

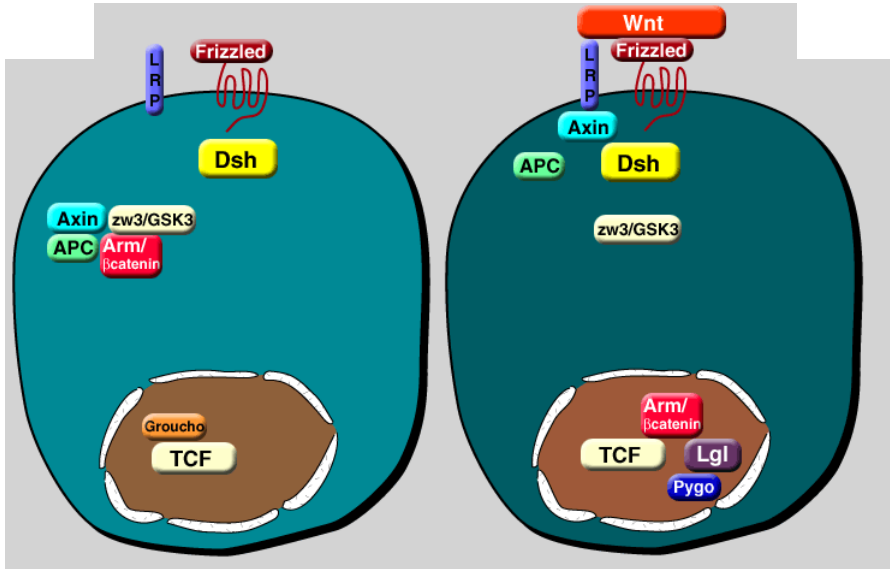
Frizzled proteins: structure and function

Anna Ajduk
Marta Busse
Anh-Tri Do
Tomasz Rygiel
Joanna Sobiesiak-Mirska
Krzysztof Wicher

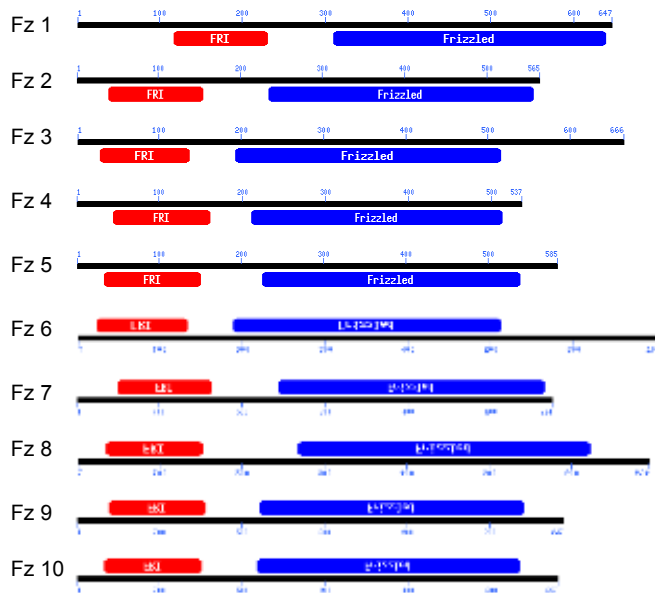
FRIZZLED and Wnt PROTEINS

- Frizzled are seven-transmembrane receptors.
- Frizzled act as receptors for Wnt proteins.
- Wnt 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.

