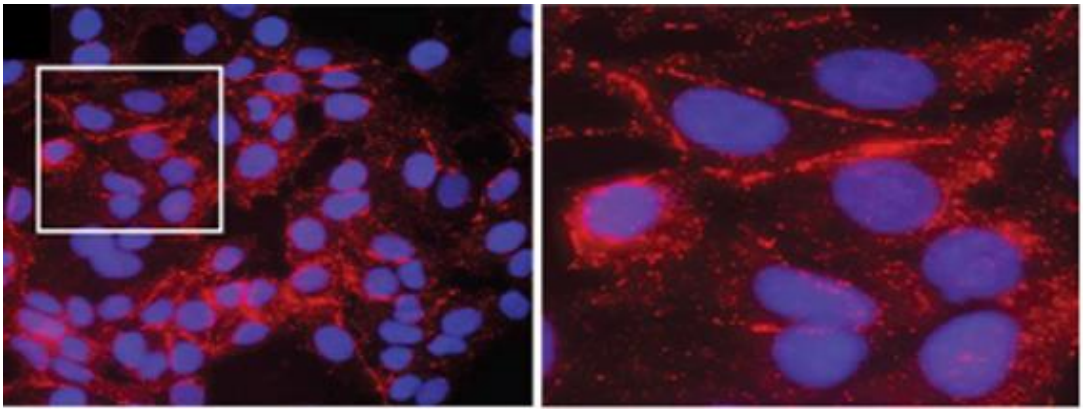


Figure 4: Visualization of WNT10B-FZD5 interaction in MCF-7 adherent cells (Lazzaroni et al., 2016).

Localisation

FZD5 is localized at the plasma membrane and it is also found at the Golgi apparatus membrane. (UniProt FZD5)

Function

FZD5 is part of the 7-transmembrane domain proteins, receptors for Wnt signalling proteins. When the Wnt signalling pathway is activated, FZD receptors are internalized in response to their Wnt ligands: internalization of FZD5 is induced by WNT3A, complexed with LRP6 (Yamamoto et al., 2006). A recent study (Terabayashi et al., 2009) demonstrated that FZD5 is internalized in response to WNT3A stimulation via the clathrin-dependent pathway to activate downstream signalling pathways. Terabayashi et al., found that the expression of SCYL2 (CVAK104), a coated vesicle-associated kinase of 104 kDa which is part of the endocytic process, induces intracellular accumulation of FZD5 and the latter is internalized and degraded by a lysosomal pathway, suggesting a model for regulating the turnover of specific subclass of FZD receptors. FZD5 protein is believed to be the receptor for the WNT5A ligand, in some contexts such as the induction of Tissue Factor (TF) expression for angiogenesis in monocytes (Arderiu et al., 2014), or in the pancreatic cancer context. This interaction between WNT5A and FZD5 results in activation of the Wnt/β-catenin canonical pathway, therefore FZD5 can be considered as a receptor for WNT5A (He et al., 1997). Other evidences of interaction of FZD5 with WNT5A have been provided by Ishikawa et al., investigating the presence of WNT5A and WNT10B in the yolk sac and inducing the formation of secondary axes in Xenopus. The synergy between WNT10B and FDZ5 has been proved by Lazzaroni et al., (2016), confirming an autocrine mechanism for Wnt signalling activation in a breast cellular model (MCF7). Moreover, FZD5 conjugated with LRP6 can interact and transduce a WNT7A signal for the activation of Wnt/β-catenin canonical signalling pathway and for the induction of proliferation in endometrial cancer cells (Carmon and Loose, 2008). WNT2 is also a FZD5 ligand, and WNT2 deficient embryos show placental defects, suggesting their role in vascular growth during the developmental stage (Ishikawa et al., 2001). FZD5 seems to have also an important role in the early stage of the eye development; this function may be species-dependent (Carole et al., 2008). Other findings have discovered a FZD5's role in neuronal development and polarity. Starting from the evidence that WNT3A is essential for neuronal differentiation of hNP cells, Bengoa-Vergniory et al., (2016) has performed the silencing of its receptors FZD4, FZD5, ROR1 and LRP6 and has shown a trend for reducing neuronal differentiation and gene expression. Instead, Slater et al., (2013) suggests a role for FZD5, in cell culture of hippocampal neurons of rat, in the establishment of neuronal polarity and in its morphogenesis, through the non-canonical Wnt mechanism.

