Analyzing Gene Relationships for Down Syndrome with Labeled Transition Graphs

Neha Rungta, Hyrum Carroll, Eric Mercer, Mark Clement, and Quinn Snell
Computer Science Department,
Brigham Young University, Provo, UT

Randall Roper
Department of Biology and Indiana University for Regenerative Biology & Medicine, Indiana University-Purdue University,
Indianapolis, IN, USA

Trisomy causes DS

- 1/600 Live Births
- 220,000 individuals per year
- Extra copy of Chr. 21

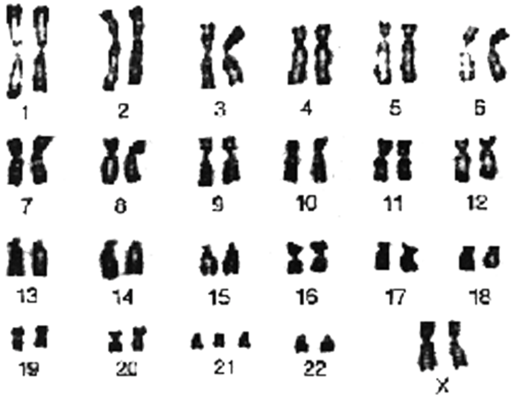
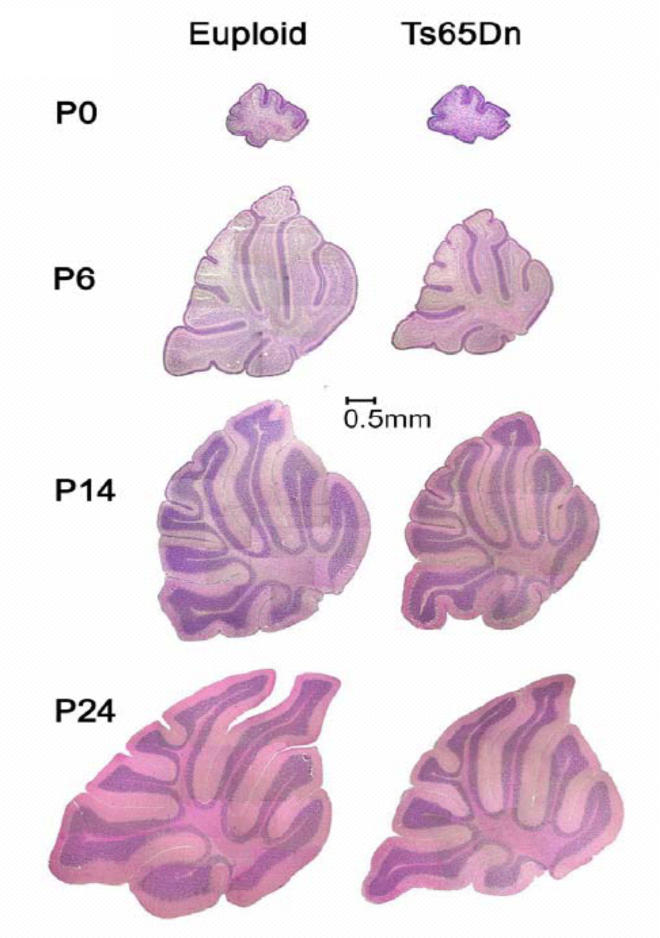


Image courtesy ndss.org

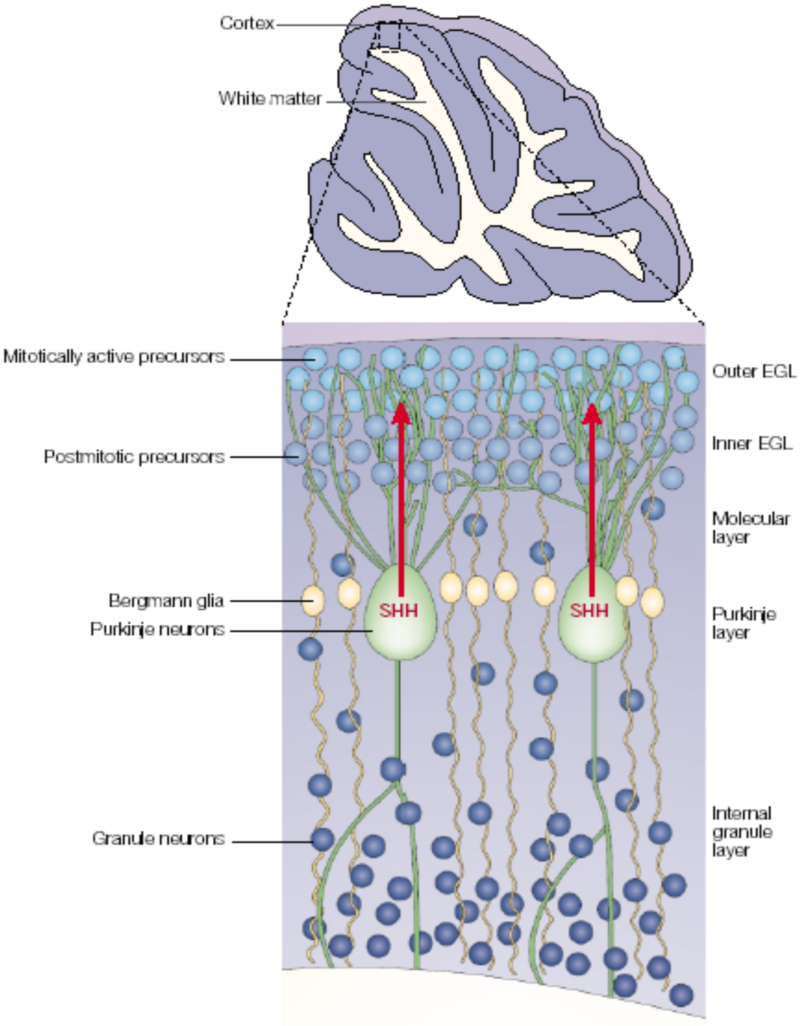
- A subset of 80 clinical features
- Some phenotypes are common
- Variable severity of phenotypes
- Modifier genes affect phenotypes

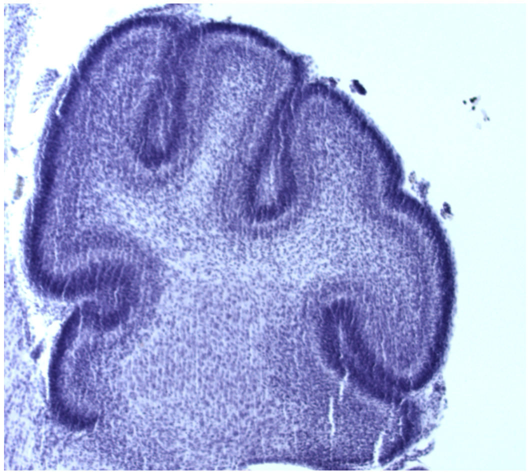
Decreased Cerebellum Size

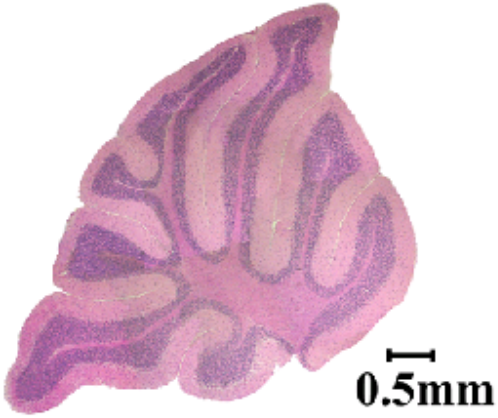


- Euploid are normal mice
- Ts65Dn are DS mouse models
- P0 is 0 postnatal days
- Same cerebellum size at birth
- Different cerebellum size in 6 days