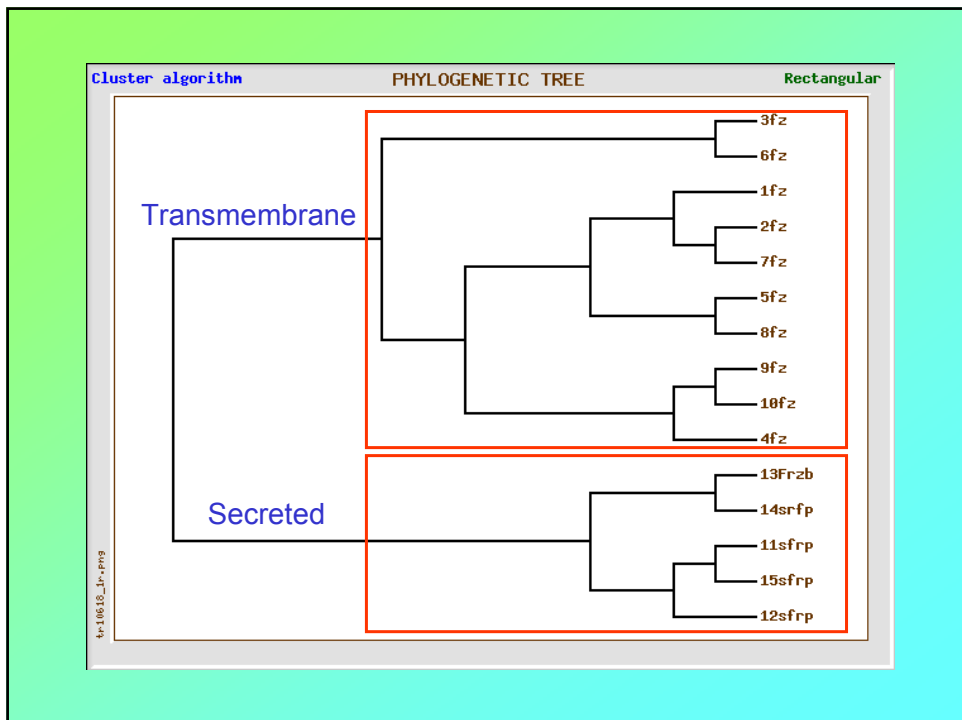
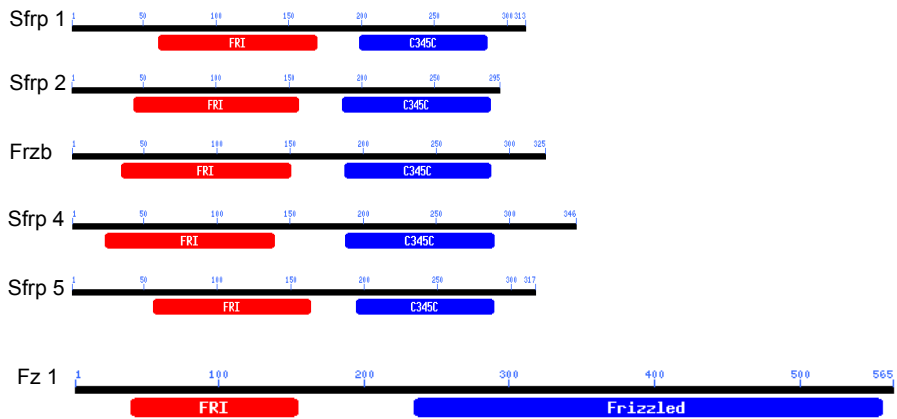
Wnt signalling: essential components in a two-state model



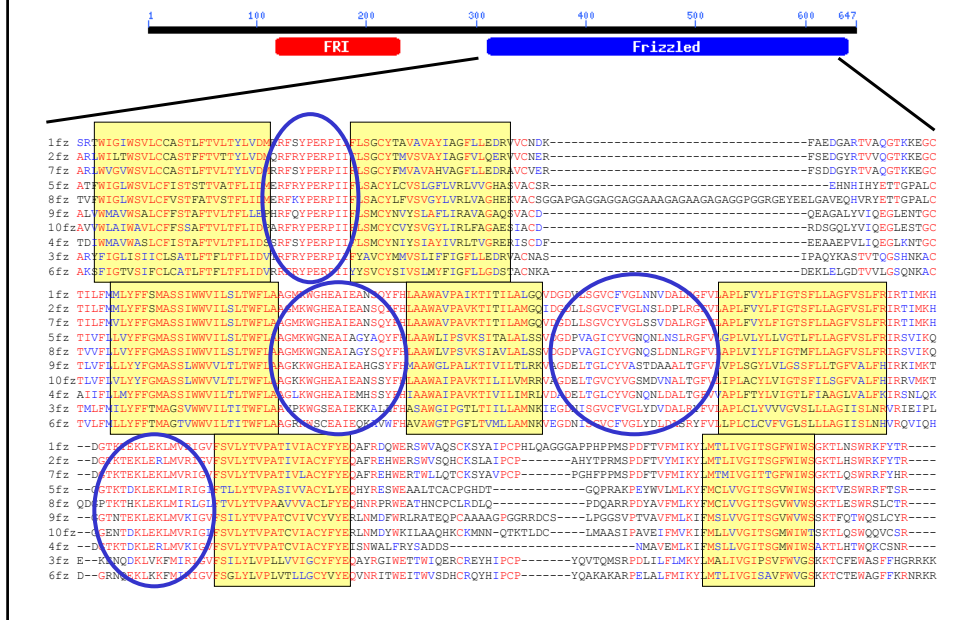
Human Frizzled proteins



Secreted Frizzled related proteins (Sfrp)



