

# Canadian Bioinformatics Workshops

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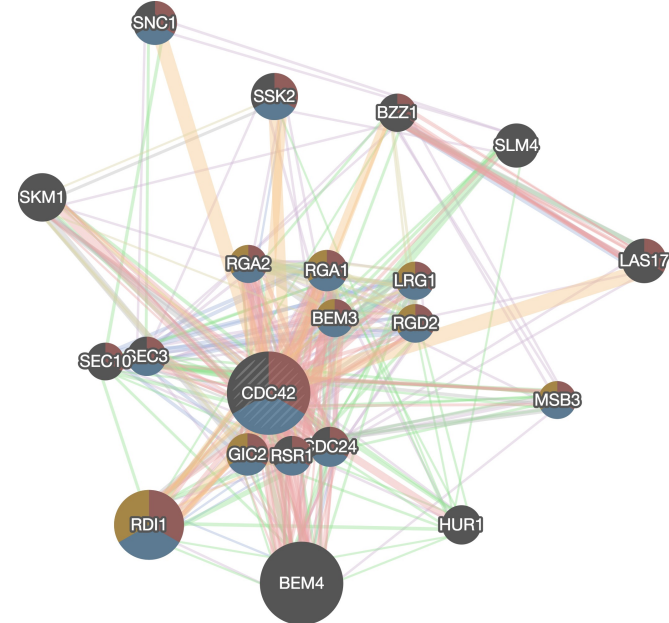
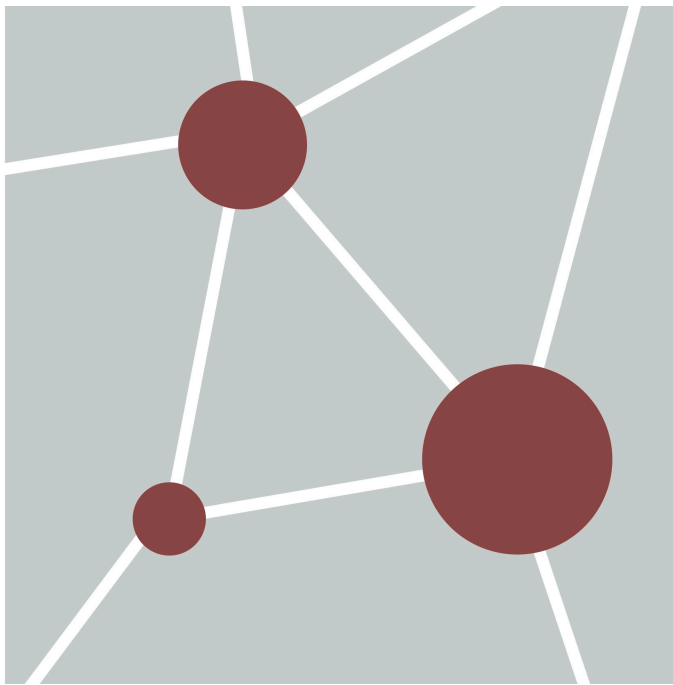
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# Gene Function Prediction

Veronique Voisin

Pathway and Network Analysis of -omics Data

June 5-7 2023



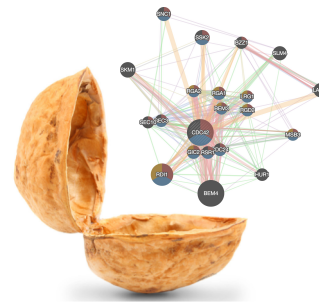
# Learning Objectives of this module

- How to use GeneMANIA
- Practical lab: website and Cytoscape app

# GeneMANIA: Two types of function prediction

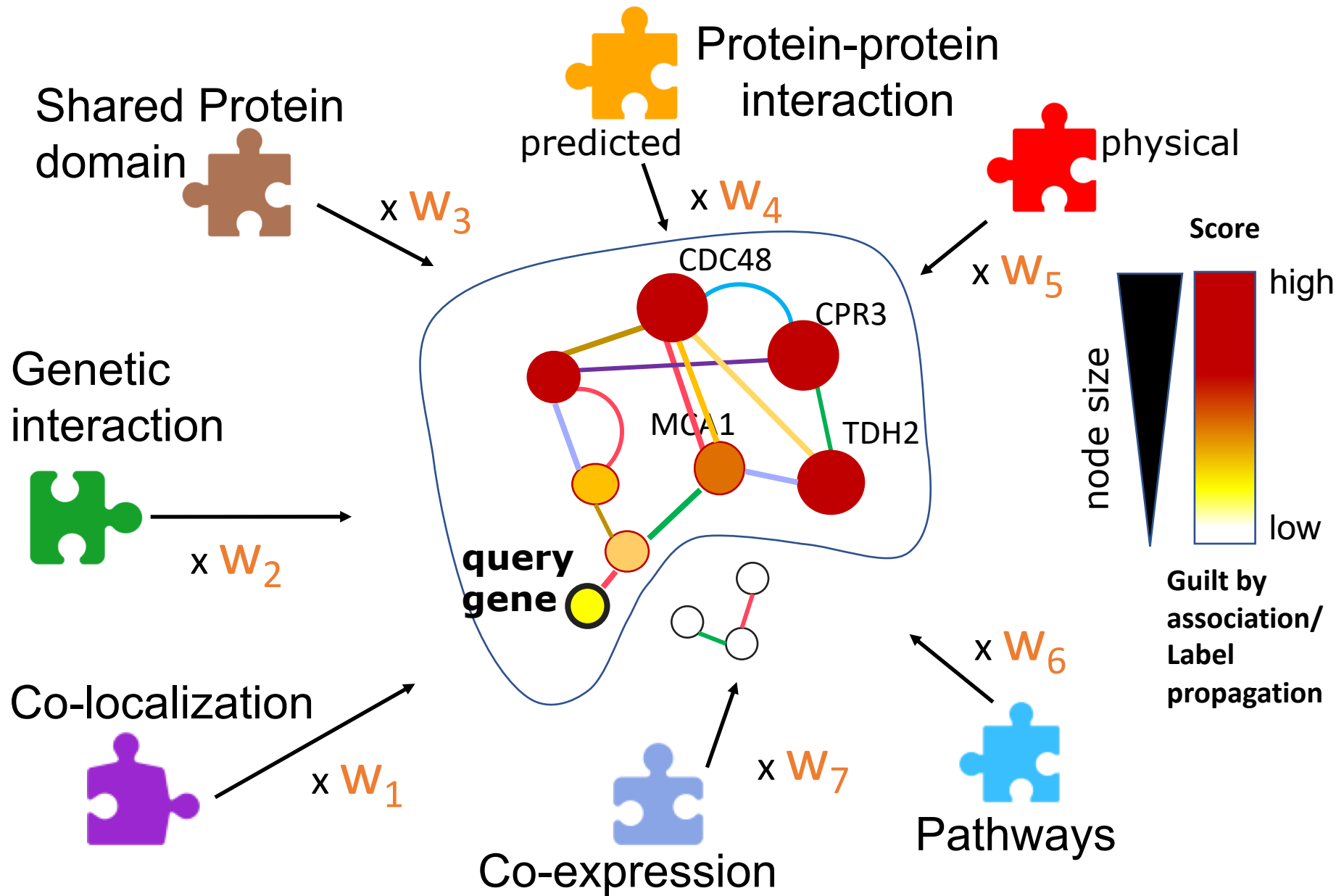
- “What does my gene do?” (1 gene as query)
- “Give me more genes like these” (gene list as query)