Homology

The FZD5 gene is conserved in chimpanzee, dog, cow, mouse, rat, chicken, zebrafish. The characteristic domain Fz, also known as CRD domain, is conserved in all the members of the Frizzled family

Mutations

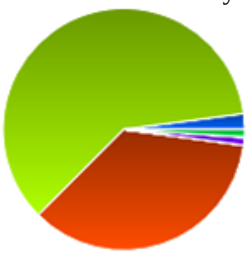
Germinal

Liu et al., (2016) reports an ultra-rare heterozygous frameshift mutation in FZD5 (p. Ala219Glufs*49) responsible of autosomal dominant non-syndromic coloboma. This frameshift variant is not a canonical substrate for nonsense-mediated decay, so the result is the production of a truncated protein, that lacks the transmembrane domain.

The truncated protein is secreted from cells and becomes a dominant-negative FZD5 receptor, so it antagonises both canonical and non-canonical WNT signalling.

Somatic

Wang et al., (2014) has observed 2 mutations in FZD5 that led to loss of functional pathway activation. The first one (p. Y46*) is a nonsense mutation that results in a premature truncation of the protein, generating a new protein (MT1) that led to a loss of Wnt-activating function. The second one (p. V290I) is a missense mutation that produces the protein named MT2. MT2, in contrast to MT1, did not change Wnt pathway activity. Some somatic mutations have been identified and described by COSMIC (Catalogue of Somatic Mutation In Cancer) and most are listed as nonsense, missense and synonymous substitutions; nevertheless, their role in disease has not yet been clarified.



Colour	Mutation type	Number of samples (%)
	Nonsense substitution	2 (2.17%)
	Missense substitution	58 (63.04%)
	Synonymous substitution	34 (36.96%)
	Inframe insertion	0 (0.00%)
	Frameshift insertion	1 (1.09%)
	Inframe deletion	0 (0.00%)
	Frameshift deletion	1 (1.09%)
	Complex mutation	0 (0.00%)
	Other	0 (0.00%)
	Total unique samples	92

Figure 5: Overview of major types of mutations occurring in FZD5.

Implicated in

Pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas. One of the most mutated gene in this type of cancer is RNF43, ubiquitin E3 ligase ring finger 43, suggested as a negative regulator of Wnt signalling. RNF43 inhibits Wnt/β-catenin signalling by reducing Frizzled levels on the membranes (Jiang et al., 2013). Considering this evident role of frizzled receptors in RNF43-mutant PDAC, has been discovered a unique requirement of Wnt/Fzd signalling: FZD5. As results, knockout of FZD5 led to robust growth inhibition in RNF43-mutant cells, and moreover they develop an anti-FZD5 antibody that inhibits the growth of RNF43-mutant PDAC through cell-cycle arrest. (Steinhart et al., 2017).

Colorectal cancer

One of the most common mutation in colorectal cancers (CRC) is RNF43, like PDAC. Like for PDAC, so for CRC using anti-FZD5 antibody has been proved that the FZD5 dependency may exist also in this type of cancer. As result, anti-FZD5 antibody inhibits survival of RNF46-mutant CRC organoids. (Steinhart et al., 2017).

Prostate cancer

Prostate cancer (PCa) is the most common malignancy in men. Because WNT5A expression was significantly higher in PC3 cells, two common WNT5A receptors (FZD5 and ROR2) were investigated and as result, FZD5 was expressed 70-fold higher in advanced PCa, while ROR2 was not significantly increased (Thiele et al., 2011).

Gastric cancer

FZD5 has a high overexpression in gastric cancer samples, due to the overexpression of its ligand, WNT5A, highly expressed in advanced stages of gastric cancer and correlated with poor prognosis (Bizama et al., 2014).

Renal cell carcinoma

FDZ5 is increased in RCC when compared to the normal kidney tissue, this can suggest a biomarker role in RCC. Moreover, its repression overcomes the chemo-resistance mediated by P-glycoprotein in RCC (Long et al., 2013).