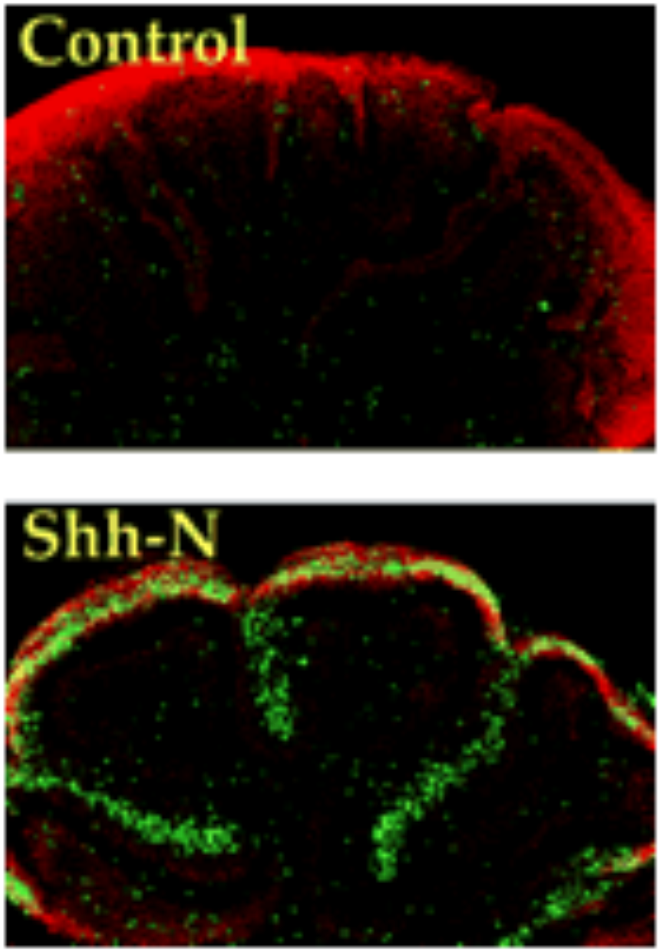
Modifier Gene - SHH



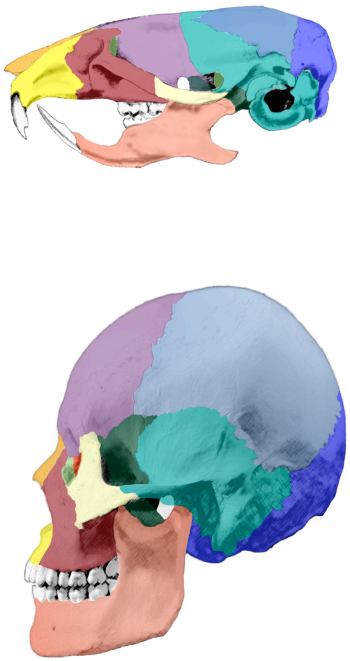


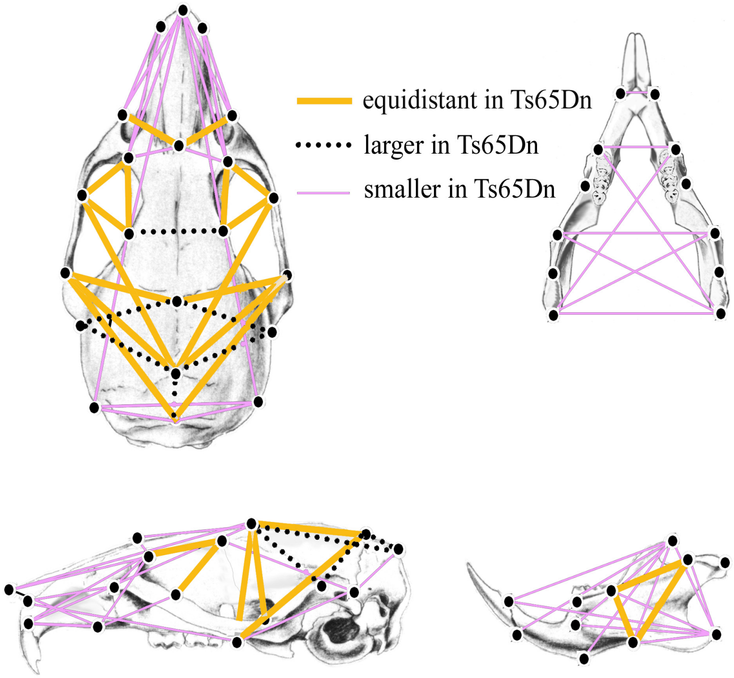


Empirical Evidence



Facial features





SHH affects neural crest

Modifier gene - SHH

- SHH is a modifier gene
- Affects DS phenotypes
- Is key factor in a lot of development
- How the SHH gene is linked to Chr. 21?
- Analyze relationships

