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Gene Section
Review

FZD6 (Frizzled class receptor 6)

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Abstract

Frizzled-6 (FZD6) gene, located on chromosome 8 (8q22.3-q23.1), encodes a seven-transmembrane-spanning protein belonging to the frizzled family of receptors for the Wnt (Wingless/Int-1) ligands. FZD6 is classified as G-protein-coupling receptor with a prevalent role in the non-canonical Wnt signaling pathway, a series of steps that affect the way cells and tissues develop. Specifically, FZD6-mediated Wnt signaling is important for cell division (proliferation), adhesion and cellular movement (migration). It is active in many tissues and is involved during embryonic development, immune cells maturation and hematopoietic regeneration.
After the Wnt-ligands binding, FZD6 protein is triggered at the cell surface to send signals into the cell and to initiate the Wnt signaling pathway. The encoded protein contains a signal peptide, a cysteine-rich domain (CRD) in the extracellular N-terminal region, and seven transmembrane domains, but unlike other family members, this protein does not contain a C-terminal PDZ binding-domain motif. This protein acts as a negative regulator of the canonical Wnt/beta-catenin signaling cascade, thereby inhibiting the processes that trigger oncogenic transformation and inhibition of apoptosis. Alternative splicing results in multiple transcript variants, some of which do not encode a protein with a predicted signal peptide.

Keywords
FZD6, frizzled family receptor; Wnt Signalling Pathway; Leukemia; self renewal stem cells

Identity

Other names: Hfz6

HGNC (Hugo): FZD6

Location: Long (q) arm of chromosome 8 at position 22.3; 8q22.3

Location (base pair)
Plus strand, starts at 103,298,433 and ends at 103,332,866 bp from pter (according to hg19-Dec)

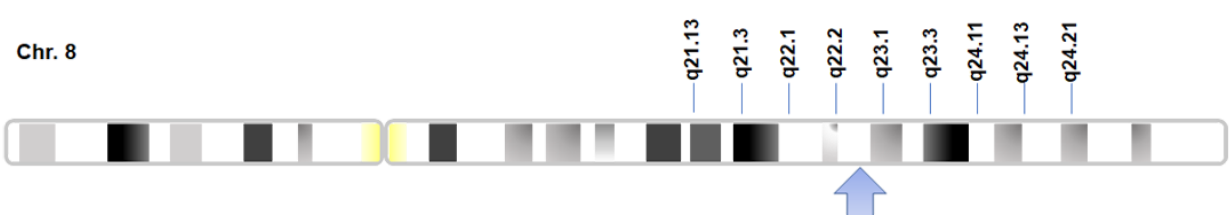

Figure 1. FZD6 gene chromosomal location.

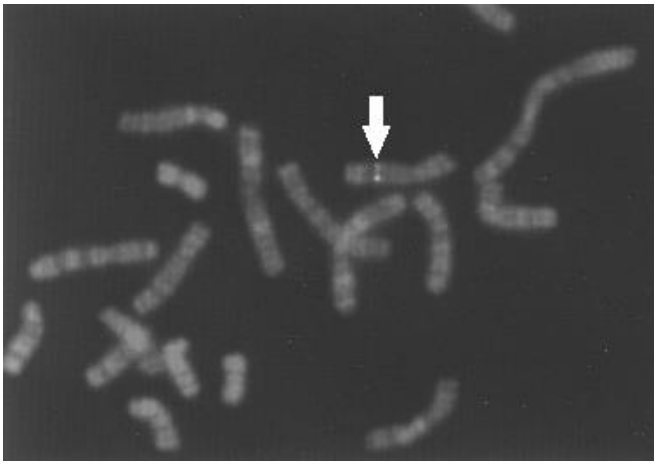

Figure 2. Chromosomal localization of FZD6 determined by FISH. Here the plasmid HF6-1 was used as a probe and the specific hybridization signals were observed on chromosome 8 at band 22.3 (Tokuhara et al., 1998).

DNA/RNA

Description

FZD6 is a protein coding gene that comprises 8 exons extending for about 41 kb of genomic DNA. It is located on human chromosome 8q22.3, it has 7 transcripts, 82 orthologues, 12 paralogues and is associated with 3 phenotypes.