Frizzled : transmembrane domain



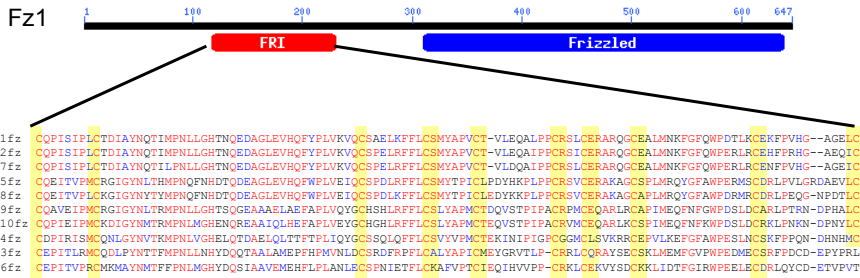
Frizzled are putative 7-transmembrane receptor

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)

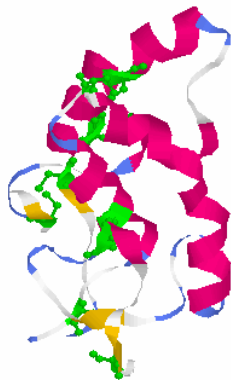
Frizzled : Cys-rich domain



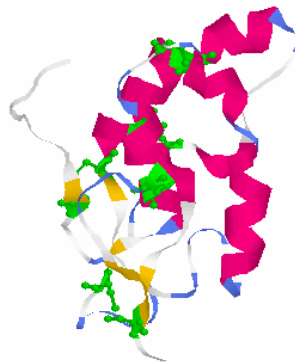
3D models of cysteine-rich domains (CRD) based on the crystal structure of the CRD mouse of Secreted Frizzled-Related Protein 3

Predicted by [SWISS-MODEL](#) tool
Rendered in [RasMol](#)