Hedgehog signal Pathway

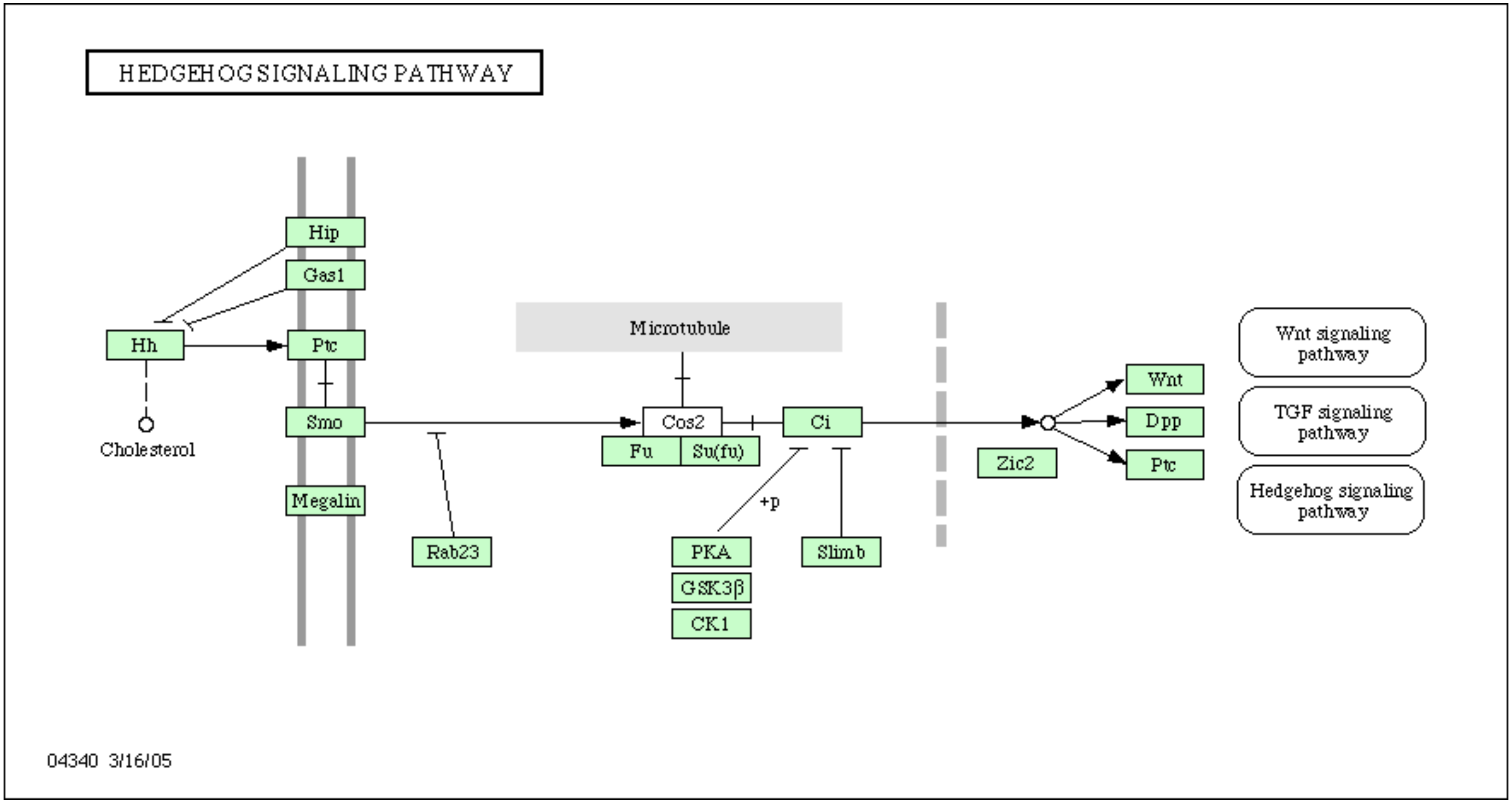


Image courtesy genome.jp

Gene Regulatory Databases

- Gene regulatory networks in systems biology
- Built from empirically curated data
- Pictoral representations are most common
- Gene regulatory database examples
  - Kegg
  - Biocyc
  - Metacyc

Kegg Database

- 1st source of data
- Largest and most comprehensible database
- 175 pathways 12,000 genes - human genome
- Pictorial and XML representation

PubMed Abstracts

- 2nd source of data
- Premier journal for bio-medical articles
- *Bunescu et al.* extract gene relationships using natural language processing algorithms

State of art pathway analysis

- Cyctoscape
- Reactome
- Bind
- Visualize gene regulatory networks
- Basic query mechanisms to probe structure

Formal Verification approaches

- *Heath et al*. (`06), *Kuwahara et al*.(`06), *Kwiatkowska et al*.(`05), and *Dill et al*.(`05).
- Models a single network in isolation
- Predicts pathway behaviors
- Models the different reactions and their rates

Our Approach

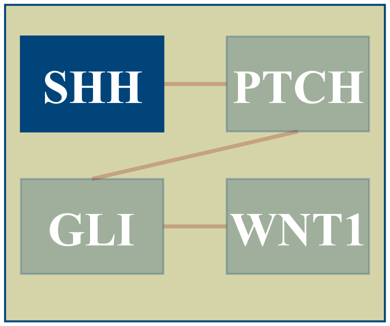
- Abstracts a large amount of information
- Connects different networks
- Single labeled transition graph
- Exhaustive search with a random BFS
- Find relations between SHH and Chr. 21

Graph Construction

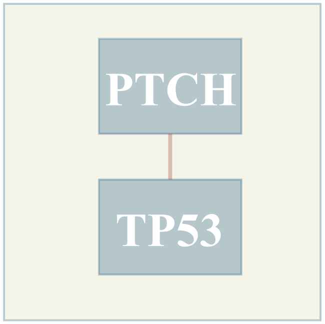
- Take a gene regulatory pathway
- Abstract away the reaction and compounds
- Create intra-pathway gene connections
- Create inter-pathway gene connections
- Add PubMed relations

Example

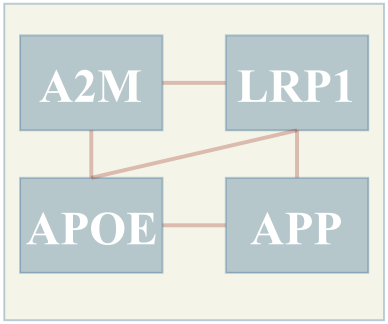
Hedgehog Signaling Pathway (HSP)



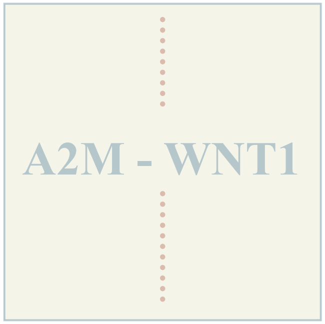
Basal Cell-Carcinoma (BCC)

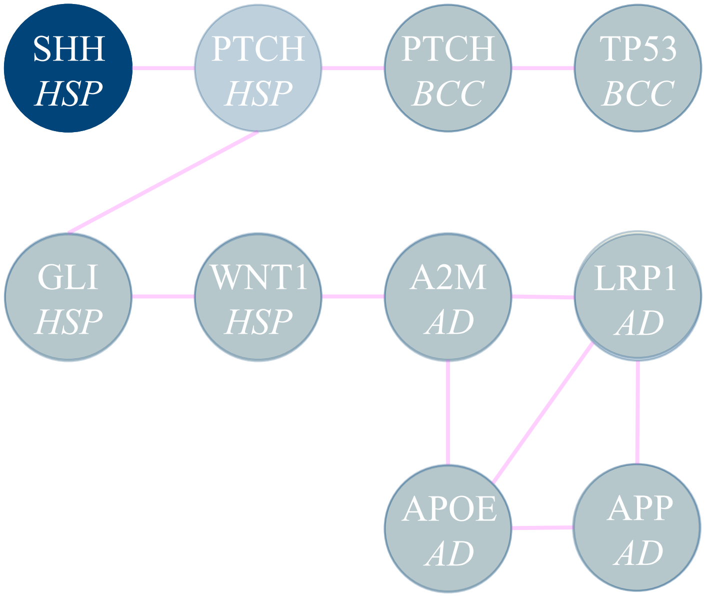


Alzheimer's Disease (AD)



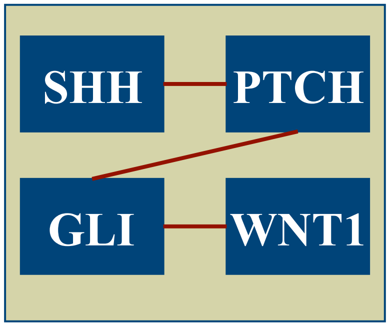
PubMed Relations



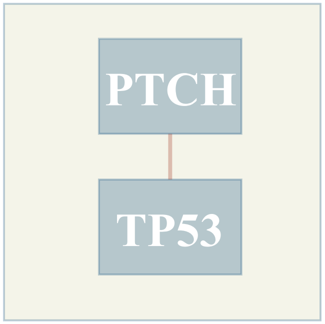


Example

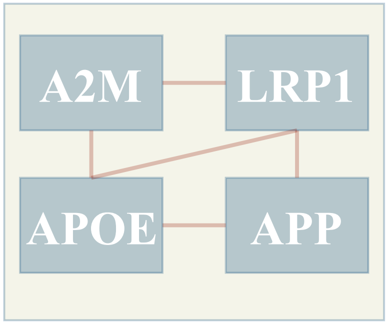
Hedgehog Signaling Pathway (HSP)



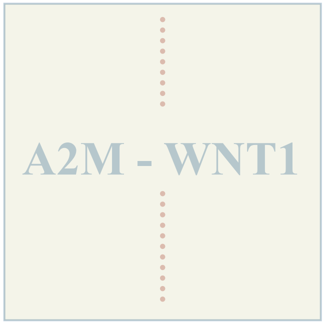
Basal Cell-Carcinoma (BCC)