Transcription

Six transcripts have been found for this gene (font: FZD6_transcript_ensembl)

FZD6-201	Link FZD6-201	mRNA 3788 bp	Protein 706 aa	Protein coding
FZD6-205	Link FZD6-205	mRNA 3719 bp	Protein 706 aa	Protein coding
FZD6-206	Link FZD6-206	mRNA 2774 bp	Protein 674 aa	Protein coding
FZD6-204	Link FZD6-204	mRNA 3646 bp	Protein 467 aa	Nonsense mediated decay
FZD6-203	Link FZD6-203	mRNA 2682 bp	Protein 64 aa	Nonsense mediated decay
FZD6-202	Link < FZD6-202	mRNA 2006 bp	Protein 60 aa	Nonsense mediated decay
FZD6-207	Link FZD6-207	mRNA 1472 bp	Protein 100 aa	Nonsense mediated decay

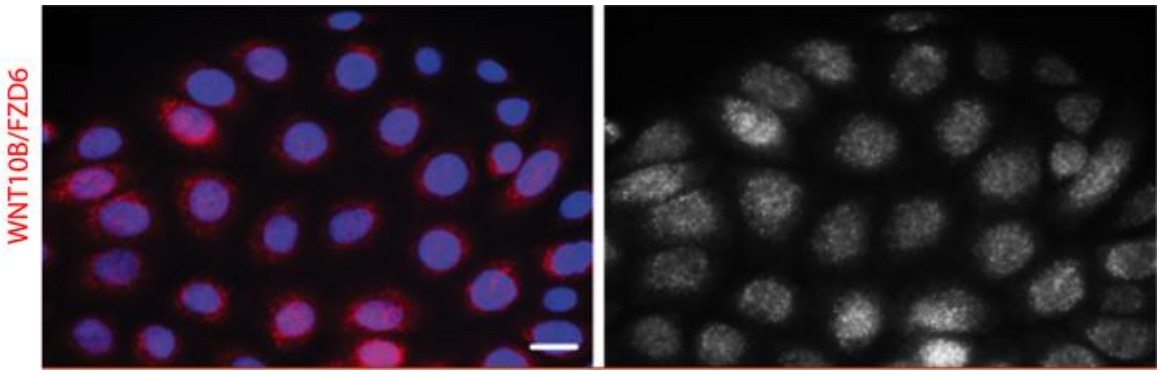

Figure 3. WNT10B-FZD6 interacting complexes in MOLT4 cell line (model of human acute T lymphoblastic leukaemia) were targeted by in situ Proximity ligation assay (PLA) with specific PLA probes. Rolling Circle Products (RCPs) were revealed with Cγ3 detection probes [Beghini A. unpublished data].