Frizzled 1

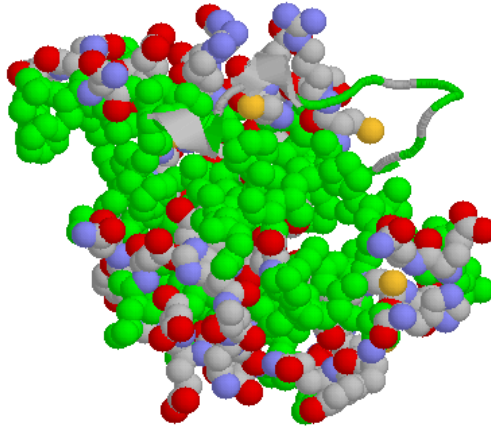


Frizzled-related protein 1

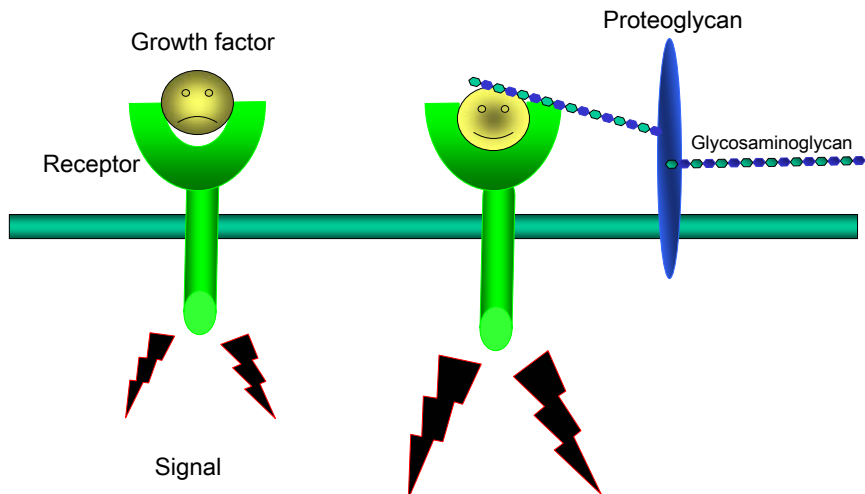


Modification of Wnt proteins with palmitate is essential for their activity

A putative palmitate binding site on the CRD of Frizzled 1

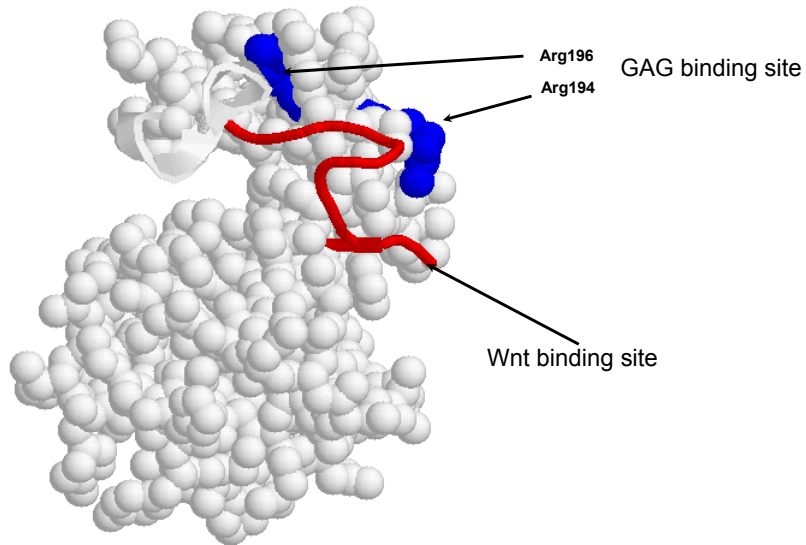


Many growth factors requires glycosaminoglycan for signalling



A putative glycosaminoglycan (GAG) binding site of Frizzled CRD

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



THANK YOU!