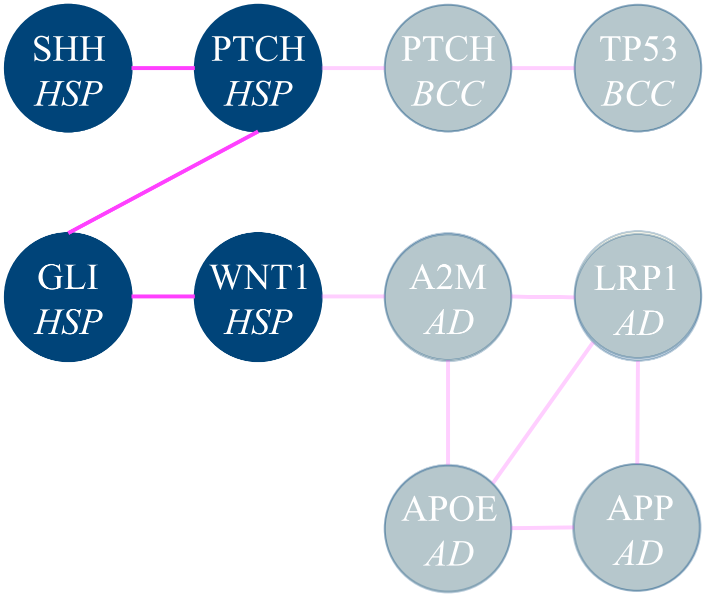


Alzheimer's Disease (AD)



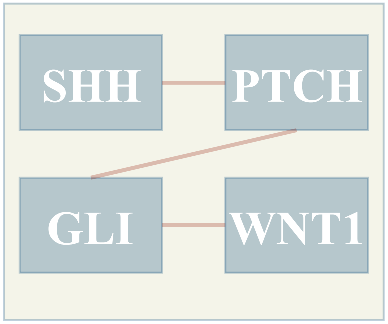
PubMed Relations



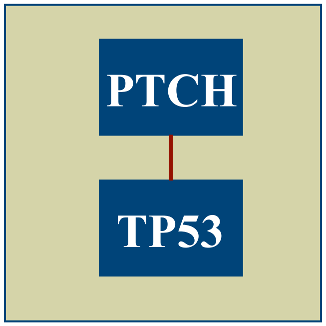


Example

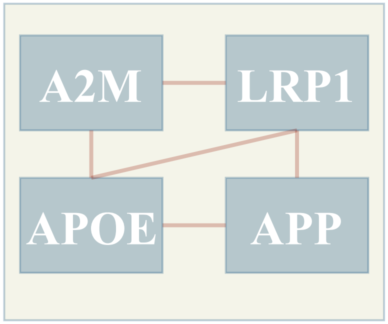
Hedgehog Signaling Pathway (HSP)



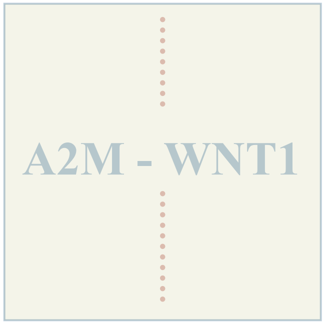
Basal Cell-Carcinoma (BCC)

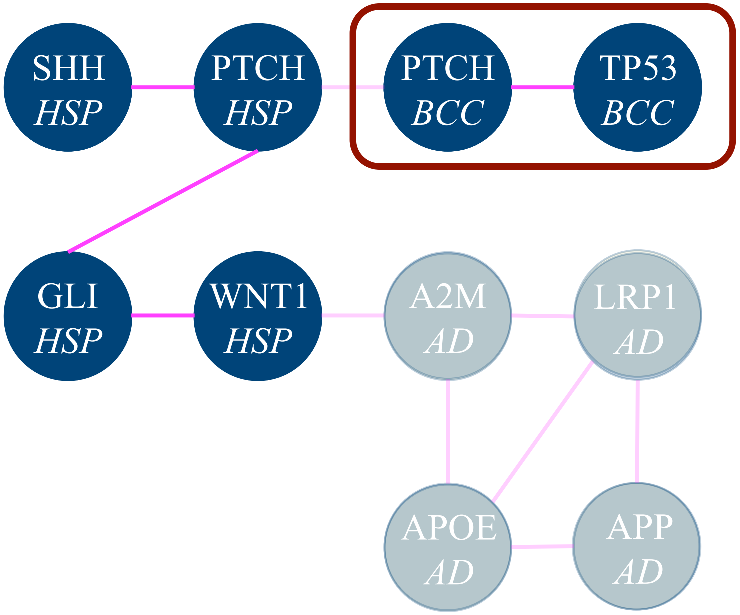


Alzheimer's Disease (AD)



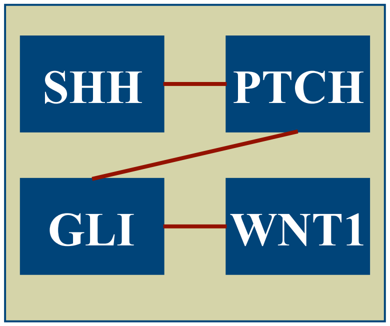
PubMed Relations



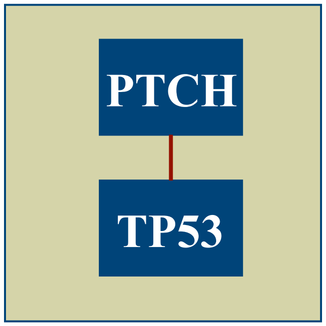


Example

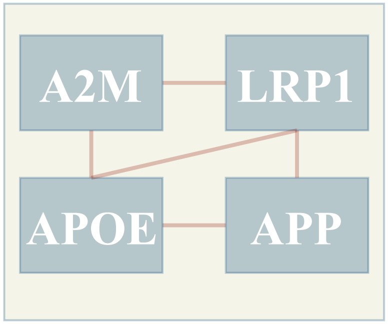
Hedgehog Signaling Pathway (HSP)



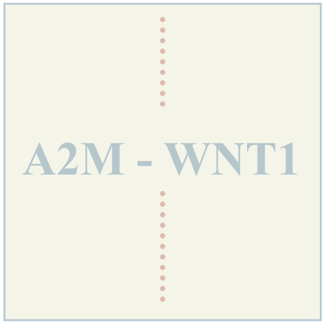
Basal Cell-Carcinoma (BCC)

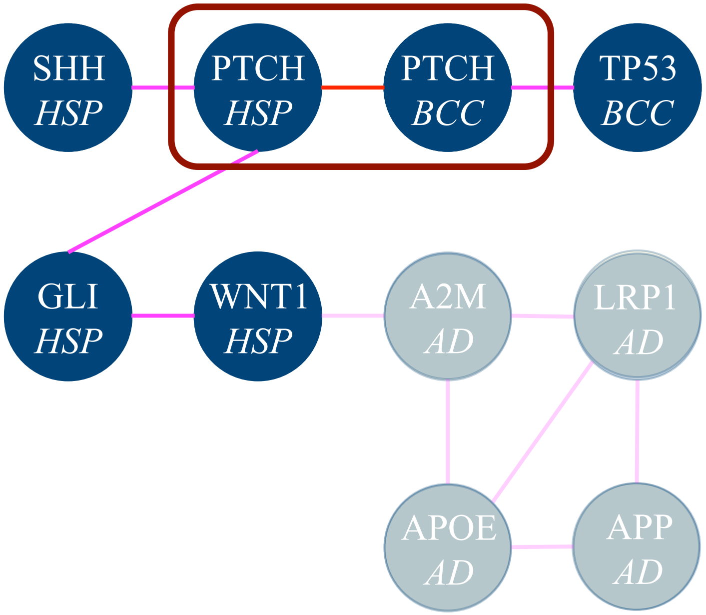


Alzheimer's Disease (AD)