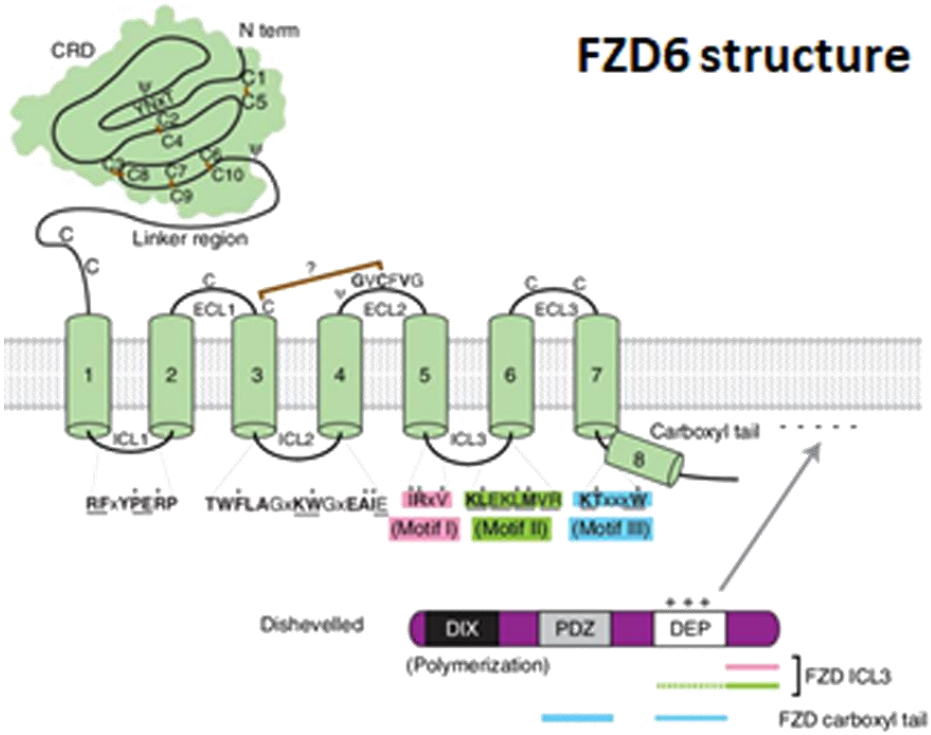

Figure 4. FZD6 structure. The CRD is shaded in green, the 10 cysteine (C) residues forming five disulfide bonds is highlighted. DVL protein is also illustrated with DIX, PDZ and DEP domains and the non-interaction with FZD6 carboxyl tail is reported with a barred arrow. &PSI;= Potential N-glycosylation sites; ECL = extracellular loop; ICL = intracellular loop (MacDonald et al., 2012).

Protein

Description

The Frizzled (FZD) gene was initially isolated as a Drosophilla tissue polarity gene (Adler et al., 1990) and later was characterized the human FZD gene homologue (Zhao et al., 1995).

The Frizzled proteins are the receptors for WNT glycoproteins. Most of FZD are coupled with the β-catenin canonical signaling pathway, which leads to nuclear translocation of these effectors and activation of Wnt target genes. Others two non-canonical signaling pathways β-catenin-independent (Wnt-Ca^{2+} and planar cell polarity) involves PKC and intracellular calcium stores or the Rho family of GTPase, to regulate intracellular calcium levels or actin cytoskeleton reorganization.

The FZD6 gene encodes a 706 amino-acid protein with seven transmembrane domains (amino acids 202-222, 234-254, 284-305, 325-345, 371-391, 417-437, 474-494) with a highly conserved cystein-rich domain (cysteine-rich domain, CRD) in the N-terminal extracellular region (amino acids 1-18), which is necessary to the binding with Wnt-ligands. Almost all FZD receptors share a C-terminal portion (amino acids 495-706), spanning the KTxxxW motif, that is a binding site for the cytoplasmatic protein containing the PDZ domain (like a Dishevelled protein). However, unlike many other Fz family members (Tokuhara et al., 1998), FZD6 does not contain a C-terminal PDZ domain-binding motif.

The molecular mass of FZD6 protein is 79 kDa and alternative splicing results in multiple transcript variants, some of which are not involved in the encoding of proteins (see transcription section).

Expression

In Tokuhara's study (Tokuhara et al., 1998), 4,4 kb FZD6 mRNA was detected in several adult human tissues, like heart, brain, placenta, lung, liver, pancreas, kidney, thymus, colon, testis, ovary and other. In the fetus is expressed in brain, lung, liver and kidney. Furthermore, it was detected in many cancer cell lines among which MOLT4 (human acute T lymphoblastic leukaemia), A549 (lung cancer), SW480 (colon cancer), G361 (melanoma) and HeLa (cervical cancer) (Figure 5).

In Wagner's study (Wagner et al., 2004), the FZD6 gene overexpression was determined in slow-dividing fraction (SDF) of hematopoietic progenitor cells (HPCs) within the $CD34^{+}$ /$CD38^{-}$ population.

