Understanding the molecular basis of human disease by mapping across tissues and organisms

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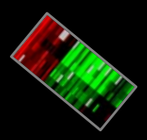
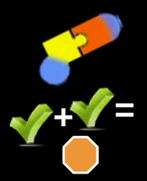
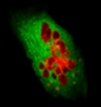
From “BIG” genomics data to understanding of biology and human disease



- Gene expression



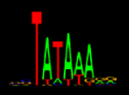
- Physical PPIs
- Epistatic interactions



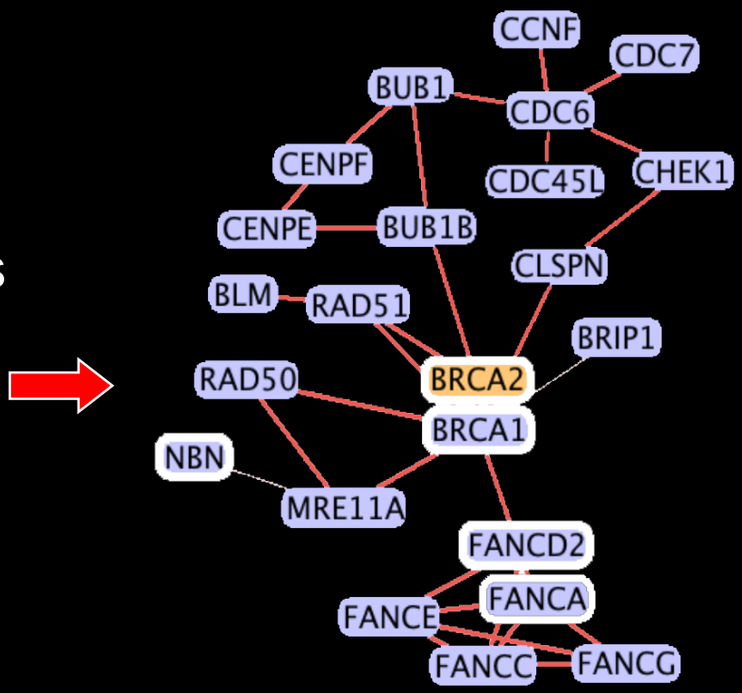
- Colocalization

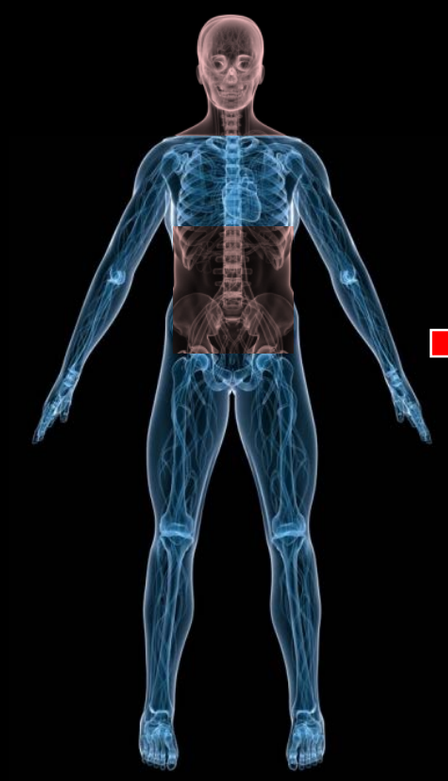
- Sequence

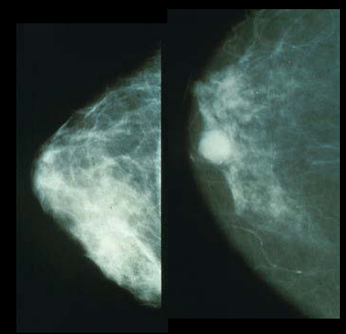
- Protein domains



- Regulatory binding sites