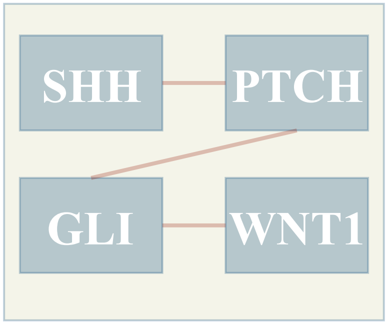
PubMed Relations



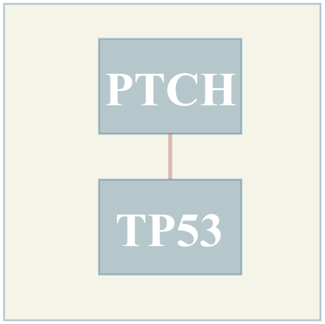


Example

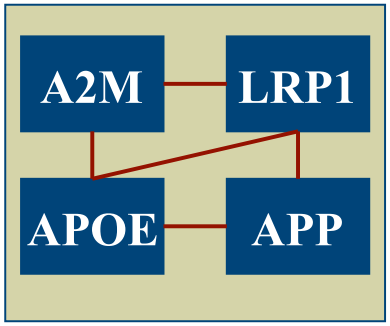
Hedgehog Signaling Pathway (HSP)



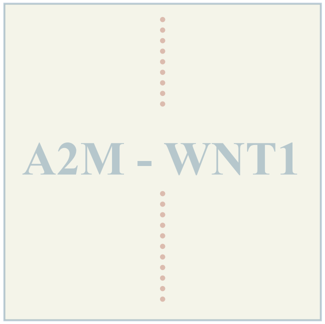
Basal Cell-Carcinoma (BCC)

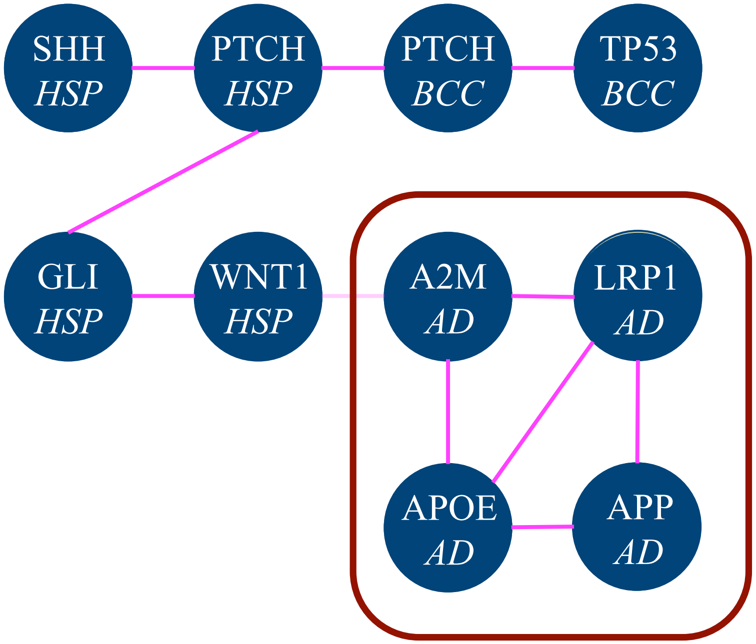


Alzheimer's Disease (AD)



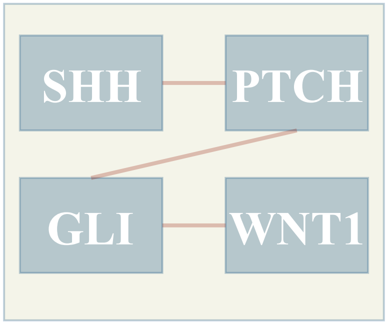
PubMed Relations



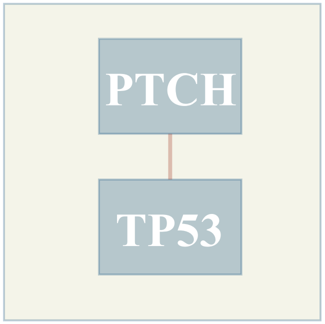


Example

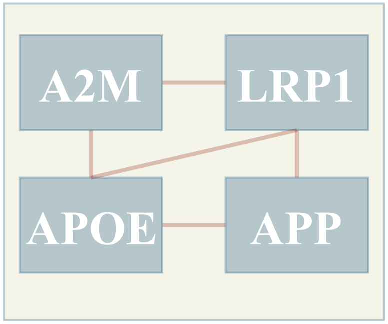
Hedgehog Signaling Pathway (HSP)



Basal Cell-Carcinoma (BCC)

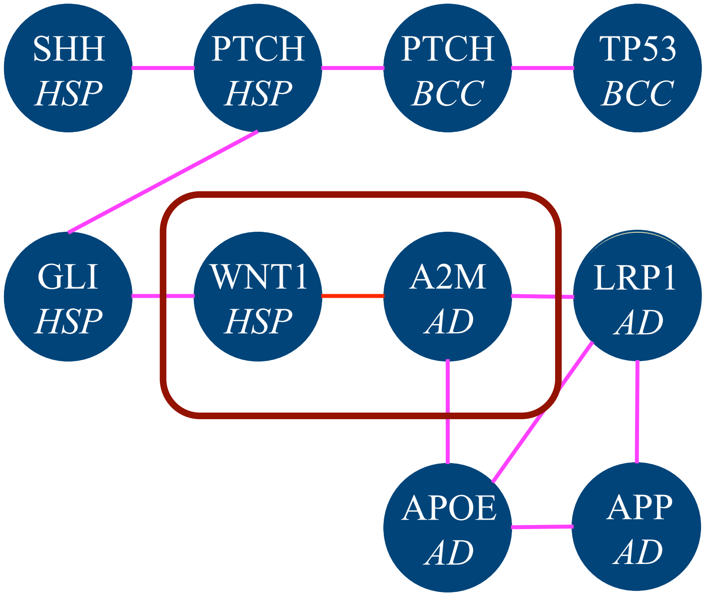


Alzheimer's Disease (AD)



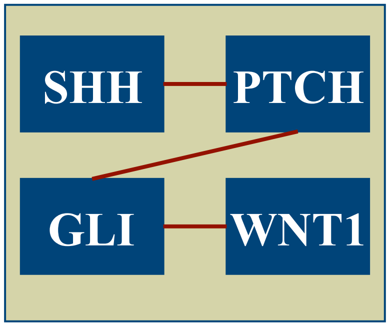
PubMed Relations

A2M - WNT1

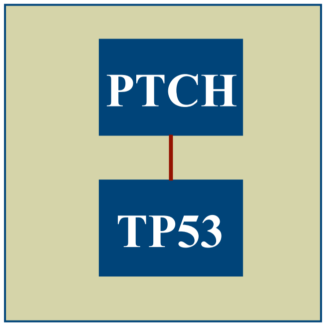


Example

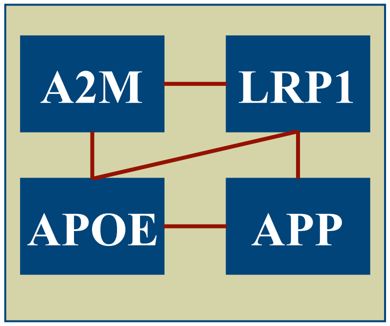
Hedgehog Signaling Pathway (HSP)



