Frizzled proteins: structure and function

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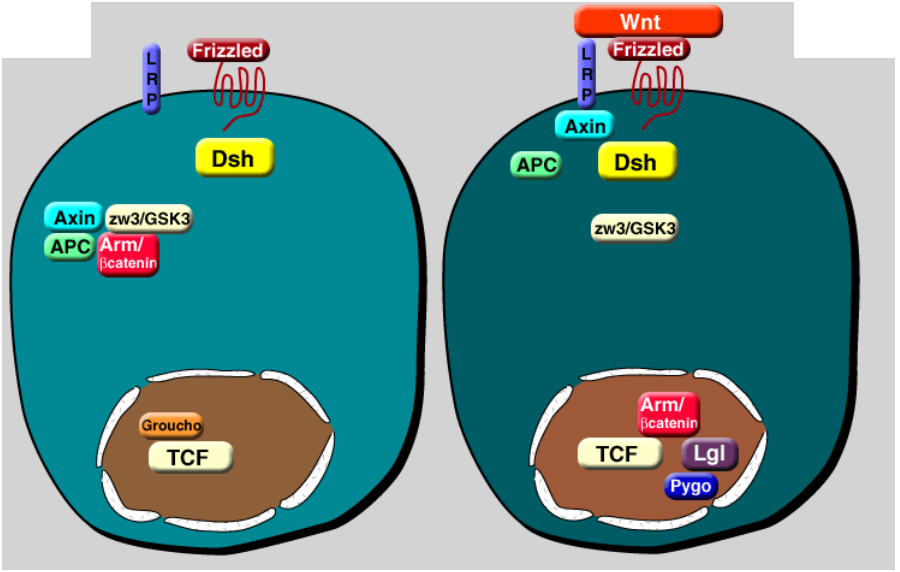
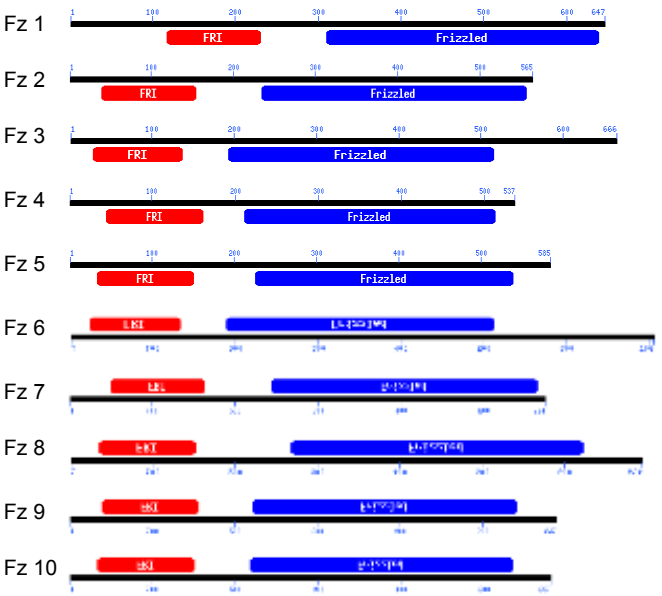
FRIZZLED and Wnt PROTEINS

- Frizzled are seven-transmembrane receptors.
- Frizzleed act as receptors for Wnt proteins.
- Wnts binds the CRD (cysteine-rich domain) of Frizzled, an extracellular part of the receptor.
- SFRP/FrzB molecules consist of the CRD only and can act as secreted antagonists of Wnt signaling.
- Little is known about the mechanism of Frizzled signaling.
- Some but not all Frizzleds stimulate Ca^{2+} release and PKC activity.