Type I endometrial carcinoma

FZD5 is downregulated in type I endometrial adenocarcinoma, concordant with the downregulation of FZD5, and its ligand WNT5A, regulated by an estrogen receptor agonist and estradiol (Menezes Mde et al., 2011). Moreover, WNT7A also shows an upregulation correlated with a worse prognosis, by a signalling involving FZD5 (Ford et al., 2015).

Breast cancer

Recently, has been suggested a role in the autocrine activation of Wnt signalling guided by the interaction between WNT10B and FZD5; this interaction has been proved in the breast cancer MCF7 cells, through PLA analysis (Lazzaroni et al., 2016).

Ovarian cancer

A high number of malignant ovarian specimens are FZD5-positive than normal ovary. FZD5 is highly expressed in ovarian cancer cell lines, associated with poor prognosis, such as its ligand WNT5a, and it is upregulated by ARID3B (the DNA-binding protein AT-rich interactive domain 3B, a protein

involved in chromatin remodelling and regulation of gene expression). This upregulation leads to increased adhesion to ECM components, such as fibronectin and collagen IV. Previously, it was demonstrated that FZD5 with its ligand WNT7A increases adhesion in ovarian cancer. As expected, knockdown of FZD5 in ovarian cancer cells leads to decreased adhesion (Bobbs et al., 2015).

Coloboma

Ocular coloboma is an eye malformation, resulting from incomplete fusion of the optic fissure during development. The classical description in medical literature is of a key-hole shaped defect in one or both the structures of the eye, in post-embryonic life. Coloboma is often associated with microphthalmia and/or contralateral anophthalmia, and together they represent the 10-15% of pediatric blindness. The Wnt receptor FZD5 mediates both canonical and non-canonical signalling in the development of the eye, depending on the organism. Recently, has been reported an ultra-rare frameshift mutation in FZD5, in zebrafish, that creates the A219Xfs*49 mutant transcript as result of a truncated FZD5 protein without the seven-transmembrane domain. This mutation converts FZD5 from a membrane-bound receptor to a secreted FZD antagonist that give dominant-negative effect to the WNT signalling. As result, retinal neuroblasts exhibit apical junction defects, leading to microphthalmia and coloboma. Liu et al., also shows that the effects on the eye were similar when both FZD5-wt and FZD5-mut were overexpressed, suggesting a key role of dosage in ocular development (Liu et al., 2016).

Alcoholic liver disease

Alcoholic liver disease (ALD) consists of a spectrum of disease that has the potentiality of progressing to hepatocellular carcinoma. Through microarray analysis has been found that FZD5 was the second key gene in the network of gene-modulating ALD. Its value in alcoholic hepatitis and cirrhosis was downregulated, leading to decreased gene activity and reduced synthesis of multi-transmembrane transport protein. This may reduce the binding between FZD5 and Wnt protein, as well as the number of β-catenin in the cytoplasm, leading to hepatocyte apoptosis (Liu et al., 2013).

Amyotrophic lateral sclerosis

FZD5 receptor is involved in the pathophysiology of ALS and in the response of neuronal cells against neurodegeneration. FZD5 shows changes in expression pattern during the progression of the disease, founding an increase immunoreactivity of this receptor (González-Fernández et al., 2016).

Psoriasis Lesion

WNT5a and FZD5 are mainly expressed in inflammatory and endothelial cells; moreover, they are expressed in healthy skin and overexpressed in psoriasis lesions (Zhang et al., 2015).

References

Arderiu G, Espinosa S, Peña E, Aledo R, Badimon L. Monocyte-secreted Wnt5a interacts with FZD5 in microvascular endothelial cells and induces angiogenesis through tissue factor signaling. J Mol Cell Biol. 2014 Oct;6(5):380-93

Bengoa-Vergniory N, Gorroño-Etxebarria I, López-Sánchez I, Marra M, Di Chiaro P, Kypta R. Identification of Noncanonical Wnt Receptors Required for Wnt-3a-Induced Early Differentiation of Human Neural Stem Cells. Mol Neurobiol. 2017 Oct;54(8):6213-6224

