

An evidence-based model for representing signaling pathways in FlyBase



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Drosophila melanogaster research has played a central role in the elucidation of the major signaling pathways. The molecular dissection of signaling pathways is still an intensive area of fly research, uncovering novel pathway members and regulators. FlyBase has initiated a project to provide a dynamic, evidence-driven pathway resource, allowing researchers to get an up-to-date overview of pathway members and regulators and the extent of experimental support for a gene's association with a pathway. We illustrate how such data can be used to present a more nuanced view of signaling pathways.

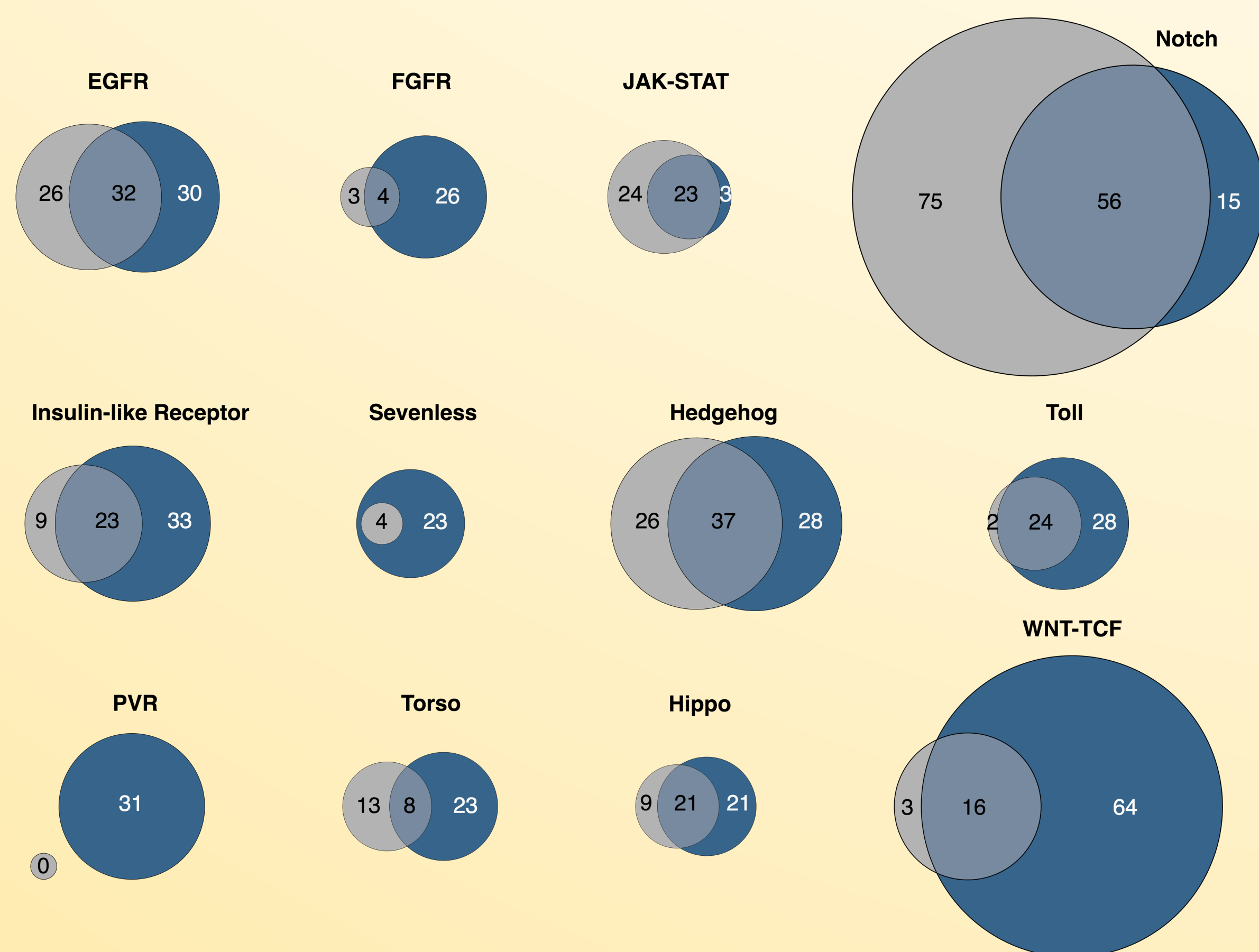
Collating experimental evidence for signaling pathways

1. Define characteristics of a core member vs regulator

2. Set evidence threshold for inclusion of a gene

3. Review annotations & research papers: Review, remove and add experimental evidence for each gene using GO annotation

● Before review
 ● After review (first pass)



Venn diagrams showing the number of genes annotated as regulating or part of a pathway from experimental observation, showing the overlap between the sets before and after the first pass review. During the review, we removed many GO annotations associating genes with a pathway or the regulation of a pathway, often these genes were found to be downstream or upstream or involved in a process that indirectly influenced the pathway.