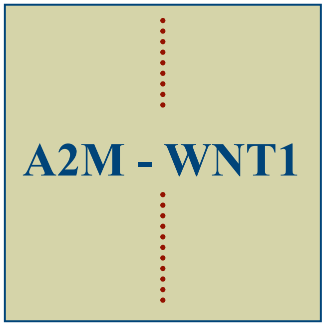
Basal Cell-Carcinoma (BCC)

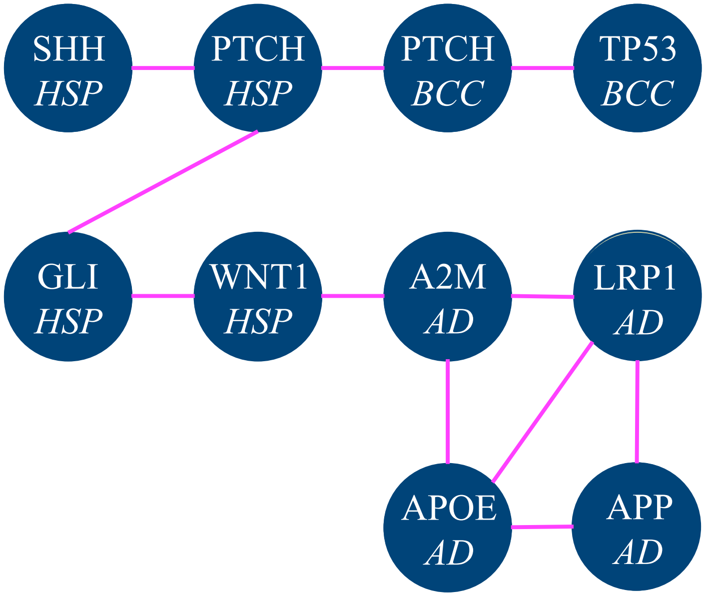


Alzheimer's Disease (AD)



PubMed Relations

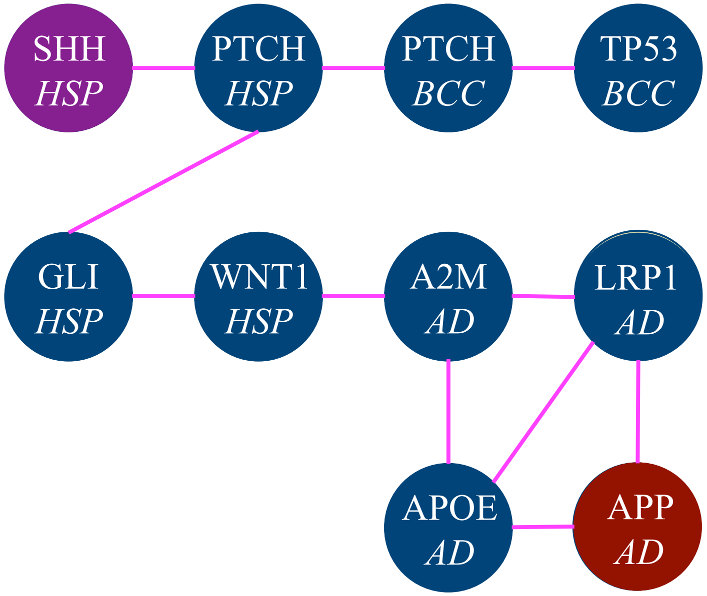




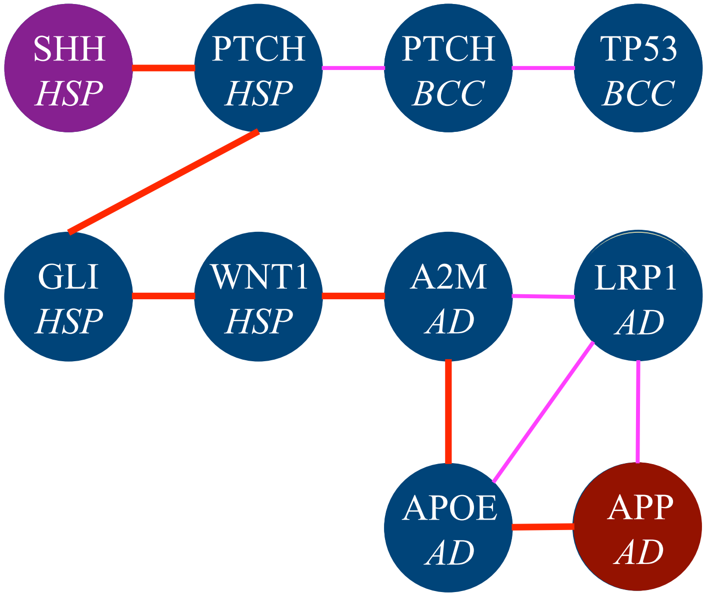
Analysis

- 12,000 nodes
- 1 million edges
- 90% connections due to abstraction
- Large unique shortest paths
- Random BFS allows sampling

Random BFS

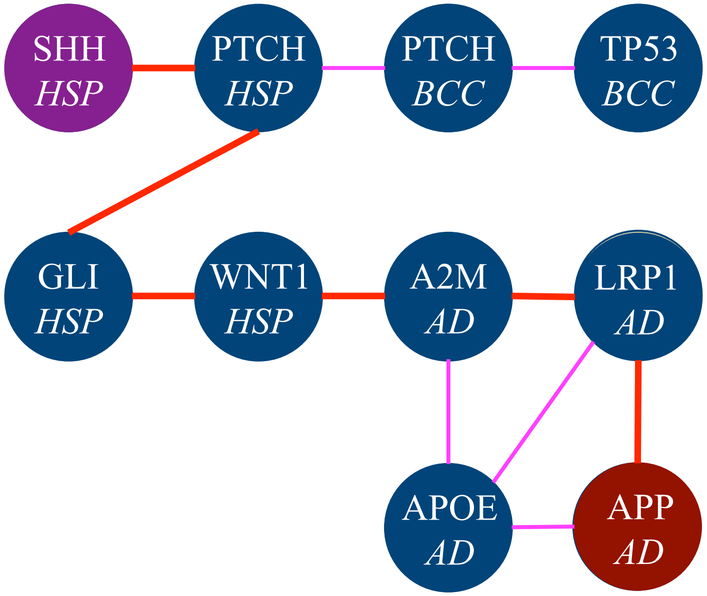

SHH
HSP
PTCH
HSP
PTCH
BCC
TP53
BCC
GLI
HSP
WNT1
HSP
A2M
AD
LRP1
AD
APOE
AD
APP
AD

Random BFS



6 steps

Random BFS



6 steps

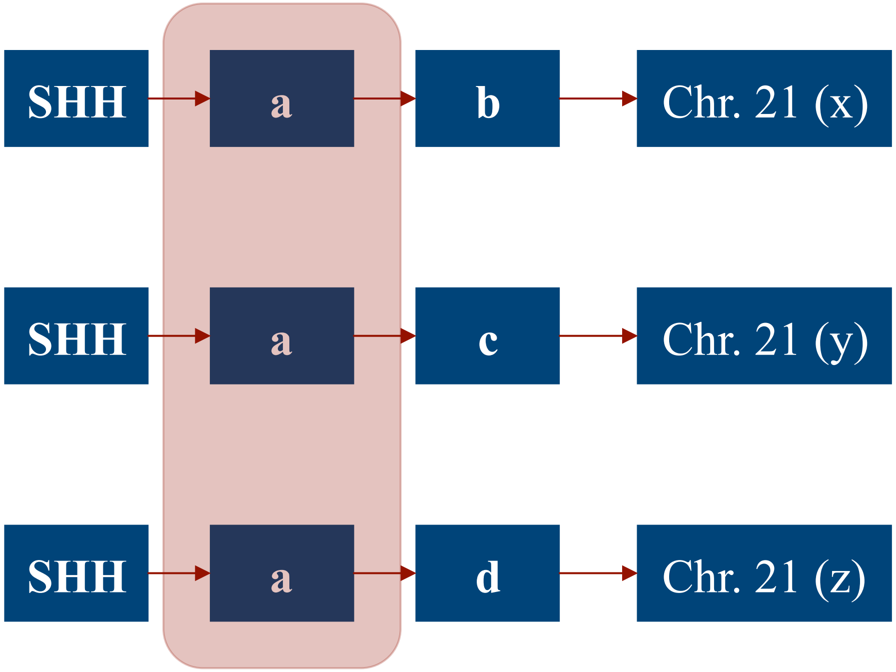
Metric

SHH → **a** → **b** → Chr. 21 (x)