# GeneMANIA in a



- Is a **functional interaction network**.
- Is a **collection of interaction networks** that are summed up into one global network. To integrate all these networks into one, there are some **weights** associated with each network that are **context dependent**.
- Is a **guilt by association/ label propagation** algorithm which finds genes and networks that are functionally associated with our **query gene list**.
- Is an interactive **web app** and a **Cytoscape app**.

# Functional interaction network

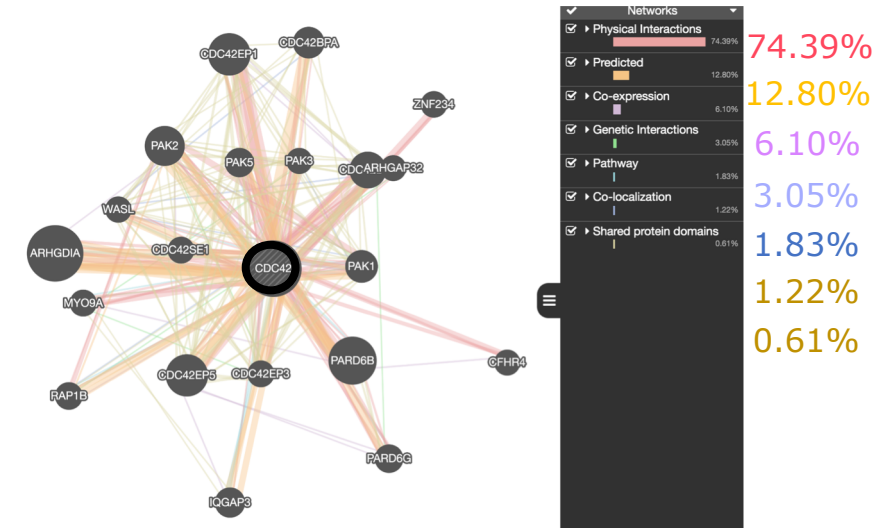
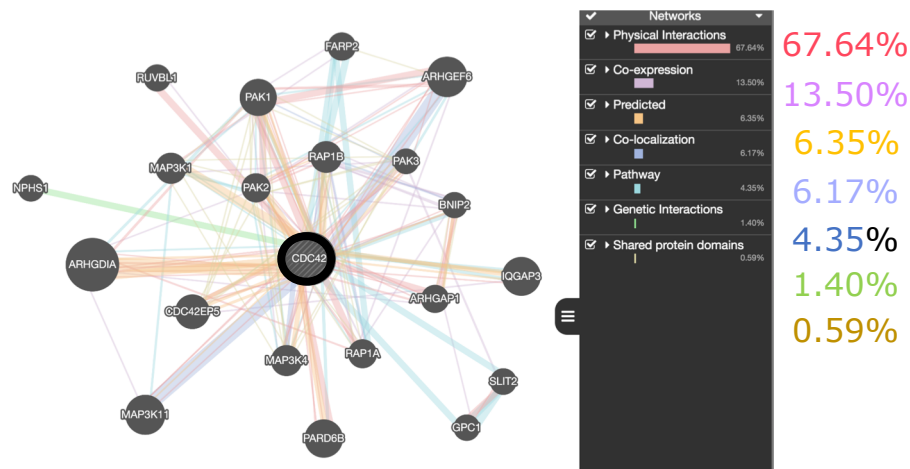