FlyBase pathway reports

More pathways, references and regulators will be added. Pathway pages will be kept up-to-date with paper curation at FlyBase.

General Information				
Name	Notch Signaling Pathway Core Components	Species	<i>D. m.</i>	
Symbol	NTCH-C	FlyBase ID	FBgn0000001	
Date last reviewed	2019-01-23	Number of members	12	
Description				
Description	The Notch receptor signaling pathway is activated by the binding of the transmembrane receptor Notch (N) to transmembrane ligands, <i>Delta</i> or <i>Serrate</i> , presented on adjacent cells. This results in the proteolytic cleavage of N, releasing the intracellular domain (NICD). NICD translocates into the nucleus, interacting with <i>Su(H)</i> and <i>mam</i> to form a transcription complex, which up-regulates transcription of Notch-responsive genes. (Adapted from FBtr0225731 and FBtr0192604).			
	Core pathway components are required for signaling from the sending cell and response in the receiving cell.			
	Notch signaling pathway			
Parent group(s)				
Parent group(s)	Notch Signaling Pathway			
Protein Complex group(s)				
Protein Complex group(s)	CSL-NOTCH-MASTERMIND TRANSCRIPTION FACTOR COMPLEX GAMMA SECRETASE COMPLEX			
Other related group(s)				
Other related group(s)	NOTCH LIGANDS			
Members (12)				
For all members: View Orthologs Export to HitList Export to Batch Download				
Gene Symbol	Gene Name	Gene Group Membership	GO Molecular Function (Experimental)	# Refs
aph-1	anterior pharynx defective 1	GAMMA SECRETASE COMPLEX	endopeptidase activity	2
DI	Delta	NOTCH LIGANDS	Notch binding receptor ligand activity	9
kuz	kuzbanian	ADAM METALLOPROTEASES	metalloendopeptidase activity Notch binding	5
mam	mastermind	CSL-NOTCH-MASTERMIND TRANSCRIPTION FACTOR COMPLEX		5
N	Notch	CSL-NOTCH-MASTERMIND TRANSCRIPTION FACTOR COMPLEX	transmembrane signaling receptor activity chromatin binding	11
Nct	Nicastrin	GAMMA SECRETASE COMPLEX		7
pen-2	presenilin enhancer	GAMMA SECRETASE COMPLEX		2
Pen	Presenilin	GAMMA SECRETASE COMPLEX	endopeptidase activity protein homodimerization activity	5
Ser	Serrate	NOTCH LIGANDS	Notch binding	5
Su(H)	Suppressor of Hairless	OTHER DNA BINDING CSL-NOTCH-MASTERMIND TRANSCRIPTION FACTOR	DNA-binding transcription factor activity RNA polymerase II, ribonucleoside, DNA binding	7
External Data				
Other resource(s)	Illustration - Notch signaling (The Interactive Fly) Wikipathways - Notch Signaling Pathway (Drosophila melanogaster) Animation - The Notch signaling pathway (Wolpert, Tickle & Martinez Arias:Principles of Development International 5e) Reactome Pathway - Signaling by Notch (computed) KEGG pathway - Notch signaling pathway - Drosophila melanogaster			

GO annotation of pathway components used to populate pathway reports with genes and references.

Links to analysis tools

Functional pointers: membership of FlyBase gene groups and experimentally characterized molecular functions