SHH → **a** → **c** → Chr. 21 (y)

SHH → **a** → **d** → Chr. 21 (z)

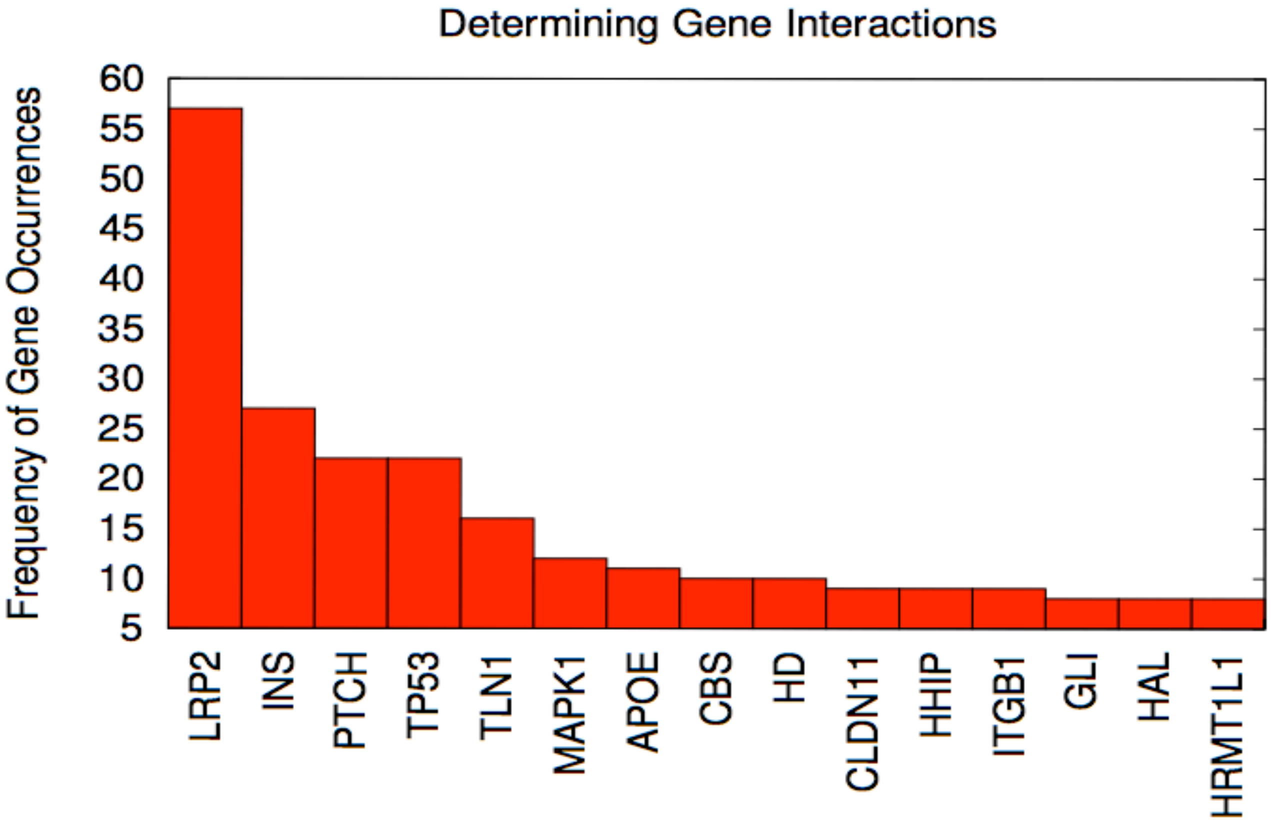
Metric


SHH → a → b → Chr. 21 (x)

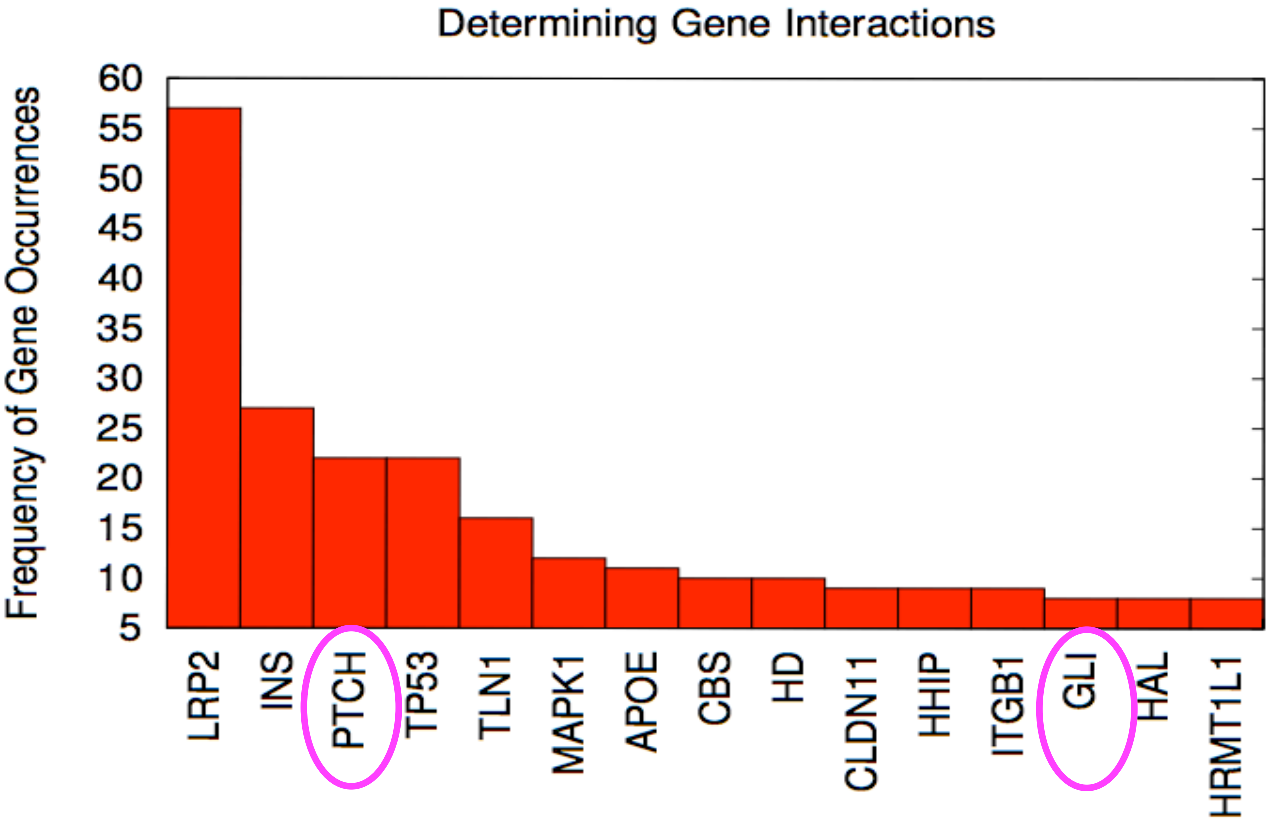
SHH → a → c → Chr. 21 (y)