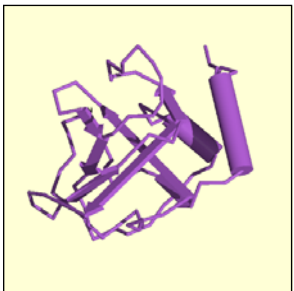
Sfrp : Netrin C-terminal domain



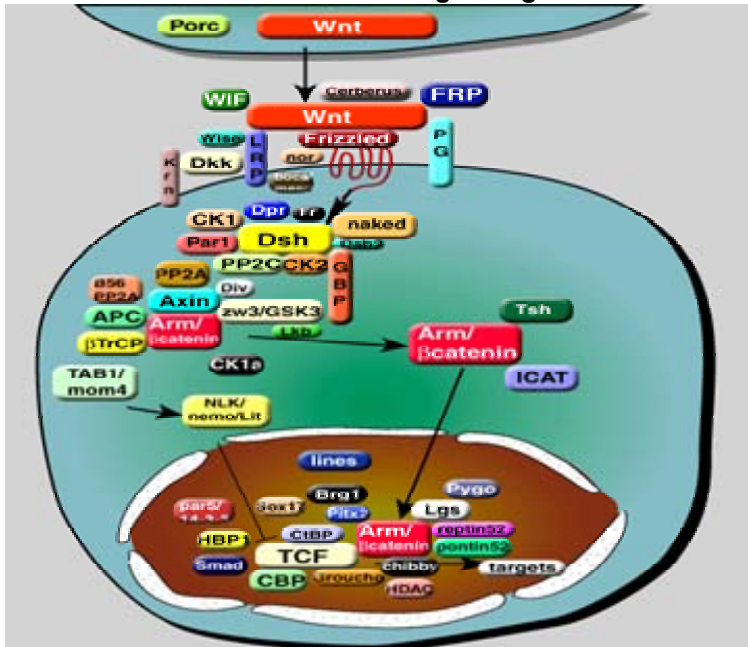
```

1sfrp GTTVCPDNEELKSEA-IIEHLCASEPALRMKIKEVKENGDKKIV--PKKKKPLKLGPIKKKDLKRLVLYLKNAGADCPCHQLDNLSHHFLIMGR
5sfrp VTKICAQCEMEHSADG-LMEQMCSSDFVVMRIKEIKIENGDRKLIQAQKKKLLRPGPLKRRDTRKRLVLMHMGAGCCPCQQLDSLGLAGSFLVMGR
2sfrp APKVCEACKNKDDDDIMEITLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLVGVSERDLKKSVLWLDKSLQCTCEEMNDINAPYLVMGQ
3Frzb RGASSERCKCKPIRATQRTYFRNNYVIVIRAKVKEIK--TKCHDVTAVVEVKEILKSSLVN---IPRDTVNLVTSSGCLCPPLN-VNEEYIIMGY
4srfp KRLSPDRCKCKKVKPTLATYLSKNYSYVIHAKIKAIK--TKCHDVTAVVEVKEILKSSLVN---IPRDTVNLVTSSGCLCPPLN-VNEEYIIMGY

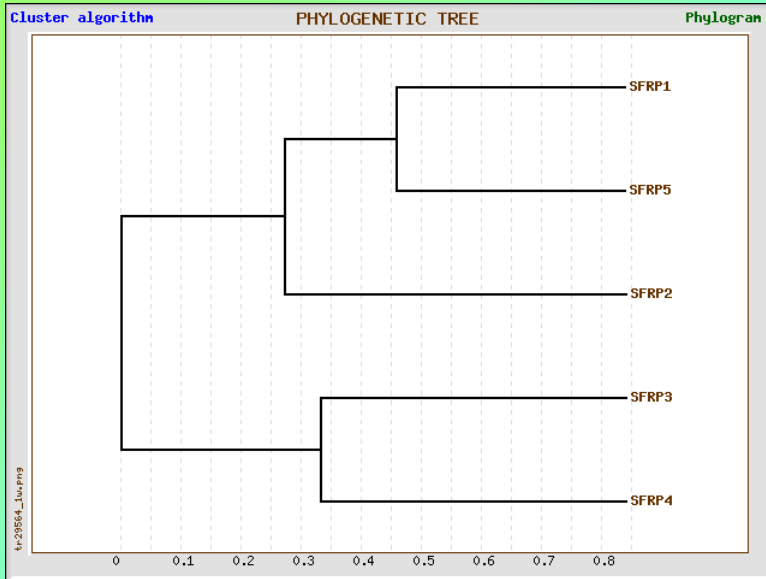
1sfrp --KVKSQYLLTA-----IHKWDKKNKEPKNFMKMKMKNHEC
5sfrp --KVDGQLLLMA-----VYRWDKKNKEPKFAVKFMSYPC
2sfrp --KGGGLVITVS-----VKRWQKQREPKRISRIRKLQCC
3Frzb EDEBERSRLLEGSIAERKWRDLGKVKRWDMKLRHLG-----LSKSDS
4srfp --EWRSRMMLLENCLVEKWRDLGKRSIQEBERLQEQRTVQDKKKTAG
    
```