Research references used to link gene to pathway from GO annotation

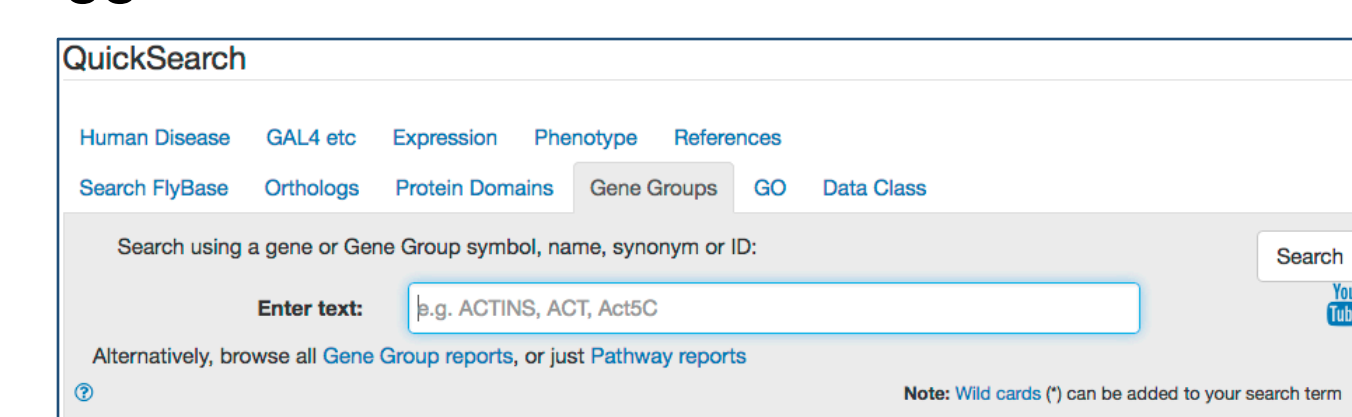
Links to pathway resources

Future developments

The pathway pages show basic information aimed at providing context and functional clues to a gene's role in a pathway. Features will be added to these pages to increase their utility, including:

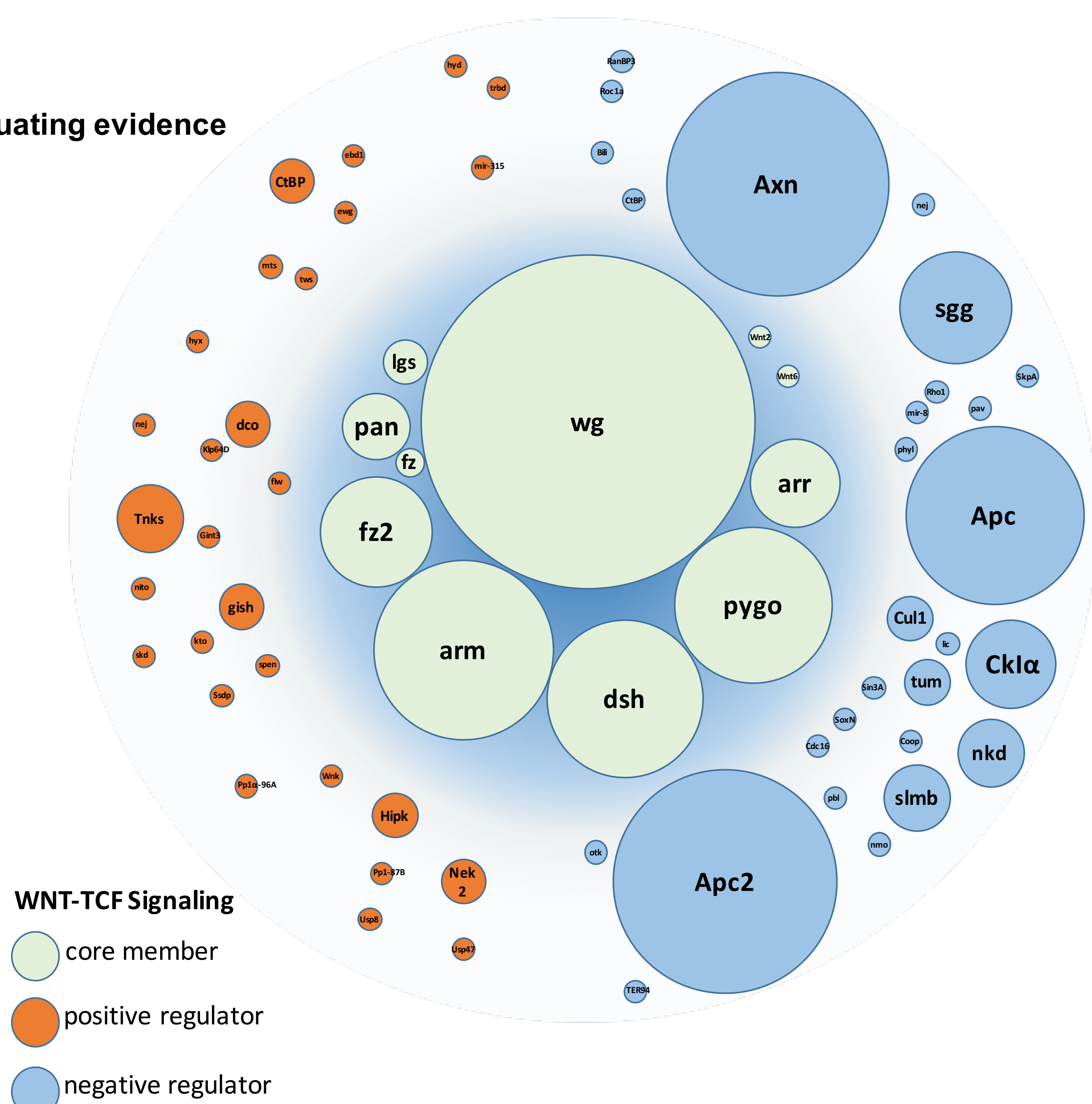
- Networks
- Tools and reagents
- Visual summary tools