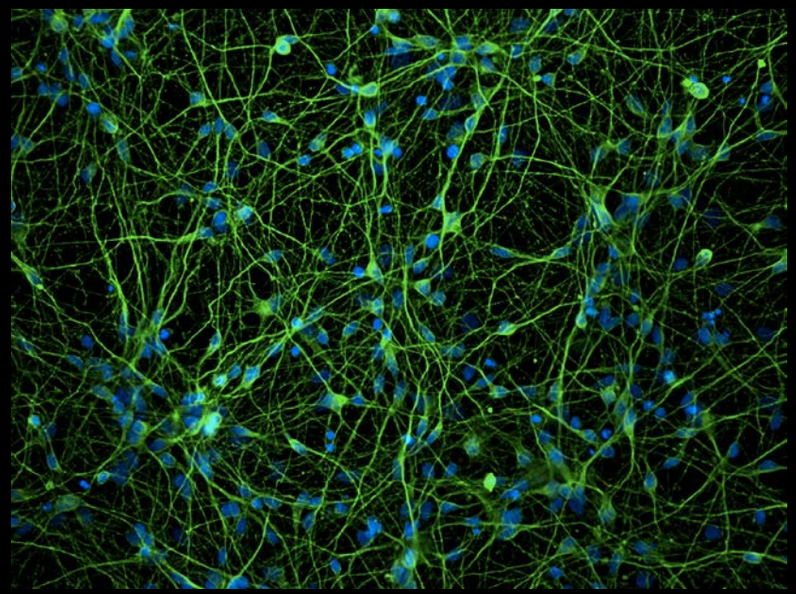


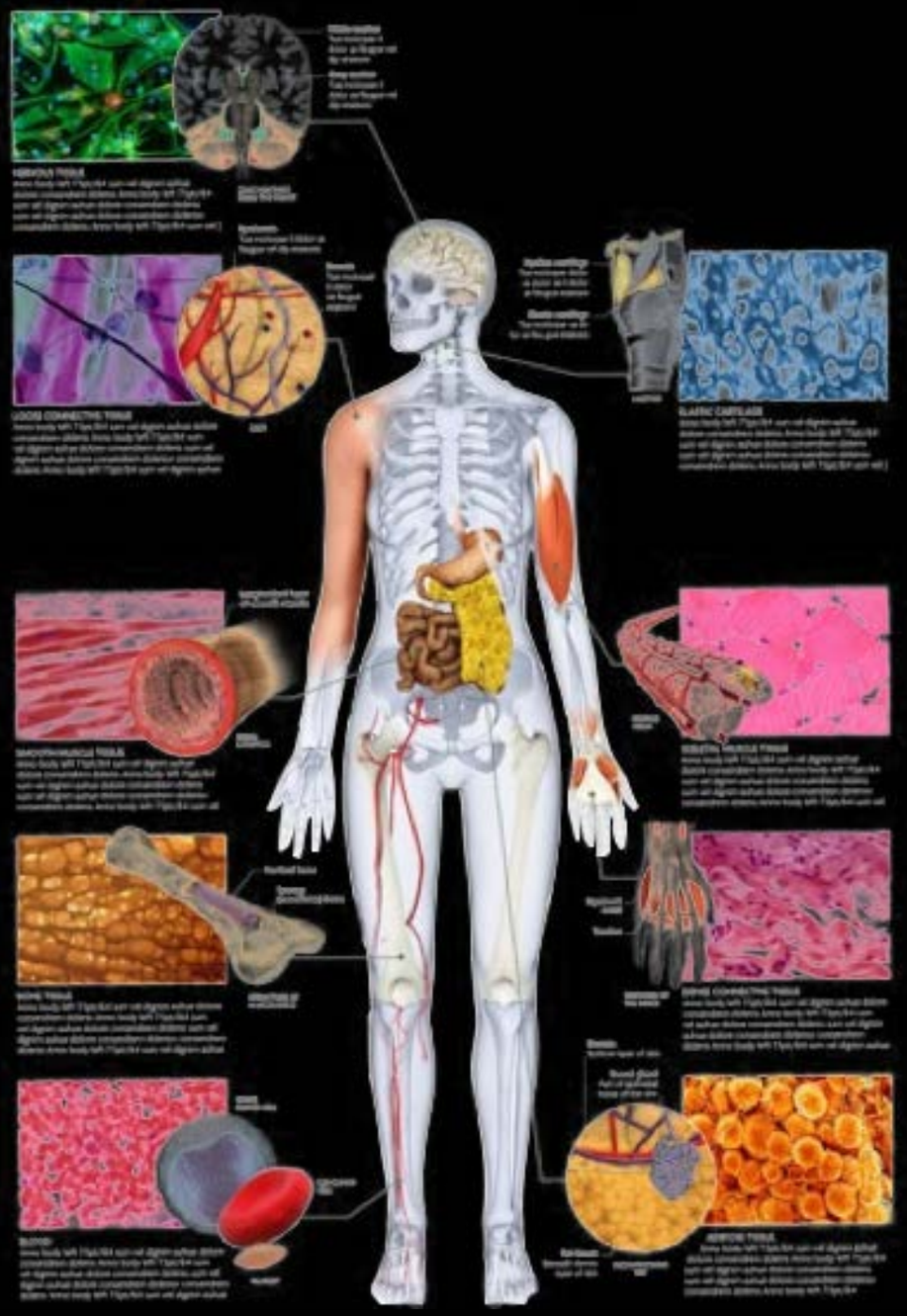


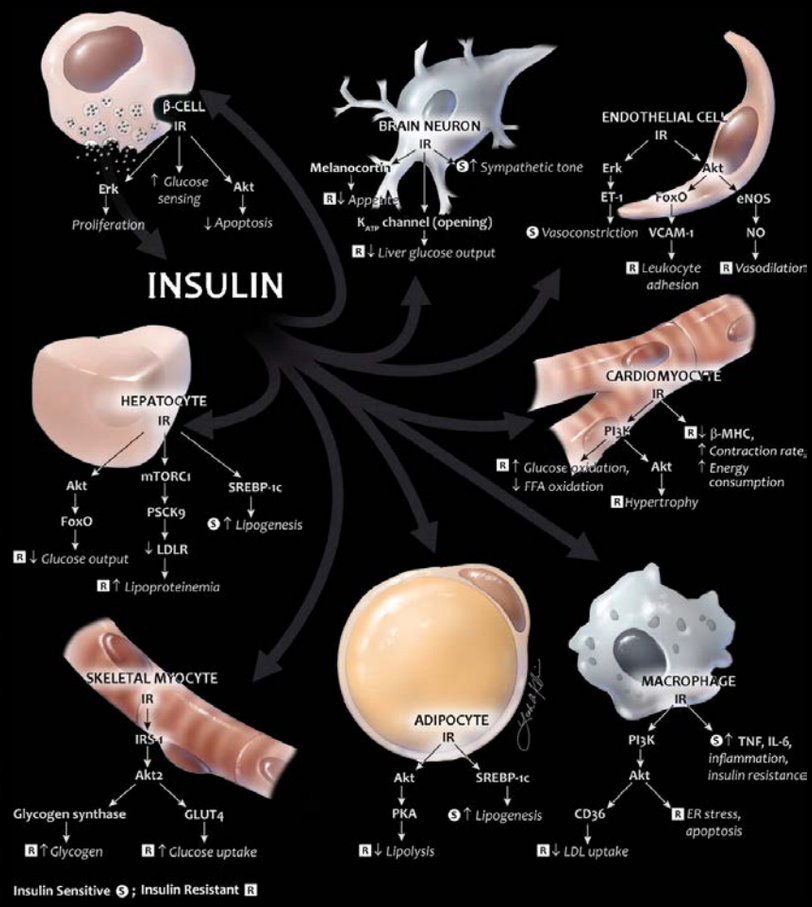


- Using functional genomics data in human to discover disease genes
- Combining functional genomics with quantitative genetics
- Leveraging the power of model organisms on a systems level