# Context-dependent networks

= weight of different networks used to measure node connection

**Network weighting=**  
Automatic (pathways)

**Network weighting=**  
Equal by network



○ query gene

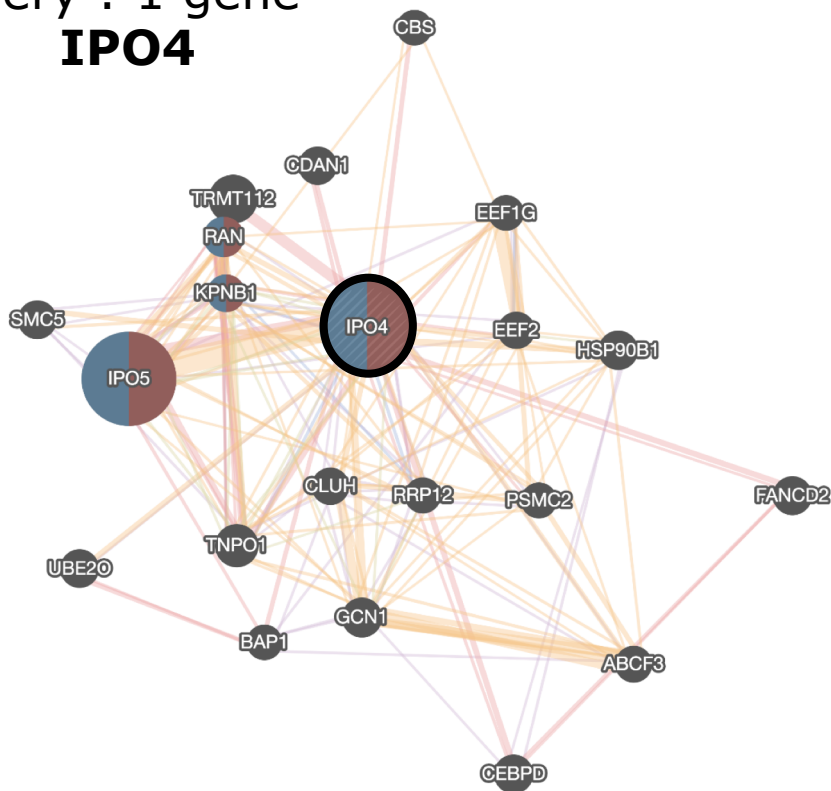
Automatic: GO-based weighting assigns network weights based on how well the networks reproduce patterns of GO co-annotations ( “Are genes that interact in the network more likely to have the same annotation?” ),



# “Function prediction: What does my gene do?”

Query : 1 gene  
**IPO4**

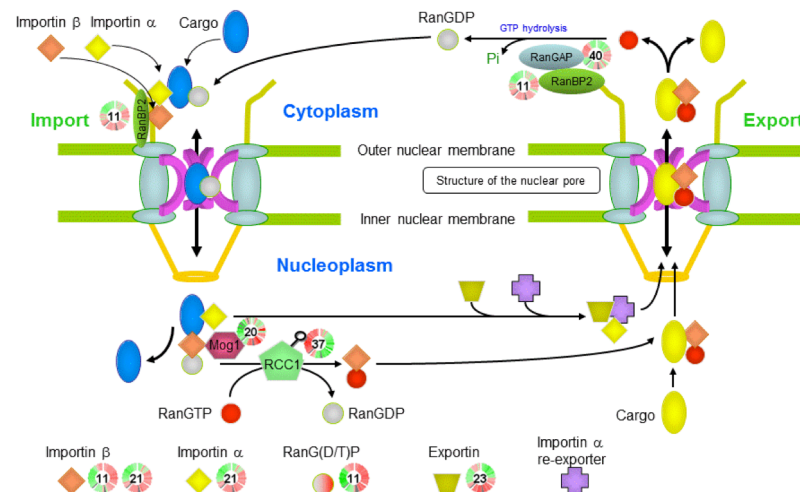
Genemania web app



Function	FDR	Coverage
pore complex	1.66e-3	4 / 47
nuclear pore	1.66e-3	4 / 41

## IPO4: importin 4

Import and export through the nuclear pore



Directionality of transport. The RanGTP gradient determines the vectorial transport of cargo. Translocation through the NPC is an energy-independent, reversible reaction. To achieve directionality of substrate transport, translocation is coupled to a second reaction. During import, this reaction is the dissociation of the import complex by RanGTP, and the subsequent binding of the import substrate to nuclear partners. The export process gains directionality by export complex disassembly in the cytoplasm involving GTP hydrolysis on Ran.