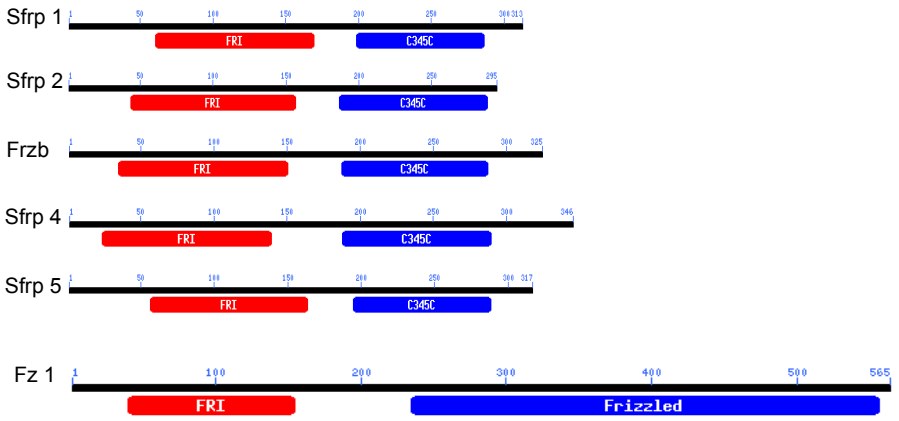
Wnt signalling: essential components in a two-state model

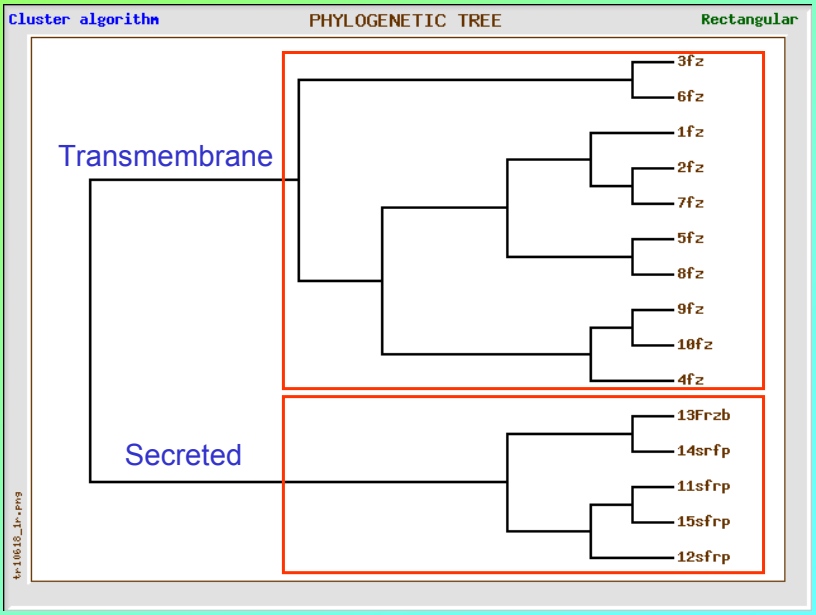


Human Frizzled proteins

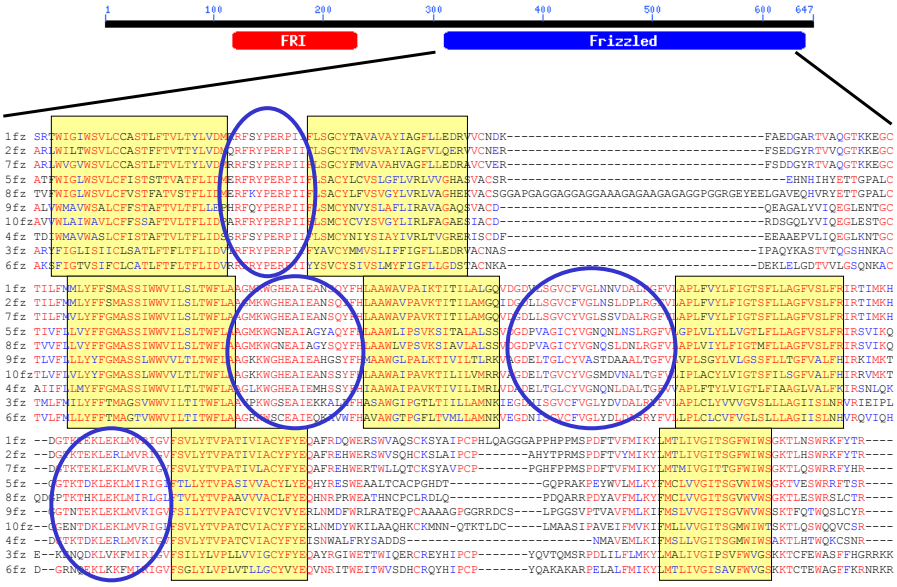


Secreated Frizzled related proteins (Sfrp)