From “Big Data” in functional genomics to disease-relevant molecular maps

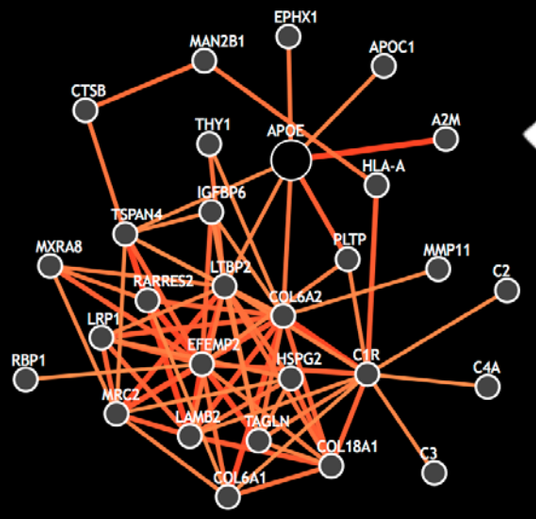


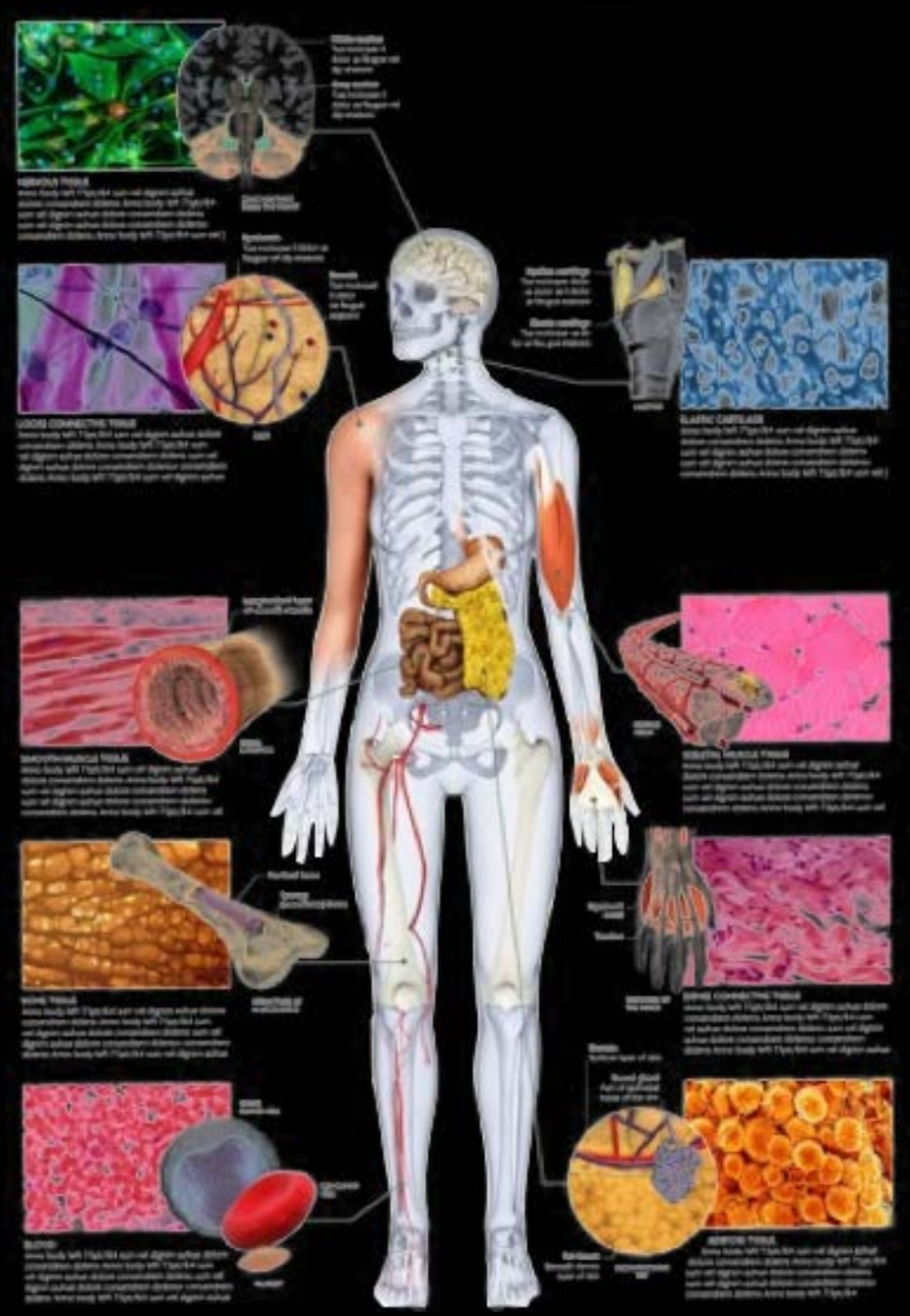


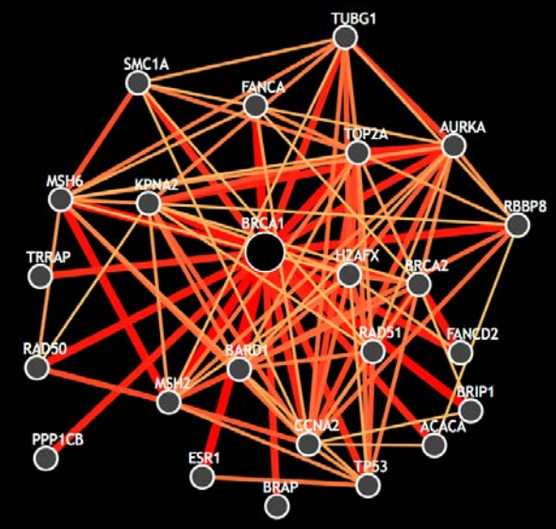


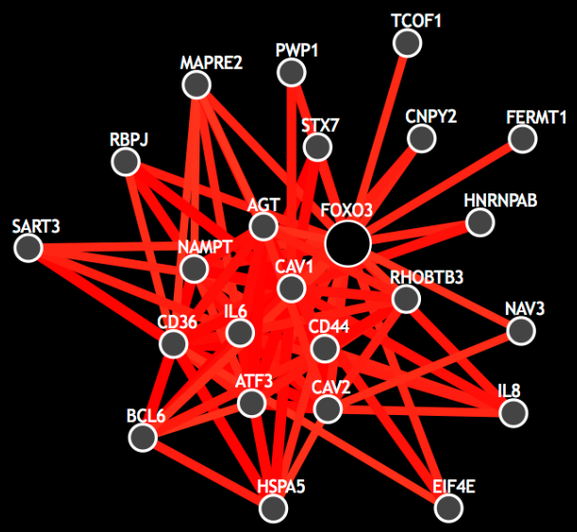
http://www.globalstem.com/image/data/Stem-Neural/Copyright%20Khvatkina-DOPA-20x-6M.jpg

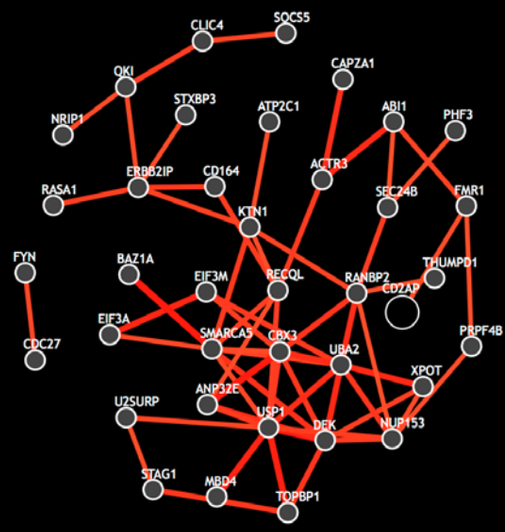
We need to understand pathways and processes in a cell- and tissue-specific context