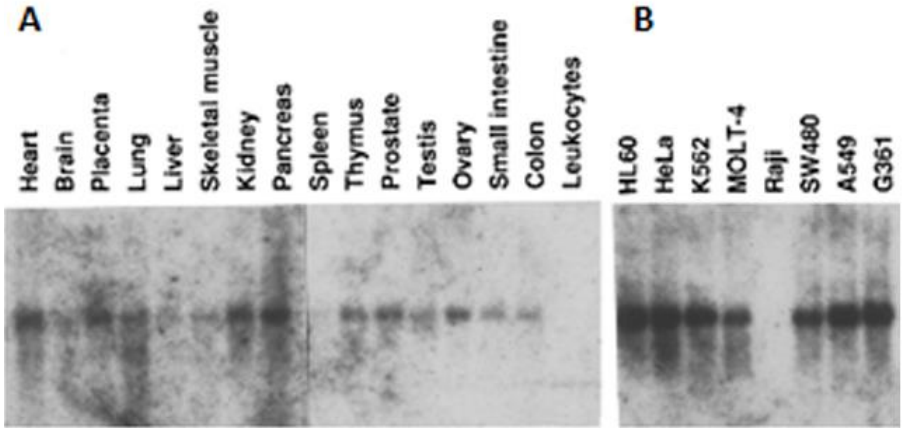

Figure 5. FZD6 mRNA expression analysis. (A) Adult human tissue. **(B)** Human cancer cell lines. The arrow indicates the FZD6 mRNA 4,4 kb position (Tokuhara et al., 1998).

Localisation

FZD6 is a multi-pass membrane protein, with seven transmembrane domains which have cysteine-rich domains (CRD) in N-terminal extracellular region and carboxyl tail in intracellular region. Trough the CRD, FZD6 receptor binds Wnt ligands in extracellular microenvironment.

Function

Frizzled receptors mediate Wnt ligand signalling, which is crucially involved in regulating tissue development and differentiation, and is often deregulated in cancer.

Fzd6 is generally associated with PCP (planar cell polarity) signaling in epithelial cells: for example, it was shown that controls macroscopic hair patterning in the mouse. Both epithelial cells and melanocytes are FZD6 expression sites (Guo et al., 2004).

Data from Golan's study (Golan et al., 2004), suggest that human FZD6 activates the transforming growth factor-β-activated kinase-NEMO-like kinase (NLK) pathway that blocks nuclear LEF1 (TCF/LEF, T cell factor/lymphoid enhancer factor) binding to target promoters, thus repressing the ability of CTNNB1 (β-catenin) to activate transcription of Wnt target genes. The FZD6 protein blocks canonical Wnt pathway through cross-talks with repressors Wnt signaling downstream of the β-catenin destruction complex. Indeed, human FZD6 does not change the cellular levels of β-catenin, suggesting that the ectopically expressed FZD6 does not destabilize the β-catenin. In this respect, the FZD6 does not interfere with nuclear translocation of β-catenin or theirs TCF-binding, but the repressive activity is mediated by inhibition of TCF/LEF binding and TCF/β-catenin complexes formation to target DNA.

Furthermore, Kilander's study (Kilander et al., 2014) identified FZD6 as a G-protein-coupled receptors (GPCR) and Disheveled (DVL1) protein as a master regulator of FZD6/G-protein coupling, which at high levels can also act as negative regulator of Wnt/FZD-induced G protein signaling. DIX domain of DVL is responsible for the negative regulation of FZD6-G-protein precoupling.

Frizzled-6 (Fzd6), regulates hematopoietic stem/progenitor cell (HSPC) expansion and survival in a hematopoietic cell-intrinsic manner.

Abidin's research (Abidin et al., 2015) showed that $FZD6^{-/-}$ HSCs are able to localize in the bone marrow but it does not reconstitute a lethally irradiated host. The FZD6 deficiency impaires the expansion and survival of HSCs, resulting in activation of caspase-3 (CASP3) and weak HSCs engraftment after bone marrow transplant in C57BL/6 mice.

The non-canonical Wnt receptor FZD6, is also necessary for HSC expansion during emergency hematopoiesis.

FZD6 is involved in the neural tube closure and plays a role in the regulation of the establishment of planar cell polarity (PCP), together with FZD3, particularly in the orientation of asymmetric bundles of stereocilia in a group of auditory and vestibular sensory cells located in the inner ear (De Marco et al., 2011).

Homology

The FZD6 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, and frog.

Mutations

De novo frameshift mutation c.1843_1844insA (p.Cys615X)= it introduces a premature stop codon and encodes for a truncated protein that lacks the last 51 amino-acids in carboxyl-terminal tail.

De novo frameshift mutation c.1843_1844insA (p.Cys615X)= it introduces a premature stop codon and encodes Missense changes c.1214G>A (p.Arg405Gln) = the mutation changes a positively charged residue into a hydrophilic uncharged residue. Its prediction suggests that it is probably a pathogenic protein.