## Default parameters

Max resultant genes: 20

Max resultant attributes: 10

Network weighting

Query-dependent weighting

Automatically selected weighting method

query gene

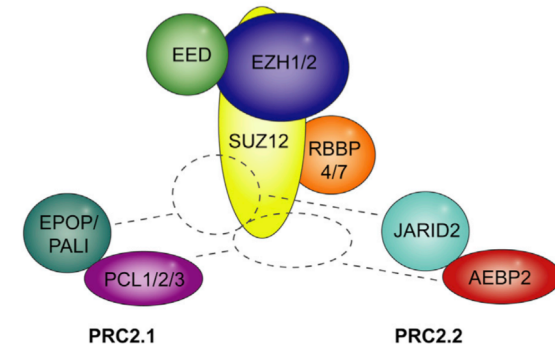
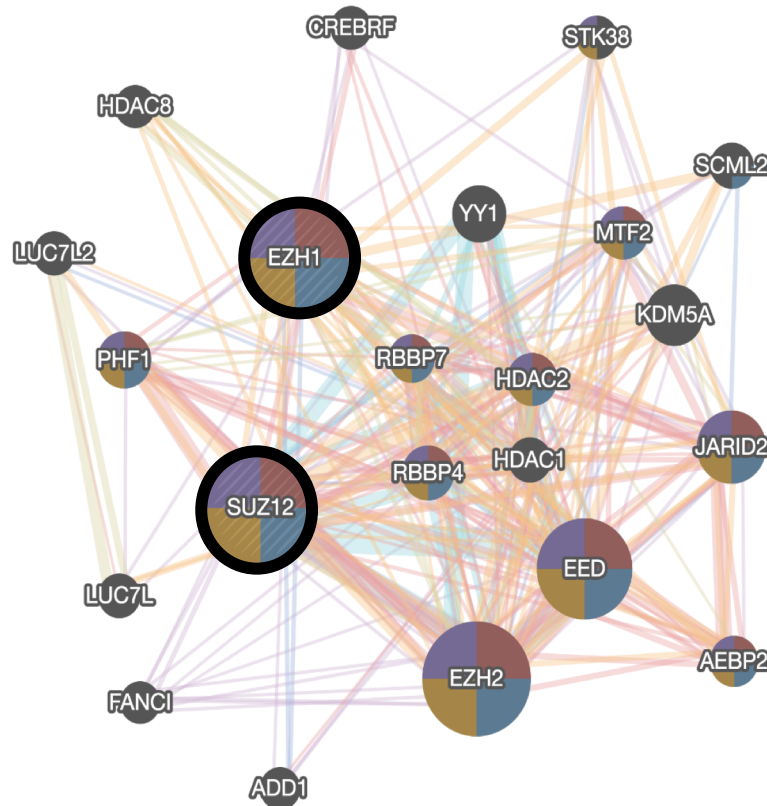
[http://mpmp.huji.ac.il/maps/import\\_export.html](http://mpmp.huji.ac.il/maps/import_export.html)

# “Give me more genes like these”

Query : 2 genes  
**SUZ12 and EZH1**

Genemania web app

Function	FDR	Coverage
<input checked="" type="checkbox"/> ESC/E(Z) complex	2.66e-28	11 / 13
<input checked="" type="checkbox"/> PcG protein complex	3.70e-24	12 / 39
<input checked="" type="checkbox"/> histone methyltransferase complex	2.05e-21	12 / 64
<input checked="" type="checkbox"/> methyltransferase complex	1.02e-20	12 / 74
<input type="checkbox"/> NuRD complex	3.32e-6	4 / 14
<input type="checkbox"/> CHD-type complex	3.32e-6	4 / 14
<input type="checkbox"/> histone deacetylase complex	3.32e-6	5 / 42
<input type="checkbox"/> SWI/SNF superfamily-type complex	1.81e-5	5 / 63
<input type="checkbox"/> Sin3-type complex	5.27e-4	3 / 12
<input type="checkbox"/> Sin3 complex	5.27e-4	3 / 12
<input type="checkbox"/> transcriptional repressor complex	5.94e-4	4 / 54
<input type="checkbox"/> positive regulation of histone methylation	5.94e-4	3 / 13
<input type="checkbox"/> histone deacetylase activity	1.16e-3	3 / 17
<input type="checkbox"/> regulation of histone methylation	1.16e-3	3 / 17
<input type="checkbox"/> protein deacetylase activity	1.30e-3	3 / 18
<input type="checkbox"/> negative regulation of histone modification	1.98e-3	3 / 21
<input type="checkbox"/> deacetylase activity	2.83e-3	3 / 24
<input type="checkbox"/> regulation of chromosome organization	3.12e-3	4 / 90
<input type="checkbox"/> chromatin remodeling	3.23e-3	4 / 92
<input type="checkbox"/> positive regulation of histone modification	3.88e-3	3 / 28
<input type="checkbox"/> nuclear chromosome	5.50e-3	5 / 240
<input type="checkbox"/> histone binding	5.68e-3	4 / 110



[https://www.cell.com/molecular-cell/pdf/S1097-2765\(19\)30185-6.pdf](https://www.cell.com/molecular-cell/pdf/S1097-2765(19)30185-6.pdf)

query gene

The polycomb repressive complex 2 (PRC2) is a chromatin-associated methyltransferase catalyzing mono-, di-, and trimethylation of lysine 27 on histone H3 (H3K27).