Bischoff DS, Zhu JH, Makhijani NS, Yamaguchi DT. Induction of CXC chemokines in human mesenchymal stem cells by stimulation with secreted frizzled-related proteins through non-canonical Wnt signaling. World J Stem Cells. 2015 Dec 26;7(11):1262-73

Bizama C, Benavente F, Salvatierra E, Gutiérrez-Moraga A, Espinoza JA, Fernández EA, Roa I, Mazzolini G, Sagredo EA, Gidekel M, Podhajcer OL. The low-abundance transcriptome reveals novel biomarkers, specific intracellular pathways and targetable genes associated with advanced gastric cancer. Int J Cancer. 2014 Feb 15;134(4):755-64

Bobbs A, Gellerman K, Hallas WM, Joseph S, Yang C, Kurkewich J, Cowden Dahl KD. ARID3B Directly Regulates Ovarian Cancer Promoting Genes. PLoS One. 2015;10(6):e0131961

Burns CJ, Zhang J, Brown EC, Van Bibber AM, Van Es J, Clevers H, Ishikawa TO, Taketo MM, Vetter ML, Fuhrmann S. Investigation of Frizzled-5 during embryonic neural development in mouse. Dev Dyn. 2008 Jun;237(6):1614-26.

Carmon KS, Loose DS. Wnt7a interaction with Fzd5 and detection of signaling activation using a split eGFP. Biochem Biophys Res Commun. 2008 Apr 4;368(2):285-91.

Ford CE, Henry C, Llamosas E, Djordjevic A, Hacker N. Wnt signalling in gynaecological cancers: A future target for personalised medicine? Gynecol Oncol 2016 Feb.

González-Fernández C, Mancuso R, Del Valle J, Navarro X, Rodrèguez FJ. Wnt Signaling Alteration in the Spinal Cord of Amyotrophic Lateral Sclerosis Transgenic Mice: Special Focus on Frizzled-5 Cellular Expression Pattern. PLoS One 2016 May 18;11(5): e0155867.

He X, Saint-Jeannet JP, Wang Y, Nathans J, Dawid I, Varmus H. A member of the frizzled protein family mediating axis induction by Wnt-5A. Science 1997 Mar 14;275(5306):1652-4.

Ishikawa T, Tamai Y, Zorn AM, Yoshida H, Seldin MF, Nishikawa S, Taketo MM. Mouse Wnt receptor gene Fzd5 is essential for yolk sac and placental angiogenesis. Development 2001 Jan;128(1):25-33.

Jiang X, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, Lu B, Hsieh MH, Bagdasarian L, Meyer R, Smith TR, Avello M, Charlat O, Xie Y, Porter JA, Pan S, Liu J, McLaughlin ME, Cong F. Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma. Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12649-54.

Lazzaroni F, Del Giacco L, Biasci D, Turrini M, Prosperi L, Brusamolino R, Cairoli R, Beghini A. Intronless WNT10B-short variant underlies new recurrent allele-specific

rearrangement in acute myeloid leukaemia. Sci Rep. 2016 Nov 17; 6:37201.

Lee HJ, Zheng JJ. PDZ domains and their binding partners: structure, specificity, and modification. Cell Commun Signal. 2010 May 28; 8:8.

Liu C, Widen SA, Williamson KA, Ratnapriya R, Gerth-Kahlert C, Rainger J, Alur RP, Strachan E, Manjunath SH, Balakrishnan A, Floyd JA; UK10K Consortium, Li T, Waskiewicz A, Brooks BP, Lehmann OJ, FitzPatrick DR, Swaroop A. A secreted WNT-ligand-binding domain of FZD5 generated by a frameshift mutation causes autosomal dominant coloboma. Hum Mol Genet. 2016 Apr 1;25(7):1382-91.

Liu Y, Chen SH, Jin X, Li YM. Analysis of differentially expressed genes and microRNAs in alcoholic liver disease. Int J Mol Med. 2013 Mar;31(3):547-54.

Long, Q.Z.; Du, Y.F.; Liu, X.G.; Li, X.; He, D.L.. miR-124 represses FZD5 to attenuate P-glycoprotein-mediated chemo-resistance in renal cell carcinoma. Tumour Biol. 2015, 36, 7017-7026.