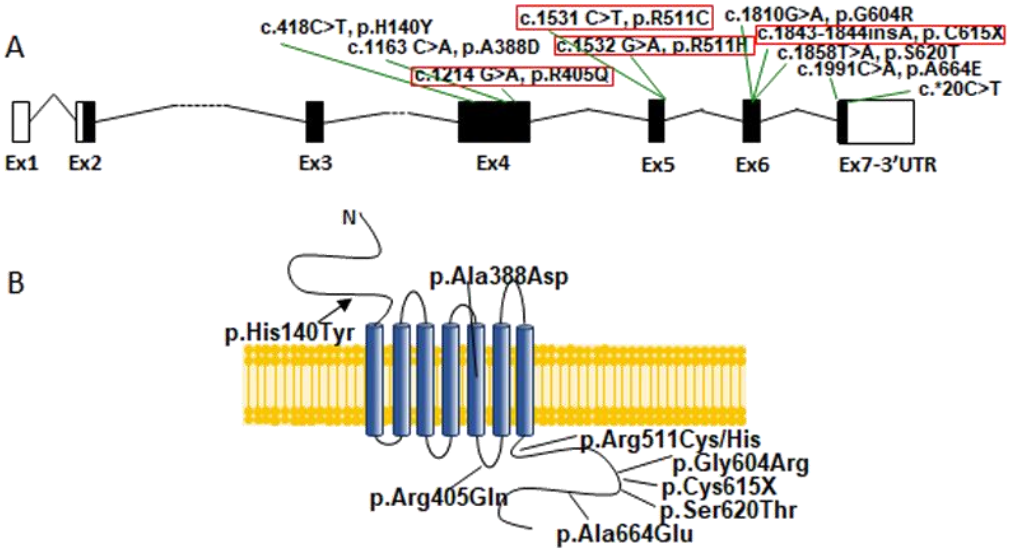

Figure 6. FZD6 variants. Schematic model of FZD6 gene **(A)** and protein **(B)** with the locations of the rare variants involved in Neural tube defects (NTDs). In red are framed FZD6 mutations which are absent in controls of NTDs and which are predicted to have a functional effect. CRD= cysteine-rich domain (De Marco et al., 2011).

Missense changes c.1531C>T (p.Arg511Cys)= this variant introduces a cysteine in a conserved region and may result in abnormal conformational changes of the protein. Missense changes c.1532G>A (p.Arg511His)= the variant represents an exchange of two basic amino-acids in a conserved region.
Single nucleotide substitution (c.20C>T) = affecting the 3' UTR of the FZD6 gene. This substitution changed the target site for miR628, whichcould cause changes in FZD6 gene regulation.
Homozygous nonsense mutation c.1750G>T (p. Glu584X) = mutation involved in autosomal-recessive nail dysplasia. The G>T transition in exon 6 of FZD6 changes the codon GAA (encoding glutamic acid) to TAA (stop codon). This induces the truncated protein formation, lacking the C-terminus. To determine his functional effect, Naz' s group (Naz et al., 2012) carried out immunofluorescence analysis, which revealed the presence of a mutant FZD6 protein in the cell membrane. The KTxxxW motif is also present in FZD6 mutant form, so could be that Wnt ligands may still be able to bind to truncated protein, leading to recruitment of DVL protein but no of other cytoplasmic mediators such as G proteins (Figure 7).
Missense mutation c.1531C>T (p.Arg511Cys) = mutation involved in autosomal-recessive nail dysplasia. The changed arginine residue is conserved in several species, supporting the potential functional importance of this variant. It was observed that FZD6 changed protein with this mutation is confined to intracellular vesicles (lysosomes), where is probably degraded (Figure 7. Fröjmark et al., 2011). Then was also seen that FZD6-Arg511Cys mutation is incapable of G-protein precoupling, even though it still binds DVL (Kilander et al., 2014)
Missense mutation c.1266G>A (p.Gly422Asp) = mutation involved in autosomal-recessive nail dysplasia. The changed glycine residue is conserved in several species, supporting the potential functional importance of this variant. Variant is located in the sixth transmembrane domain of the mutant FZD6 protein, suggesting that FZD6 mutant can affect binding of Wnt ligand. It is highly likely that also this mutant FD6 is confined and degraded in the lysosome.(Figure 7. Raza et al., 2012).