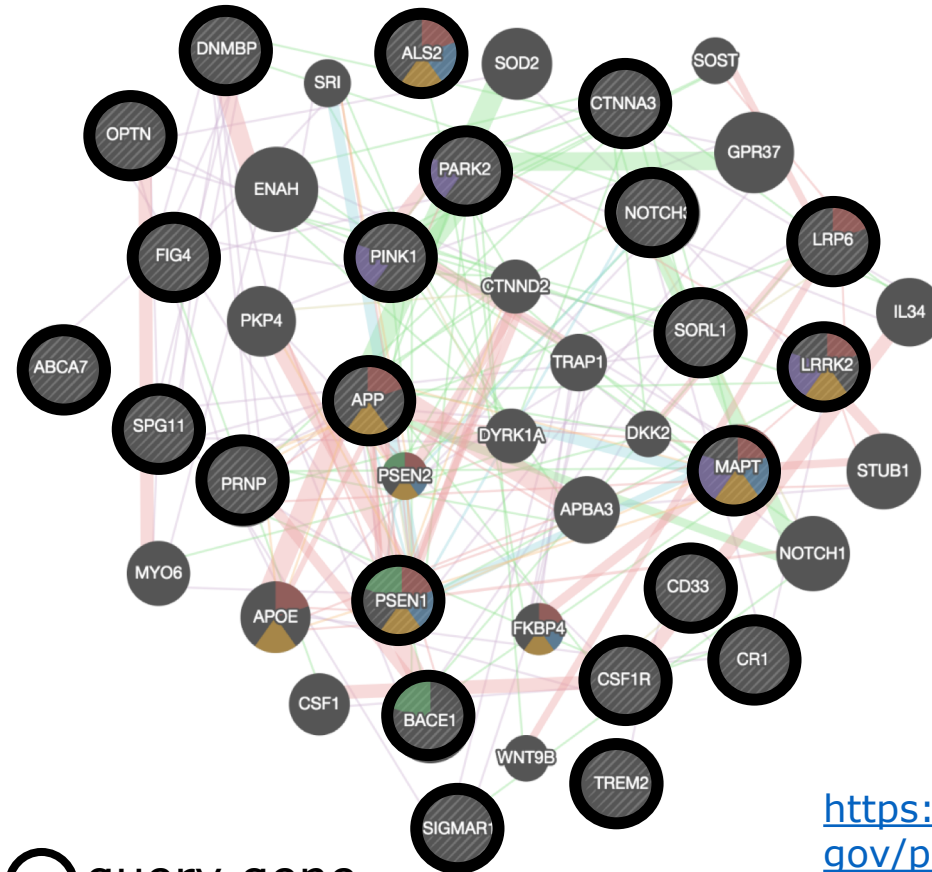
Default parameters

# “Give me more genes like these”

Query : 23 genes  
**genes with mutations and associated with Early-Onset Alzheimer’s Disease**



Function	FDR	Coverage
<input checked="" type="checkbox"/> neuron part	2.73e-4	9 / 298
<input checked="" type="checkbox"/> site of polarized growth	2.82e-4	5 / 47
<input checked="" type="checkbox"/> neuron projection	2.82e-4	8 / 233
<input type="checkbox"/> growth cone	2.82e-4	5 / 45
<input type="checkbox"/> perinuclear region of cytoplasm	4.35e-4	8 / 276
<input type="checkbox"/> Notch receptor processing	4.35e-4	4 / 21
<input type="checkbox"/> dendrite	4.39e-4	6 / 112
<input type="checkbox"/> developmental growth involved in morphogenesis	5.34e-4	5 / 61
<input type="checkbox"/> neuronal cell body	6.06e-4	5 / 64
<input type="checkbox"/> cell body	7.24e-4	5 / 69
<input type="checkbox"/> receptor complex	7.24e-4	7 / 213
<input type="checkbox"/> membrane protein ectodomain proteolysis	1.29e-3	4 / 33
<input checked="" type="checkbox"/> beta-amyloid metabolic process	1.64e-3	3 / 10
<input type="checkbox"/> dendritic shaft	1.64e-3	3 / 10
<input type="checkbox"/> neuron death	2.49e-3	5 / 94
<input type="checkbox"/> membrane protein proteolysis	2.69e-3	4 / 43
<input type="checkbox"/> axon	2.69e-3	5 / 97
<input type="checkbox"/> developmental growth	4.93e-3	5 / 112
<input type="checkbox"/> negative regulation of multicellular organismal process	1.08e-2	6 / 230
<input type="checkbox"/> regulation of anatomical structure size	1.90e-2	5 / 151
<input type="checkbox"/> neuron apoptotic process	2.63e-2	4 / 80
<input checked="" type="checkbox"/> autophagy	5.47e-2	4 / 98