Model of Wnt signalling

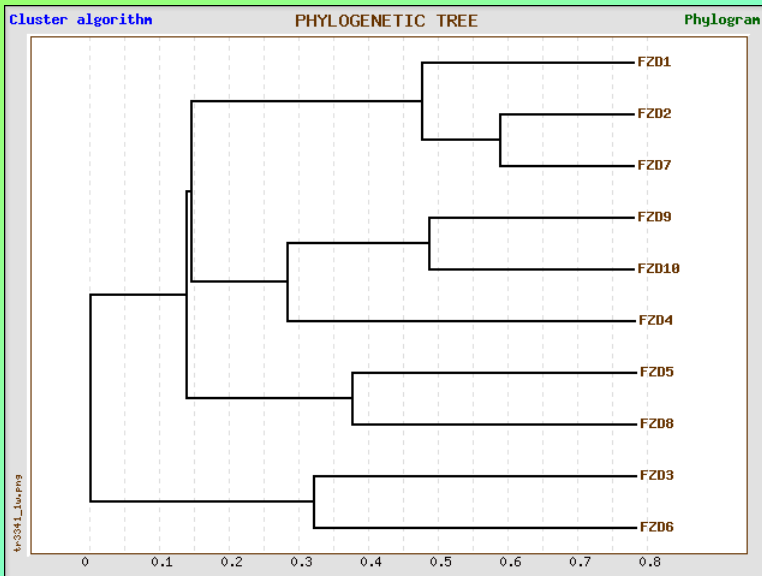


Sfrp phylogenetic tree

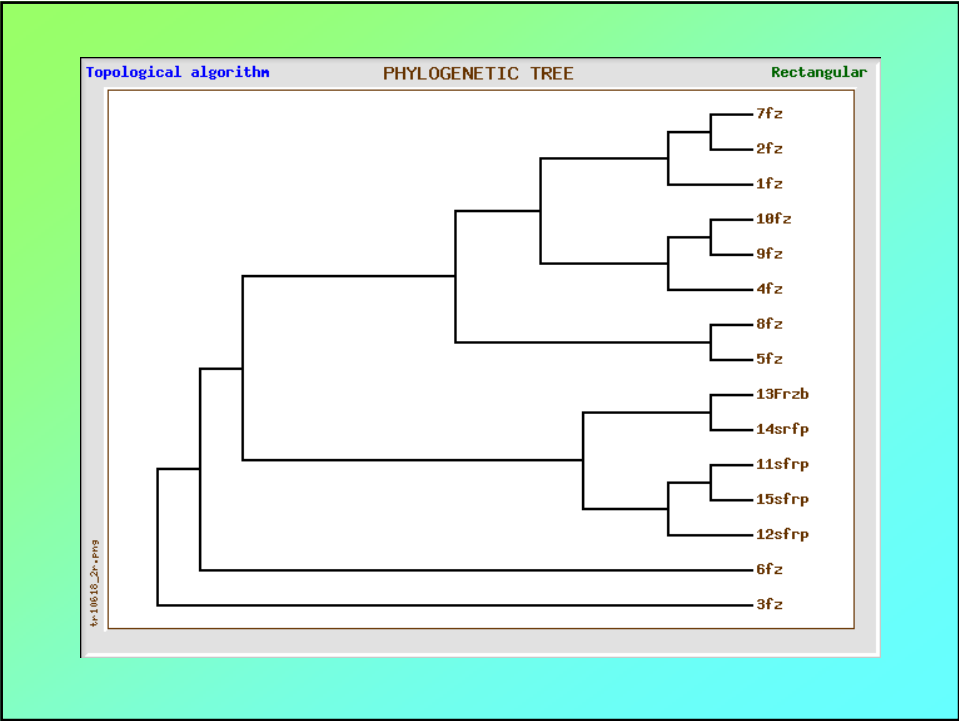
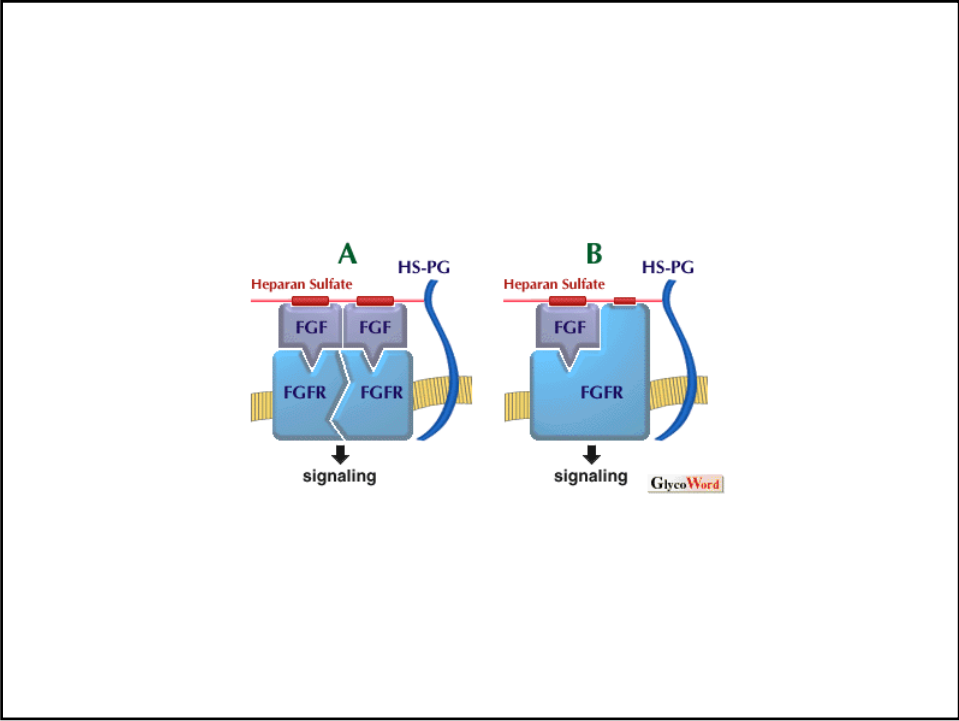


GeneBee service

Frizzled proteins phylogenetic tree



GeneBee service



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.