Implicated in

Chronic Lymphoproliferative Disorders (CLD)

The Wu's study (Wu et al., 2009) showed that, during the leukemogenesis in Eμ-TCL1 mouse model of chronic lymphocytic leukemia, the expression of FZD6 is dramatically up-regulated in the transformed CD5+ B cells of this animal model. FZD6 gene ablation strongly decreases the development and tumor growth of chronic lymphocytic leukemia. The dramatic up-regulation of FZD6 was recorded both during a preleukemic clonal expansion and during the transformation to a monoclonal leukemia. Mouse FZD6 differs from its human homolog, which is able to inhibit the canonical signaling pathway. Indeed, in Eμ-TCL1 mouse model, it was highlighted the over-expression of intracellular β-catenin levels in $FZD6^{+/+}$ leukemic B cells, while in $FZD6^{-/-}$ leukemic cells the β-catenin levels were physiological. This evidence suggests that mouse FZD6 receptor up-regulation activates the Wnt canonical pathway.

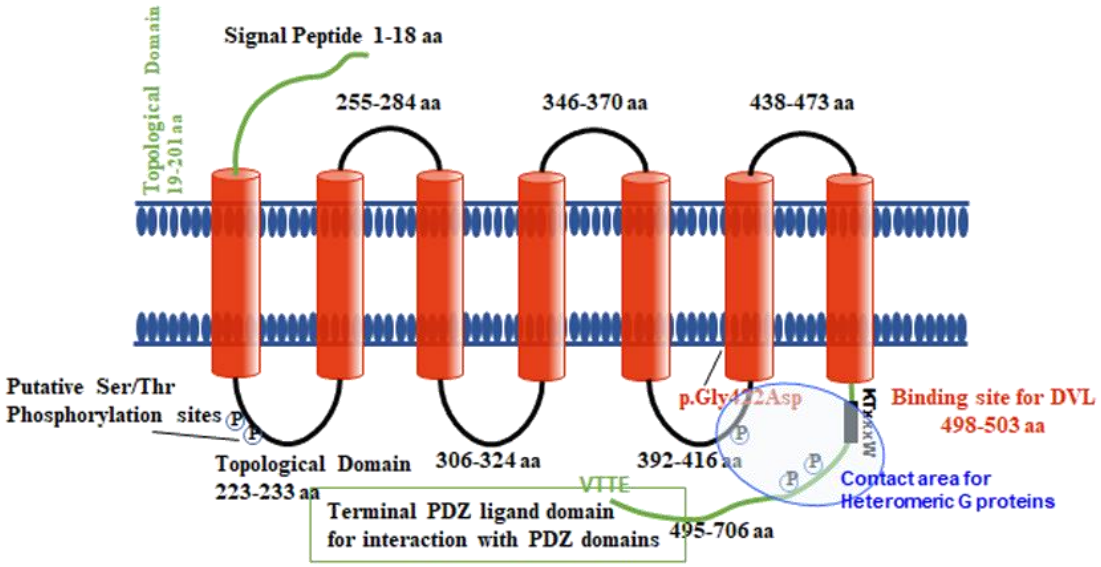

Figure 7. Representation of the human FZD6 protein domains. Positions of the FZD6 mutations involved in autosomal-recessive nail dysplasia are shown with an arrow.