Default parameters

Max resultant genes: 20

Max resultant attributes: 10

Network weighting

Query-dependent weighting

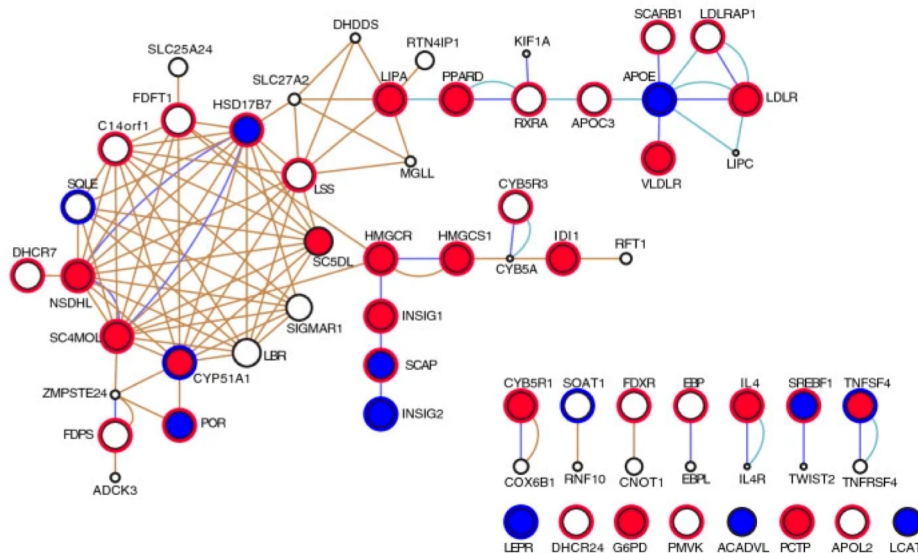
Automatically selected weighting method

query gene

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6471359/>

# “Give me more genes like these”

Query : 43 genes  
**cholesterol metabolism related genes**



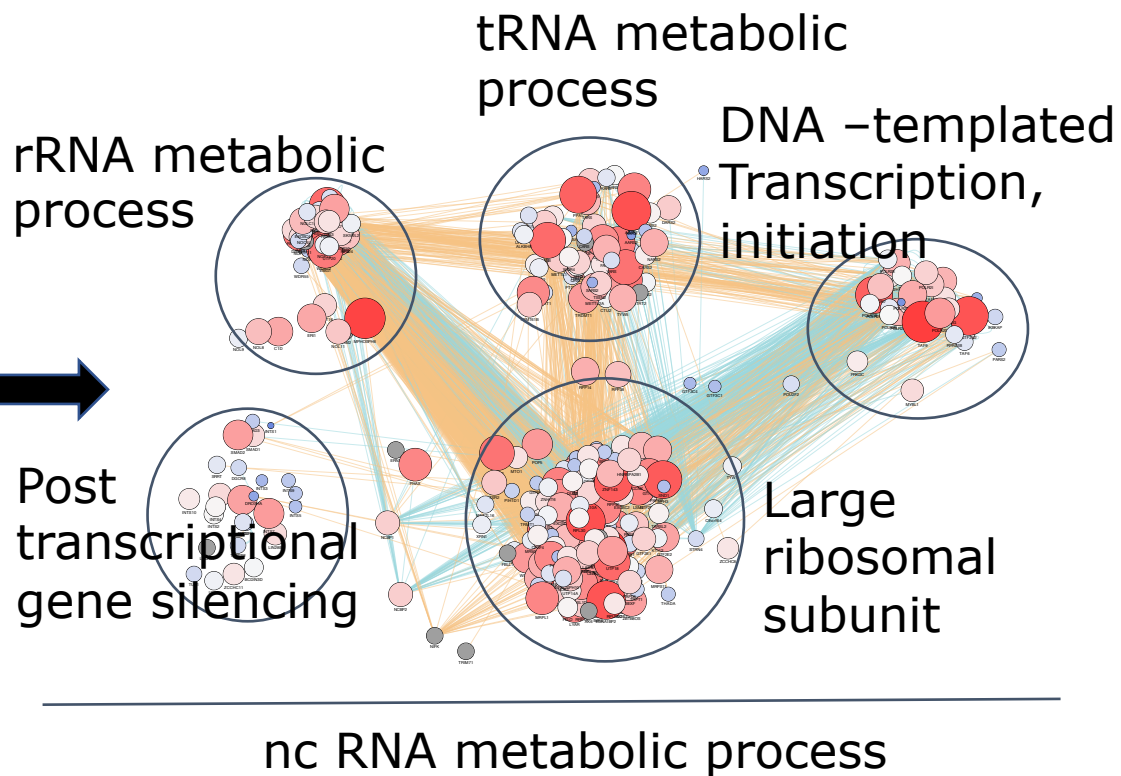
Larger nodes: query genes  
smaller white nodes: related genes  
Red: up-regulation  
Blue: down-regulation  
2 time points: 3h and 21h (node center and node border)

## Model of Atherosclerosis

Quiescent human coronary artery SMCs were treated with minimally-oxidized LDL (moxLDL), for 3 hours and 21 hours, respectively.

# “from EnrichmentMap to GeneMANIA”

Query : 502 genes  
nc RNA metabolic process



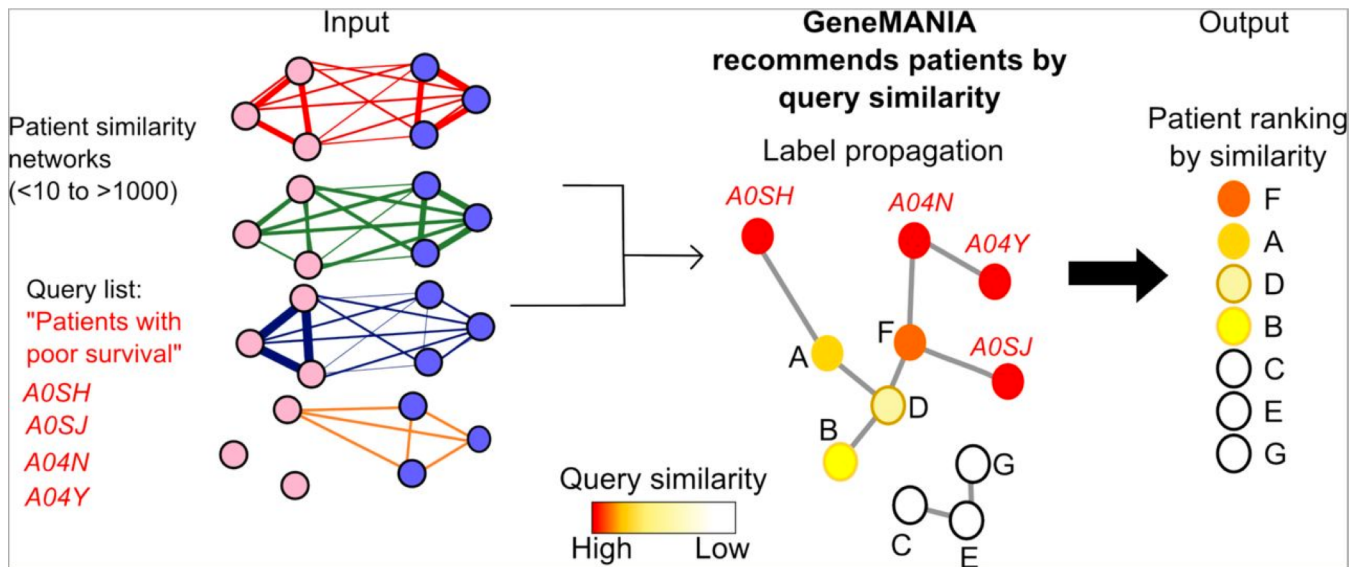
- Right click on pathway of interest
- Select 'Apps'
- Select 'EnrichmentMap – Show in GeneMANIA'