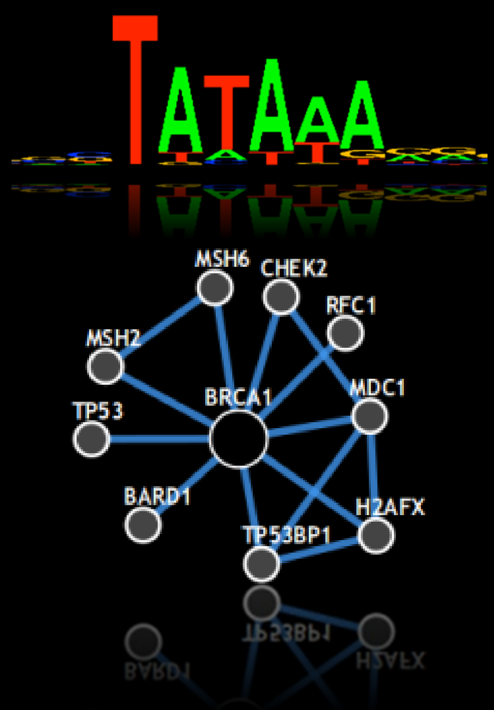


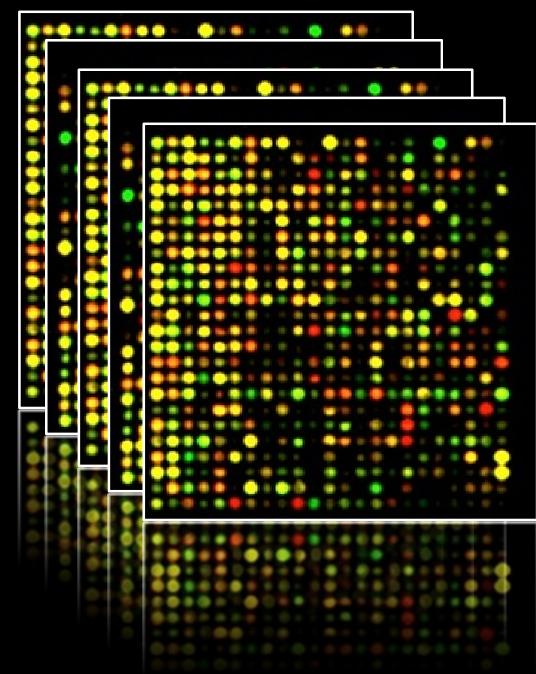
Casey Greene Aaron Wong Arjun Krishnan

With Garret Fitzgerald's and Tilo Grosser's groups (Penn), Daniel Chasman (Brigham and Women's Hospital, Harvard), Kara Dolinski (Princeton)

Greene et al. ***Nature Genetics***, 2015

There’s a *flood* of high-throughput genomic data





987 datasets with genome-wide measures; ~38,000 conditions from ~14,000 publications

- Physical & genetic interactions
- TF-binding / miRNA-target sites
- Gene expression profiles

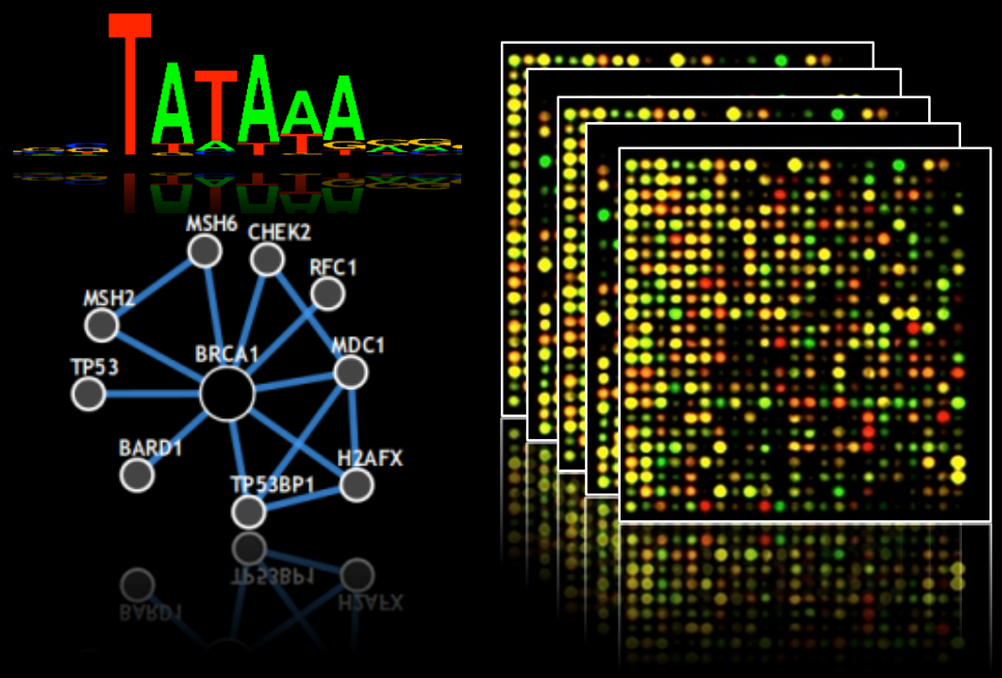
- Noisy & Heterogenous
- Not resolved to cell types & tissues
  - Many datasets are not annotated to cell-type/tissue of origin
  - Most sample are cell-type/tissue mixtures
  - Many cell-types are hard to isolate or not enough to profile