Frizzled : transmembrane domain



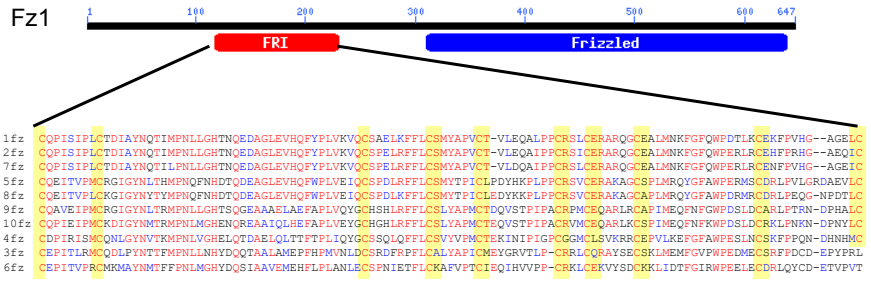
Frizzled are putative 7-transmembrane receptor

According to Sosui
transmembrane domains & topology tool prediction:

Human frizzled	Number of predicted transmembrane domains
1	6
2	9
3	9
4	8
5	8
6	8
7	9
8	8
9	9
10	8

Protein	Predicted (assumed)
Muscarinic acetylcholine receptor M1	7 (7)
Tetraspanin	4 (4)
ETL	9 (7)
Rhodopsin	7 (7)

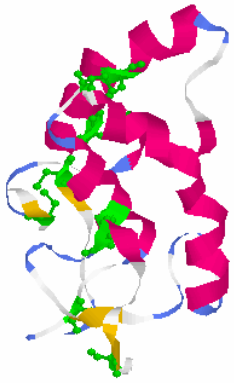
Frizzled : Cys-rich domain



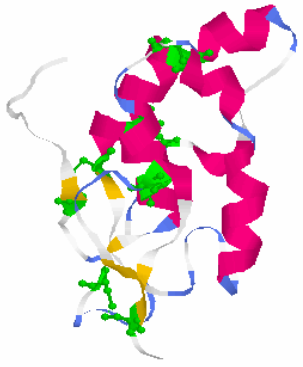
3D models of cysteine-rich domains (CRD) based on the crystal structure of the CRD mouse of Secreted Frizzled-Related Protein 3