Node size and color: relative to gene expression

# “Advanced topics”

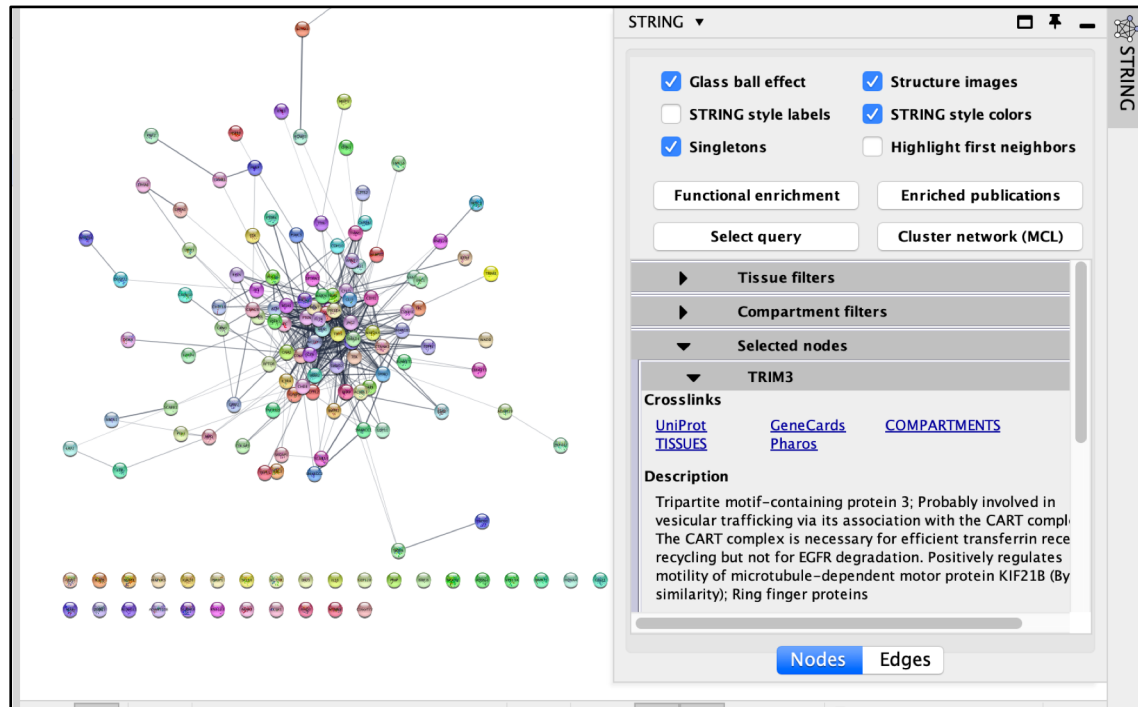
- Possibility to add your model organism if you can construct or have access to interaction networks for it.
- Possibility to use GeneMANIA as an example to assemble different interaction networks that you might have for your research question.

Example: netDx is a **patient classifier** algorithm based on the GeneMANIA algorithm



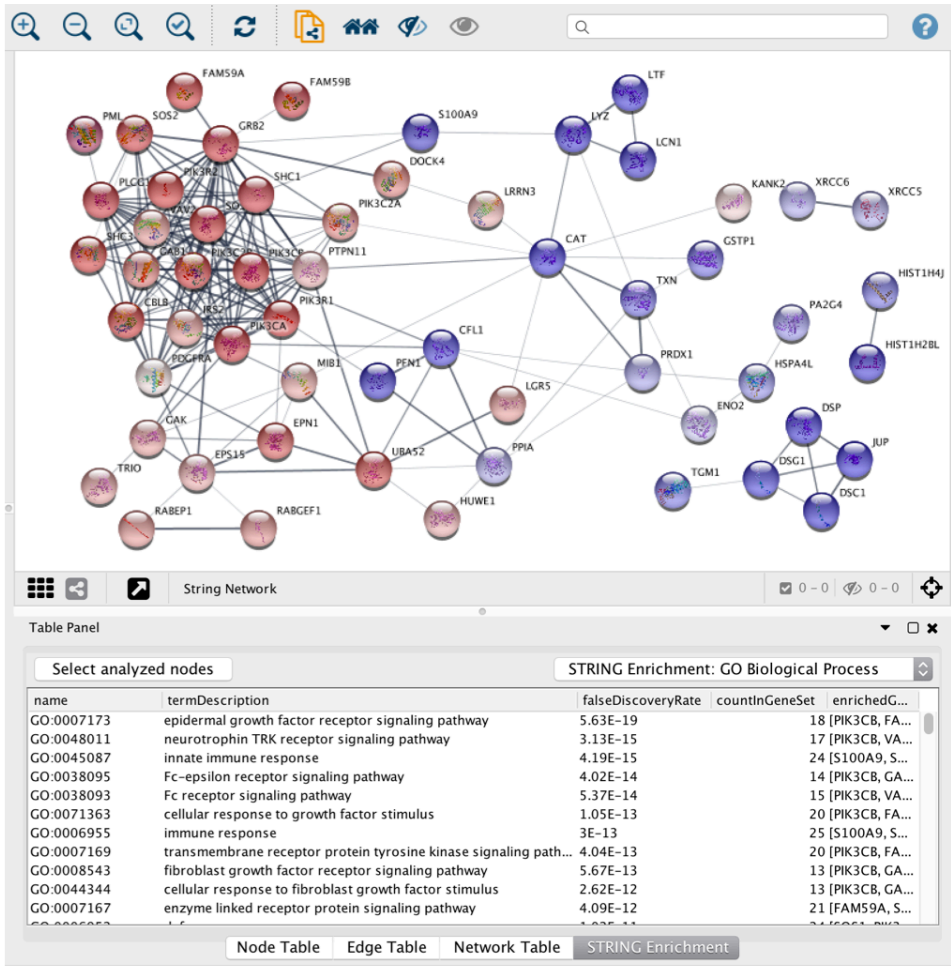
# stringApp

*stringApp* imports **functional associations** or **physical interactions** between protein-protein and protein-chemical pairs from [STRING](https://string-db.org/) (<https://string-db.org/>), [Viruses.STRING](#), [STITCH](#), [DISEASES](#) and from PubMed text mining into Cytoscape.