Expert advisors sought – check your favorite pathway. Pathways can be found using the QuickSearch Gene Groups tab of the FlyBase homepage. Please contact us with comments, suggestions and corrections.

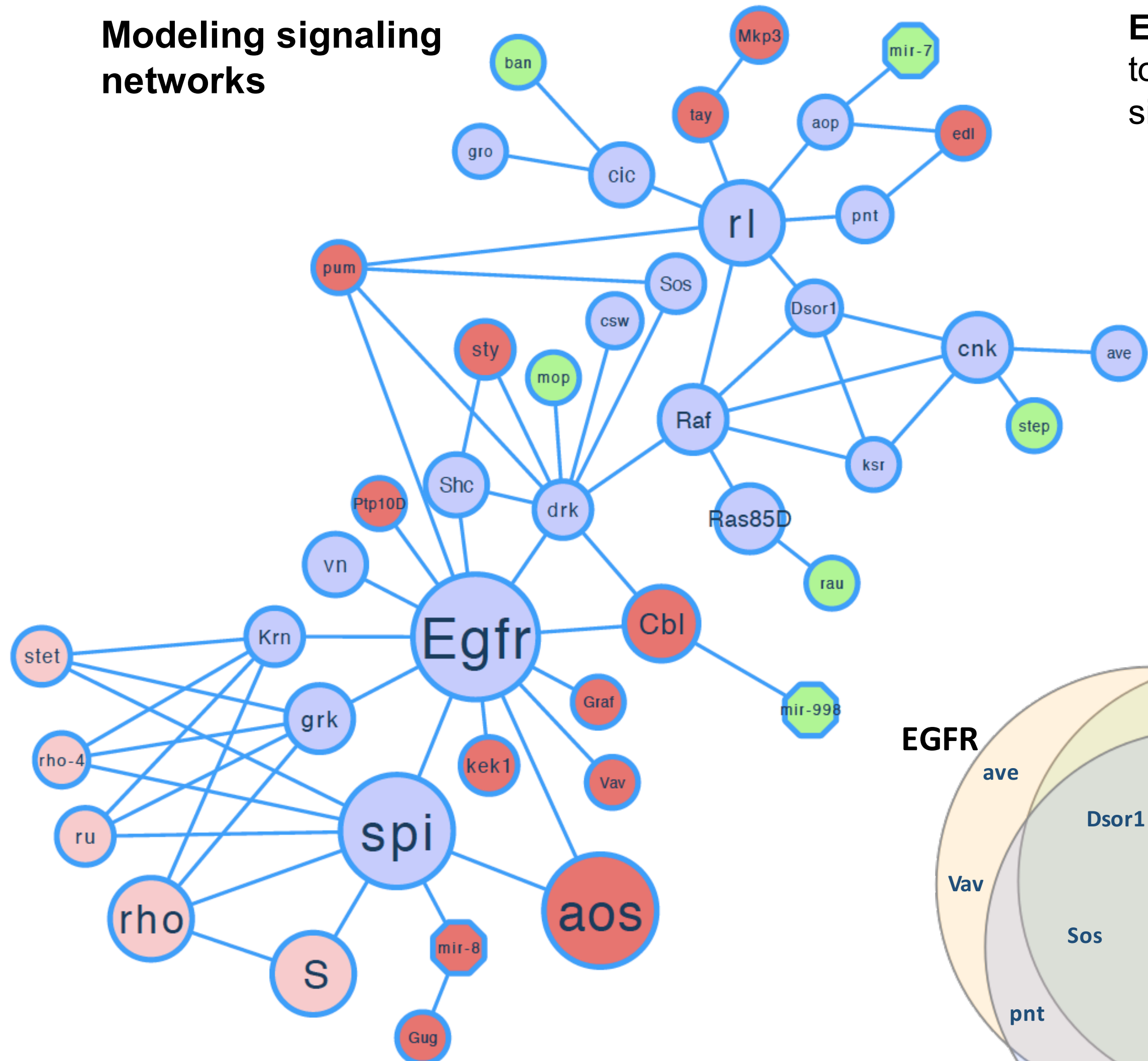


Using the experimental evidence-weighted model to reveal features of signaling pathways