Predicted by SWISS-MODEL tool
Rendered in RasMol

Frizzled 1

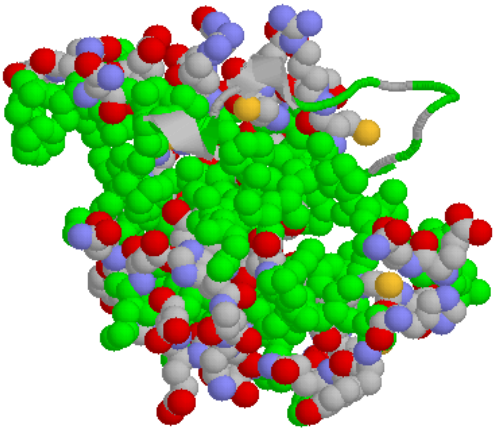


Frizzled-related protein 1

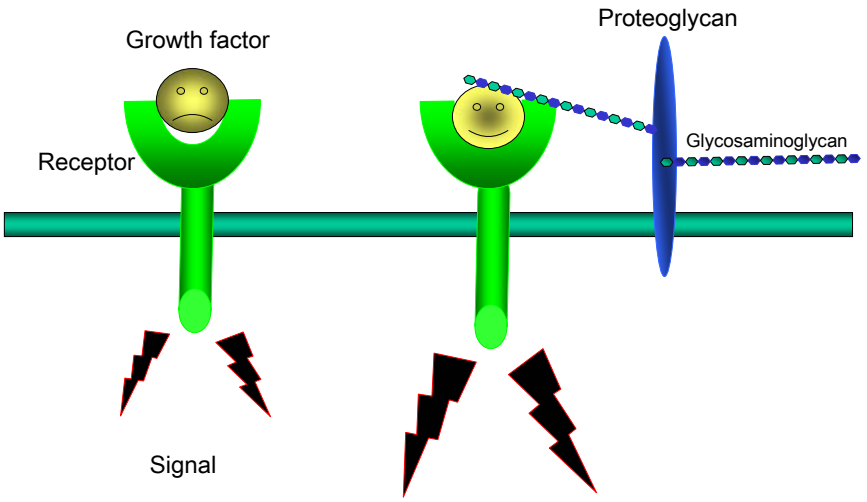


Modification of Wnt proteins with palmitate is essential for their activity

A putative palmitate binding site on the CRD of Frizzled 1

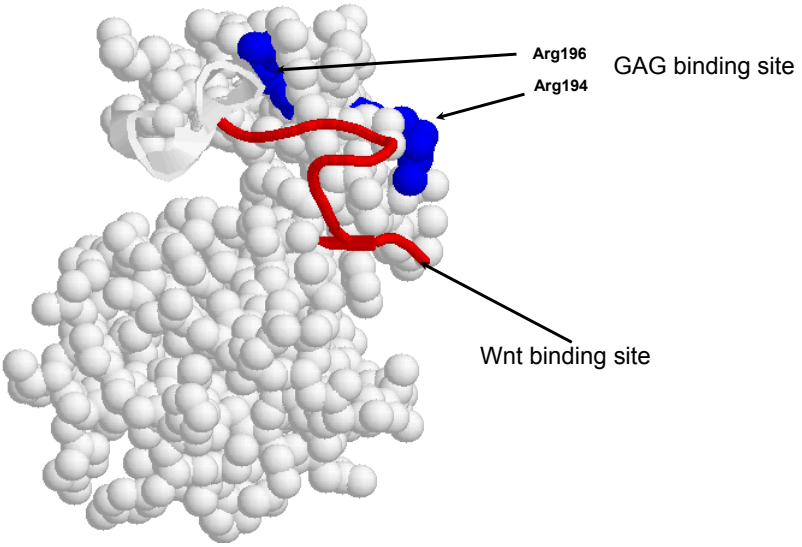


Many growth factors requires glycosaminoglycan for signalling



A putative glycosaminoglycan (GAG) binding site of Frizzled CRD

Consensus sequence of GAG binding site: **RXR**



THANK YOU!