SHH → a → d → Chr. 21 (z)

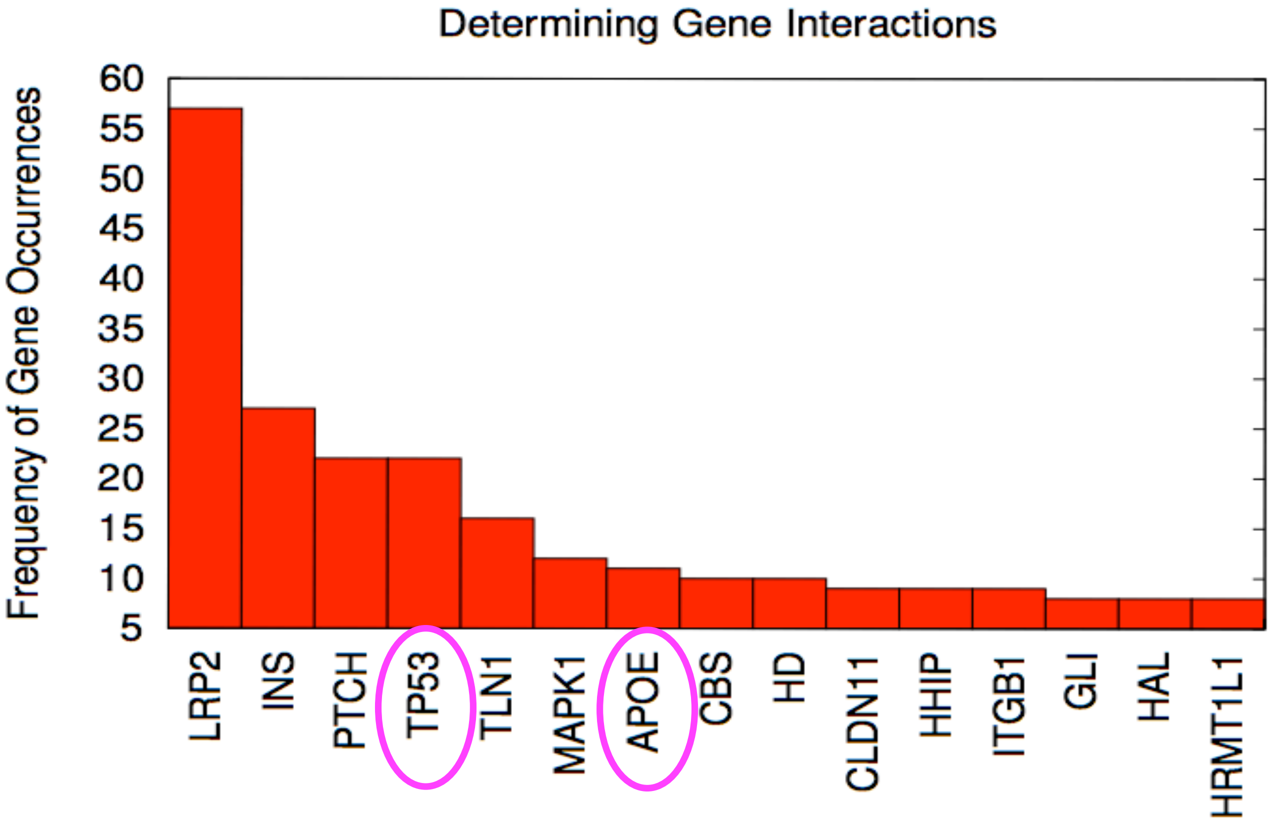
Gene Relations



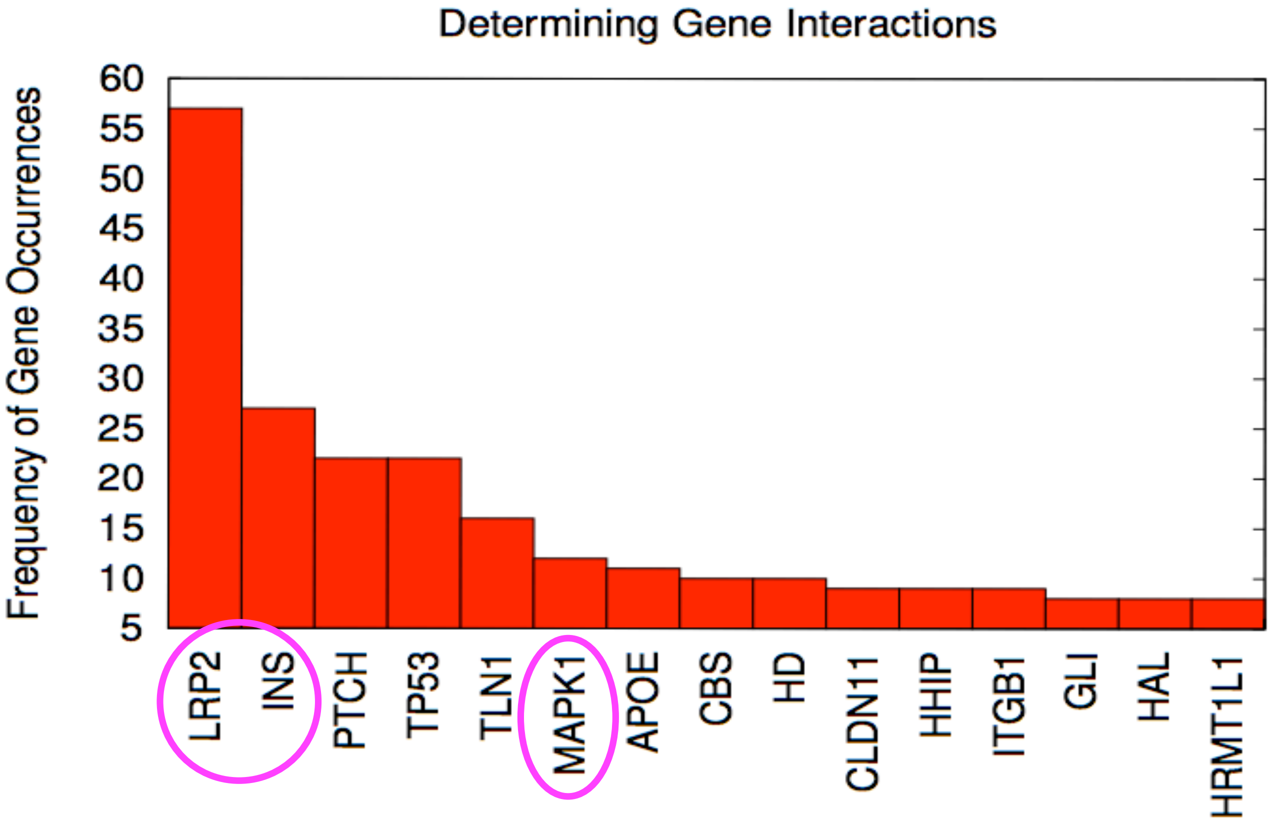
Gene Relations



Gene Relations



Gene Relations



Conclusions & Future Work

- New technique to combine different gene regulatory networks with a transition graph
- Discovers new relations

- More refined analysis with transition graphs
- Use temporal logic to pose interesting questions

Questions ?

History?

Image courtesy amazon.com

History?

Image courtesy
hedgehogs.org