Breast Cancer

Corda's study (Corda et al., 2017) describes that, in according to Sanger Institute Cosmic repository, about 20% of breast sample showed FZD6 copy number gains or gene overexpression. Particularly, FZD6 copy number increase was more frequent in triple-negative (TNBC; 87.1%) than in non-triple-negative (61.7%) or ER-positive (72%) breast cancer cases. Expression of Wnt non-canonical FZD6 ligands, as WNT11 and WNT5B, was also increased in TNBC samples, suggesting that a non-canonical pathway may be involved downstream of FZD6 receptor. Furthermore, they investigated FZD6 role in motility, proliferation and invasion of breast cancer cell lines. The depletion or inhibition with short-hairpin RNAs (shRNAs) or small interfering RNAs (siRNAs) respectively caused a significant reduction of these functions. Next they used an organoid 3D cultures to determine the degree of transformation of breast cancer cells: the overexpression of FZD6 induces disorganized 3D growth, supporting a more aggressive phenotype and suggesting the hypothesis that the receptor is a mammary protooncogene. Finally, they carried out immunohistochemical analysis with an FZD6 antibody in a retrospective Italian cohort with node-negative early breast cancer. Kaplan-Meier analysis indicated that FZD6 expression was associated with reduced distant relapse-free survival (DFRS) in the TNBC patient subtype. In other subgroup, there was not significant association.

However, the Wnt10B/FZD6 interaction in adherent and tumorsphere culture of MCF-7 breast cancer cell line has been investigated, using proximity ligation assay (PLA) (Lazzaroni et al., 2016), results did not detect any interacting complexes in MCF7.

Colorectal cancer (CRC)

The CRC is one of the most common neoplasms worldwide and Wnt signalling is among the biochemical pathways involved in pathogenesis, because it drives a stem molecular program in several intestinal cells. FZD6 is highly expressed in CRC tissue and cell lines, such as FZD3 and FZD7, but its role in the disease is still unclear (Vincan et al., 2008).

Prostate tumors

In Wissmann's study (Wissmann et al., 2003) a FZD6 high gene expression was detected by chip hybridization in primary prostate cancer samples. At the RNA level in microdissected prostate tumor samples, FZD6 was found up-regulated.

This evidence was confirmed in another study (Saramäki et al., 2006): the analysis was performed by cDNA microarray expression on prostate cancer cell lines (LNCaP, DU145, PC-3, 22Rv1 and LAPC-4) and xenografts. The FZD6 gene showed significant association between increased copy number and overexpression.

Neuroblastoma

According to Cantilena's work (Cantilena et al., 2011), the presence of FZD6 anticipates poor survival in neuroblastoma patients and remarks HIF1/2 α-positive cells in cancer hypoxic areas.

Neuroblastoma is an early cancer developing neural crest and Wnt signalling plays an important role in formation and migration of these multipotent cells. The study initially found out that only FZD6, among FZD family receptors, was statistically significantly associated with poor survival of neuroblastoma patients.

FZD6 positive neuroblastoma cells are rare highly tumorigenic stem-like cells, which form resistant-doxorubicin neurospheres. FZD6 activity is crucial in neurospheres formation, because this phenomenon is very reduced in cell transfected with FD6-siRNA, as well as the expression of non-canonical Wnt-target genes CD44 and TH. FZD6 expression is also associated with aggressive growth and capacity to metastasize in vivo, as highlighted by high expression of NOTCH1, ki67 (proliferation marker) and mesenchymal stem cell marker TWIST1 in $FZD6^+$ cells.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) originates mostly in cirrhotic livers and the dysregulation of pleiotropic growth factors, such as Wnt signaling pathway, plays an essential role in hepatocarcinogenesis. Wnt is involved in proliferation and antiapoptotic behavior of cancer cells. In Bengochea's research (Bengochea et al., 2008), was detected the FZD6/FZD3/FZD7 overexpression in HCC cells in association with the concomitantly upregulation of three Wnt agonists (WNT3, WNT4 and WNT5A) and downregulation of two Wnt antagonists (SFRP1 and SFRP5). Furthermore, the study showed that at least one over the three Wnt/FZD pathways (canonical β-catenin, or noncanonical PKC and JNK) during carcinogenesis is activated in most cases of HCC samples.

Squamous cell carcinoma

Squamous cell carcinoma (SCC) typically has an aggressive behavior and is made up of epithelial cells, which are hyperplastic and invasive. Upregulation of FZD6 RNA level in malignant samples was detected by global gene expression profiling performed on SCC cells and on normal skin cells from patients. The FZD6 expression was not increased in psoriasis samples and it was absent in benign hyperplasia. According to this data, it is possible that FZD6 is involved in noncanonical Wnt-signalling in SCC (Haider et al., 2006).