Sfrp : Netrin C-terminal domain


```
1sfrp  GTTVCPPCDNELKSEA-IIEHLCASEFALRMKIKEVKKENGDKKIV--PKKKKPLKLGPIKKKDLKKLVLYLKNGADCPCHQLDNLSHHFLIMGR
5sfrp  VTKICAQCEMEHSADG-LMEQMCSSDFVVKMRIKEIKIENGDRKLIGAQKKKKLLKPGPLKRKDTKRLVLHMKNGAGCPCPQLDSLAGSFLVMGR
2sfrp  APKVCEACKNKNDDDNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLNGVSERDLKKSVLWLKDSLQCTCEEMNDINAPYLVMGQ
3Frzb  RGASSERCKCKPIRATQKTYFRNNYNYVIRAKVKEIK--TKCHDVTAVVEVKEILKSSLVN---IPRDTVNLYTSSGCLCPPLN-VNEEYIIMGY
4srfp  KRLSPDRCKCKKVKPTLATYLSKNYSYVIHAKIKAIK--TKCHDVTAVVEVKEILKSSLVN---IPRDTVNLYTSSGCLCPPLN-VNEEYIIMGY

1sfrp  --KVKSQYLLTA--------------IHKWDKKNKEFKNFMKKMKNHEC
5sfrp  --KVDGQLLLMA--------------VYRWDKKNKEMKFAVKFMFSYPC
2sfrp  --KQGGELVITS--------------VKRWQKGQREFKRISRSIRKLQC
3Frzb  EDEERSRLLLVEGSIAEKWKDRLGKKVKRWDMKLRHLG-----LSKSDS
4srfp  --EWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKTAG
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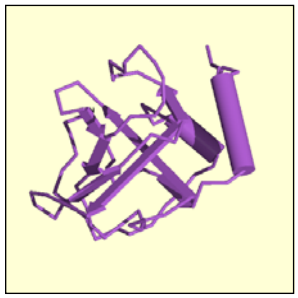
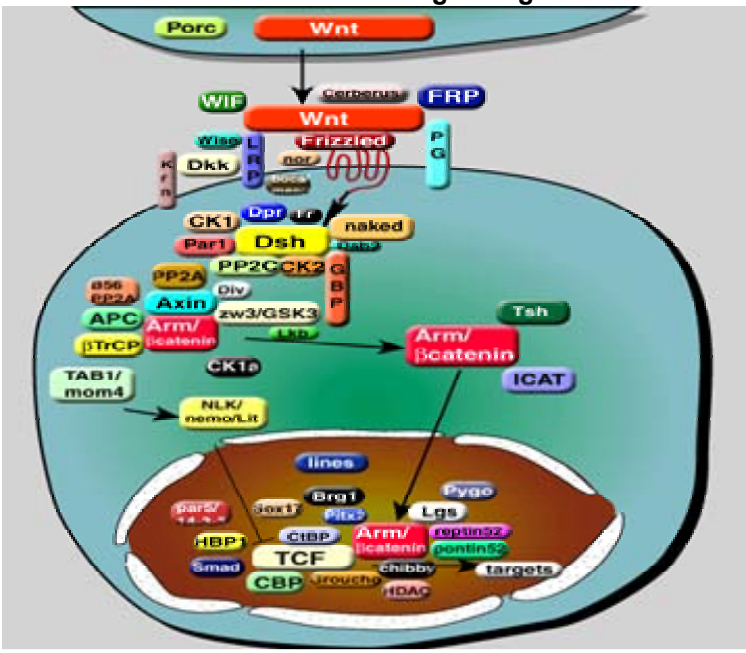
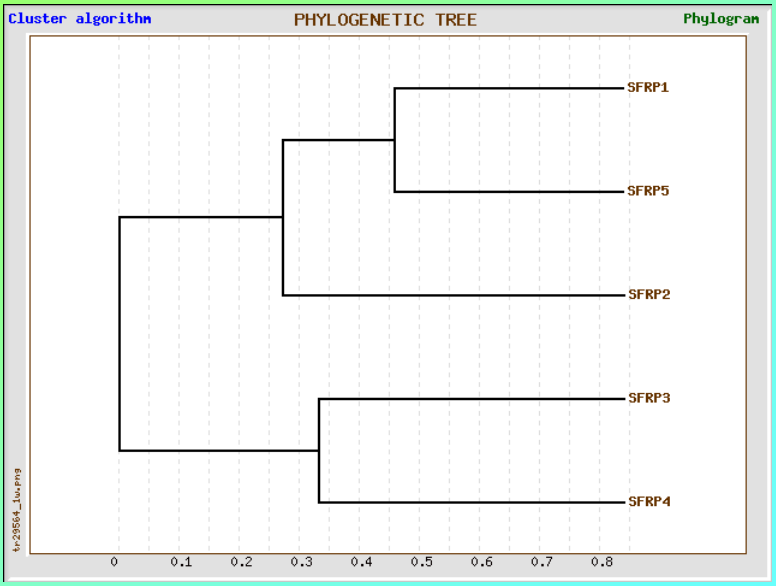


Model of Wnt signalling

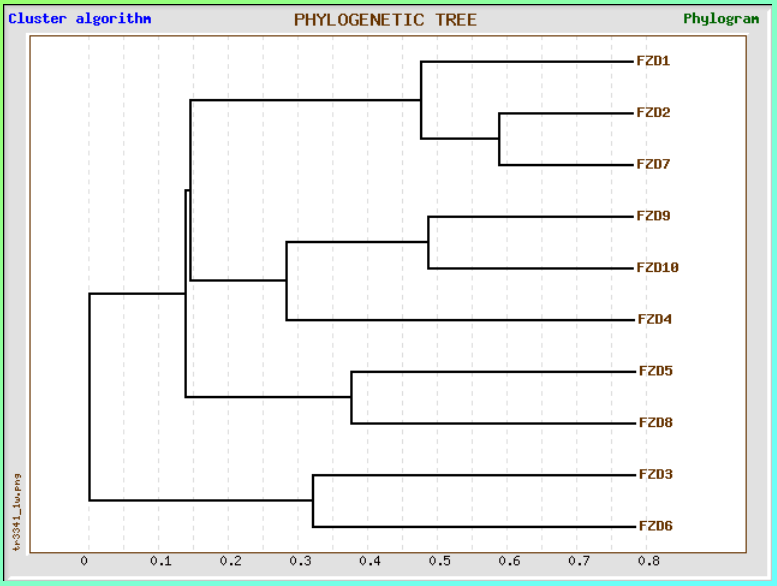


Sfrp phylogenetic tree

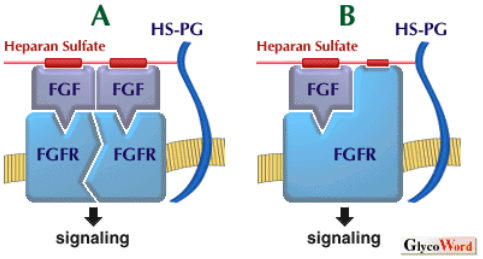