Menezes Mde P, Oshima CT, Filho LB, Gomes TS, Barrezueta LF, Stávale JN, Gonçalves WJ. Canonical and noncanonical Wnt pathways: a comparison between endometrial cancer type I and atrophic endometrium in Brazil. Sao Paulo Med J. 2011;129(5):320-4.

Povelones M, Howes R, Fish M, Nusse R. Genetic evidence that Drosophila frizzled controls planar cell polarity and Armadillo signaling by a common mechanism. Genetics. 2005 Dec;171(4):1643-54. Epub 2005 Aug 5.

Rehn M, Pihlajaniemi T. Identification of three N-terminal ends of type XVIII collagen chains and tissue-specific differences in the expression of the corresponding transcripts. The longest form contains a novel motif homologous to rat and Drosophila frizzled proteins. J Biol Chem. 1995 Mar 3;270(9):4705-11.

Saitoh T, Hirai M, Katoh M. Molecular cloning and characterization of human Frizzled-5 gene on chromosome 2q33.3-q34 region. Int J Oncol. 2001 Jul;19(1):105-10.

Slater PG, Ramirez VT, Gonzalez-Billault C, Varela-Nallar L, Inestrosa NC. Frizzled-5 receptor is involved in neuronal polarity and morphogenesis of hippocampal neurons. PLoS One. 2013 Oct 18;8(10): e78892.

Steinhart Z, Pavlovic Z, Chandrashekhar M, Hart T, Wang X, Zhang X, Robitaille M, Brown KR, Jaksani S, Overmeer R, Boj SF, Adams J, Pan J, Clevers H, Sidhu S, Moffat J, Angers S. Genome-wide CRISPR screens reveal a Wnt-FZD5 signaling circuit as a druggable vulnerability of RNF43-mutant pancreatic tumors. Nat Med. 2017 Jan;23(1):60-68.

Terabayashi T, Funato Y, Fukuda M, Miki H. A coated vesicle-associated kinase of 104 kDa (CVAK104) induces lysosomal degradation of frizzled 5 (Fzd5). J Biol Chem. 2009 Sep 25;284(39):26716-24.

Thiele S, Rauner M, Goettsch C, Rachner TD, Benad P, Fuessel S, Erdmann K, Hamann C, Baretton GB, Wirth MP, Jakob F, Hofbauer LC. Expression profile of WNT molecules in prostate cancer and its regulation by aminobisphosphonates. J Cell Biochem. 2011 Jun;112(6):1593-600.

Ueno K, Hirata H, Hinoda Y, Dahiya R. Frizzled homolog proteins, microRNAs and Wnt signaling in cancer. Int J Cancer. 2013 Apr 15;132(8):1731-40.

Umbhauer M, Djiane A, Goisset C, Penzo-Méndez A, Riou JF, Boucaut JC, Shi DL. The C-terminal cytoplasmic Lys-Thr-X-X-X-Trp motif in frizzled receptors mediates Wnt/beta-catenin signalling. EMBO J. 2000 Sep 15;19(18):4944-54.

Wang L, Shalek AK, Lawrence M, Ding R, Gaublomme JT, Pochet N, Stojanov P, Sougnez C, Shukla SA, Stevenson KE, Zhang W, Wong J, Sievers QL, MacDonald BT, Vartanov AR, Goldstein NR, Neuberg D, He X, Lander E, Hacohen N, Regev A, Getz G, Brown JR, Park H, Wu CJ. Somatic mutation as a mechanism of Wnt/beta-catenin pathway activation in CLL. Blood. 2014 Aug 14;124(7):1089-98.

Yamamoto H, Komekado H, Kikuchi A. Caveolin is necessary for Wnt-3a-dependent internalization of LRP6 and accumulation of beta-catenin. Dev Cell. 2006 Aug;11(2):213-23.

Zhang Y, Tu C, Zhang D, Zheng Y, Peng Z, Feng Y, Xiao S, Li Z. Wnt/?-Catenin and Wnt5a/Ca Pathways Regulate Proliferation and Apoptosis of Keratinocytes in Psoriasis Lesions. Cell Physiol Biochem. 2015;36(5).

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