Neural tube defects (NTDs)

Neural tube defects (NTDs) are a set of pathological conditions of the central nervous system (CNS) and are one of the most common birth defects, affecting 1 of 1000 live births. De Marco's study (De Marco et al., 2011) identified five rare FZD6 variants predicted to have a functional effect by computational analysis, suggesting an involvement of FZD6 mutations in NTDs pathogenesis. One of the main cellular event occurring during early development of CNS is convergent extension, that is mediated by planar cell polarity (PCP) pathway and its Frizzled receptors family. Expression studies in humans showed that FZD6 is highly expressed in both embryonic and adult tissues, including brain and CNS (Tokuhara et al., 1998).

The five rare FZD6 variants are: one de novo frameshift mutation that introduces a premature stop codon (Cys615X), three missense variants (Arg405Gln, Arg511Cys and Arg511His) and a single nucleotide substitution (20C>T), affecting 3'UTR (see mutations section). Most of the mutations are located in the FZD6 protein intracellular domains and they are absent in all the investigated controls and suggesting a high involvement of FZD6 gene in the pathogenesis of a minority of NTDs (De Marco et al., 2011).

Based on this evidence, Shi's study (Shi et al., 2014) analyzed FZD6 single nucleotide polymorphisms (rs827528, rs3808553 and rs12549394) in a group of 135 NTD patients and 135 controls in the Han population of northern China. The children with genotype rs3808553 (G>T, localized at residue 345 of exon 4) had an increased risk of NTDs, but the other two genotypes did not shown correlation with NTDs. The s3808553 polymorphism in the fourth transmembrane domain of FZD6 protein could be a potential genetic risk factor for NTDs in this Chinese population.

Autosomal recessive nail dysplasia

Isolated nail dysplasia is a rare disorder and the FZD6 gene was identified in families with autosomal-recessive nail dysplasia. Naz et al. (2011), investigated two Pakistani families with this disorder and performed a genetic analysis on the chromosome 8q22.3, where FZD6 gene is located. Sequence analysis identified a homozygous nonsense mutation (c.1750G>T) in exon 6 of FZD6 in all affected individuals from both family. This transition changes the codon GAA (encoding glutamic acid) to TAA (stop coding), producing a premature block of translation and a truncated protein lacking the C-terminus. The glutamic acid residue is highly conserved among species, thus indicating its functional importance. In vitro assays have shown that the FZD6 mutant protein abolishes FZD6 repressive activity on canonical Wnt/β-catenin pathway. It is already known that the loss of inhibition of the canonical signaling, due to FZD6 mutant, leads to excessive nail growth in humans.

The previous study also confirmed another homozygous missense mutation (c.1531C>T [p.Arg511Cys]) and a nonsense mutation (c.1750G>T [p.Glu584X]), identified by Fröjmark' s research (Fröjmark et al. 2011) by two Pakistani families similarly affected by autosomal-recessive isolated nail dysplasia. Both FZD6 mutations result in alterations of the intracellular tail, which could cause an increased protein degradation, that is an improper receptor integration into the cell membrane or a reduced capability to DVL recruitment.

The Raza's study (Raza et al., 2012) carried out on six Pakistani individuals, showed a FZD6 missense mutation c.1266G>A (p.Gly422Asp). Furthermore, a panel of 300 unaffected control individuals was screened, to exclude the possibility that the missense mutation does not represent a nonpathogenic polymorphism and the mutation c.1266G>A was not identified (see mutations section).

Depression

FZD6 mRNA level were significantly increased in the hippocampus, following chronic electroconvulsive seizure (Chr-ECS), one of the most effective treatments for depressed patients. Indeed, Chr-ECS increases the level of transcription factor CREB1, which is able to regulate the gene expression of FZD6, whereas FZD6 mRNA level was decreased in a depressed rodent model after exposure to chronic unpredictable stress (CUS). ShRNA strategy experiments were performed to achieve FZD6 mRNA knockdown in the adult rat hippocampus and the FZD6 mRNA levels reduction was confirmed. In this animal model, the knockdown of FZD6 causes anhedonic behavior, a core symptom of depression. Furthermore, the anxiety in the novelty suppressed feeding test was increased, a typical behavior of CUS exposure. This evidence suggests that FZD6 could represent a novel target for development of novel antidepressants (Voleti et al., 2012).

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