- Using STRING protein, it creates a protein-protein interaction network from an input gene list.
- It is possible to use the interaction score to reduce the number of interactions and keep the interactions associated with the strongest scores.

- It is possible to perform functional enrichment using the genes on the network



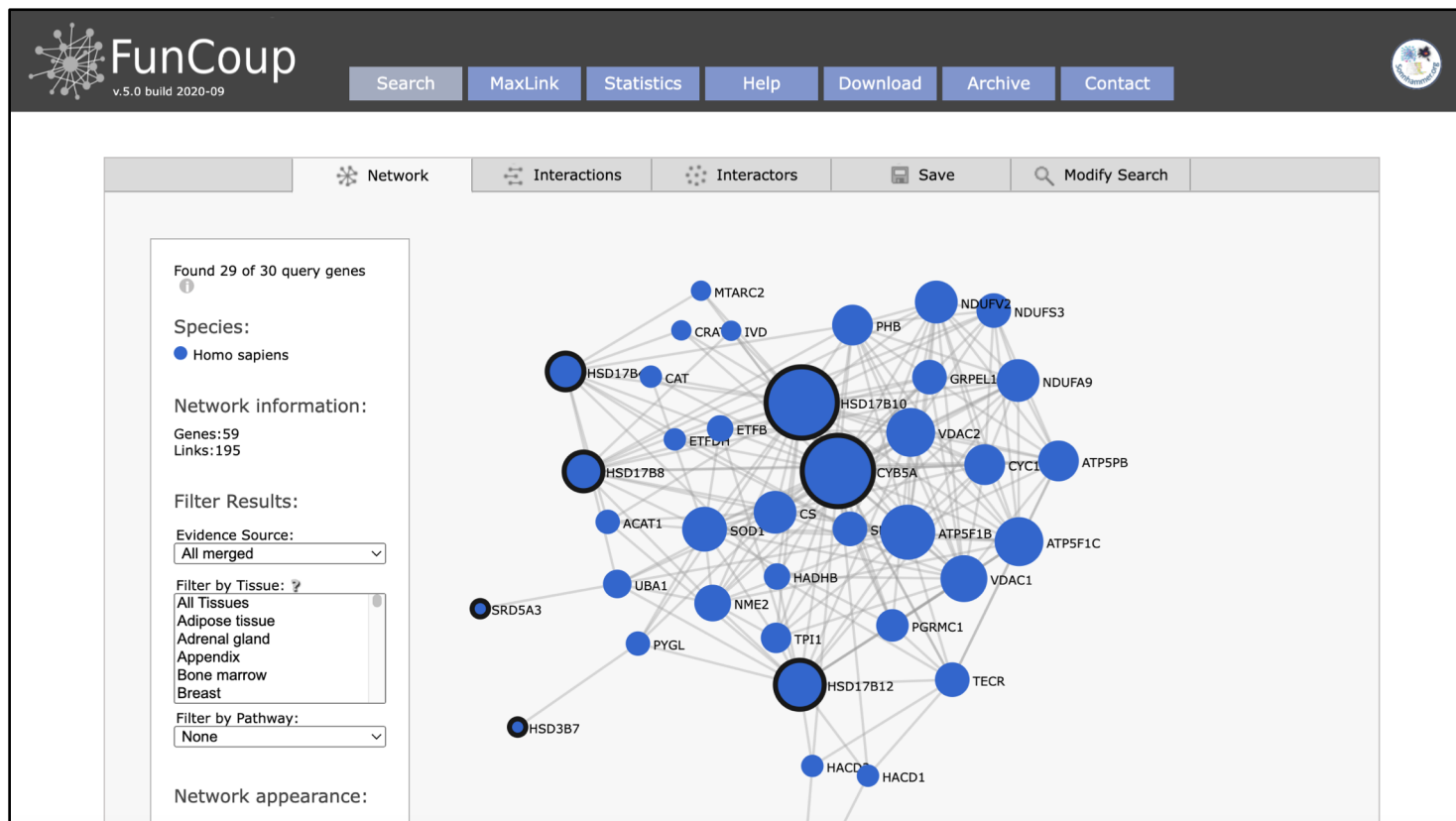
STRING network visualization within Cytoscape for a set of proteins identified using mass spectrometry-based quantitative proteomics (top) and the corresponding enriched GO Biological Process terms (bottom). Figure adapted from Szklarczyk et al., NAR, 2016.



# FunCoup

<https://funcoup.org>

The name FunCoup [fən kəp] stands for functional coupling. FunCoup is a framework to infer genome-wide functional couplings in 21 model organisms. Functional coupling, or functional association, is an unspecific form of association that encompasses direct physical interaction but also more general types of direct or indirect interaction like regulatory interaction or participation in the same process or pathway.



# Acknowledgment

Quaid Morris for his slides and lecture:

<https://www.youtube.com/watch?v=2KrUq9ad2xc&list=PL3izGL6oi0S9amh6Cza1bUo4ICcvZlWF0&index=6>

GeneMANIA developer team: Christian Lopez, Max Franz, Ruth Isserlin, Quaid Morris , Gary Bader

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