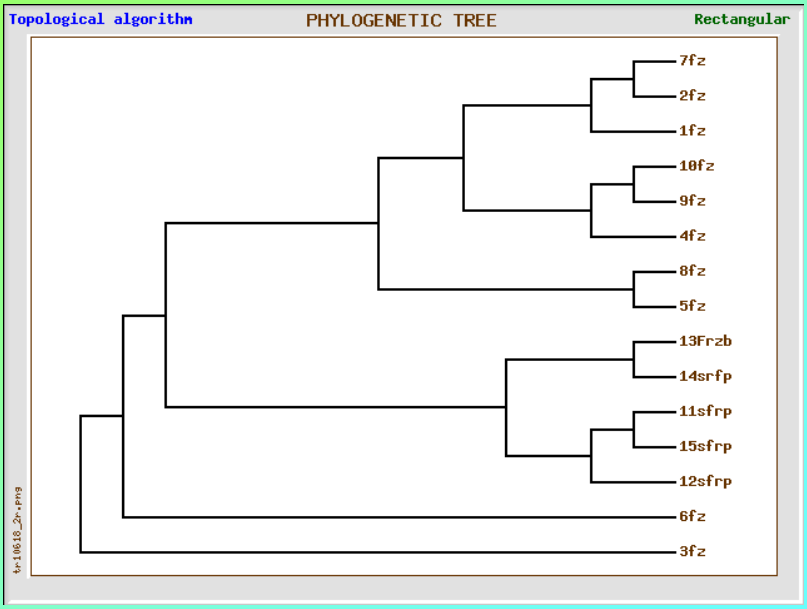
GeneBee service

Frizzled proteins phylogenetic tree



GeneBee service


A
HS-PG
Heparan Sulfate
FGF
FGF
FGFR
FGFR
signaling
B
HS-PG
Heparan Sulfate
FGF
FGFR
signaling
GlycoWord


Topological algorithm
PHYLOGENETIC TREE
Rectangular
7fz
2fz
1fz
10fz
9fz
4fz
8fz
5fz
13Frzb
14srfp
11sfrp
15sfrp
12sfrp
6fz
3fz

Frizzled genes encode integral membrane proteins that function in multiple signal transduction pathways. They have been identified in diverse animals, from sponges to humans. The family is defined by conserved structural features, including seven hydrophobic domains and a cysteine-rich ligand-binding domain. Frizzled proteins are receptors for secreted Wnt proteins, as well as other ligands, and also play a critical role in the regulation of cell polarity. Frizzled genes are essential for embryonic development, tissue and cell polarity, formation of neural synapses, and the regulation of proliferation, and many other processes in developing and adult organisms; mutations in human frizzled-4 have been linked to familial exudative vitreoretinopathy. It is not yet clear how Frizzleds couple to downstream effectors, and this is a focus of intense study.