Evaluating evidence



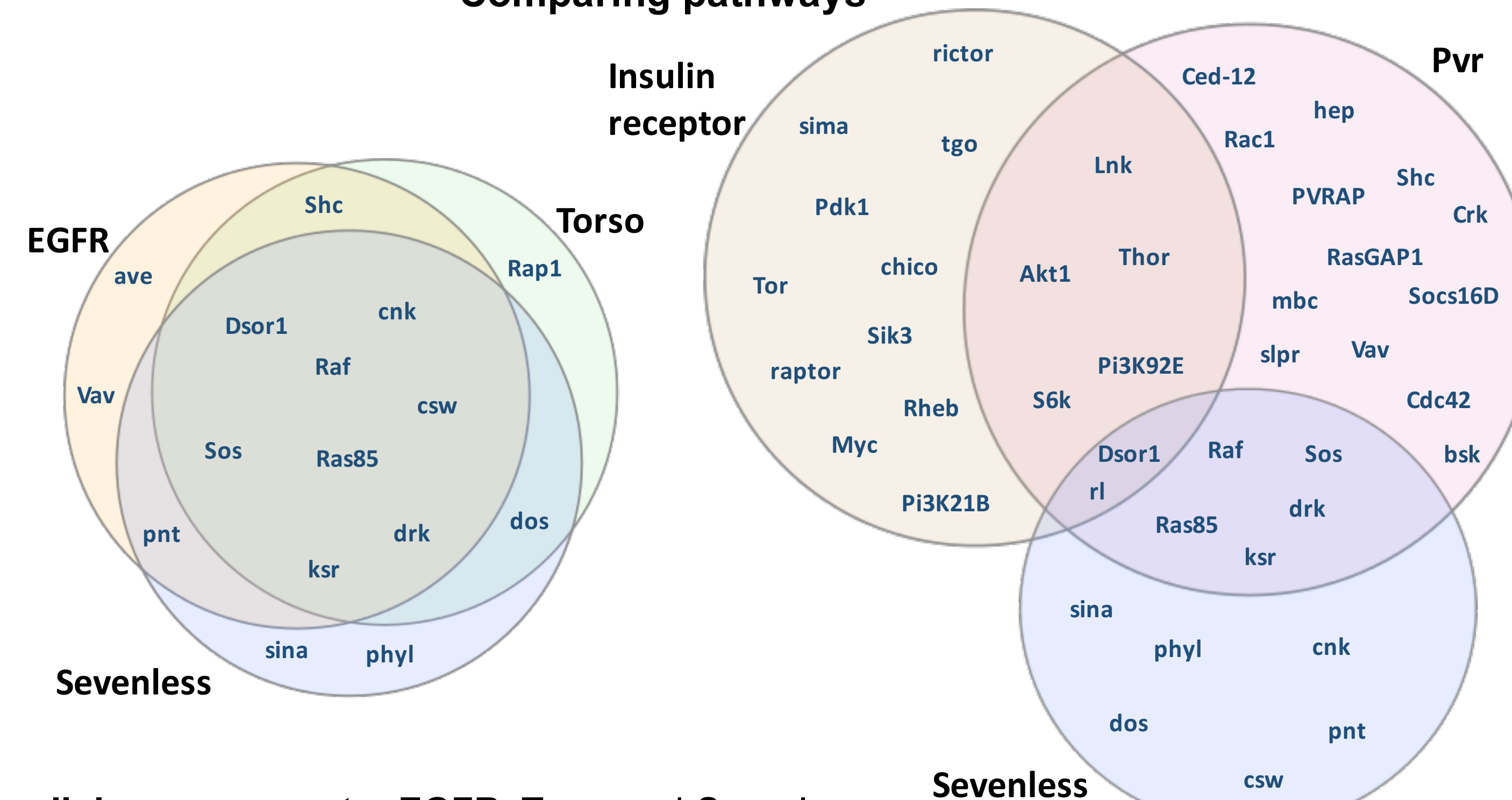
Modeling signaling networks



EGFR network: Accurate pathway membership assignment allows us to build highly connected network models using interaction data. Node size is based on weight of curated experimental evidence.

- Negative Regulators
- Core members
- Positive Regulators
- Ligand Biogenesis

Comparing pathways



RTK pathway core intracellular components: EGFR, Torso and Sevenless pathway members show a high degree of overlap in components, corresponding to the Ras/Raf/MAP kinase signaling module. The Insulin receptor and PVR pathways diverge from the 'classical' RTK pathway.