1

We need to extract tissue-specific signal from data that is not resolved to tissue/cell-type

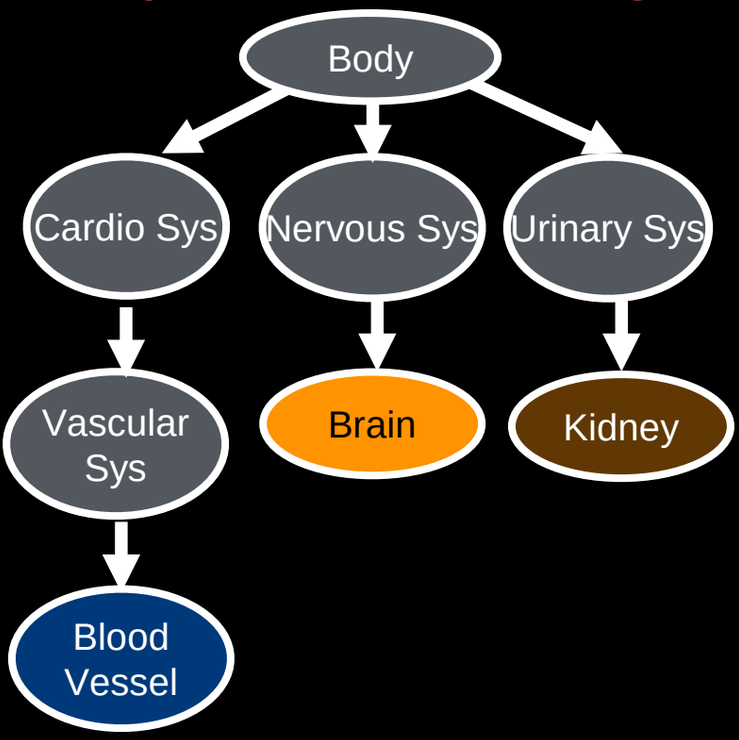
Integrating human tissue-specific networks

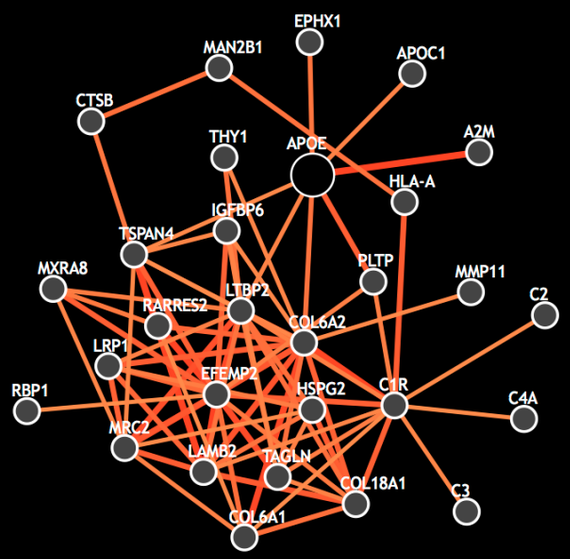
1 1000s of Genomic datasets



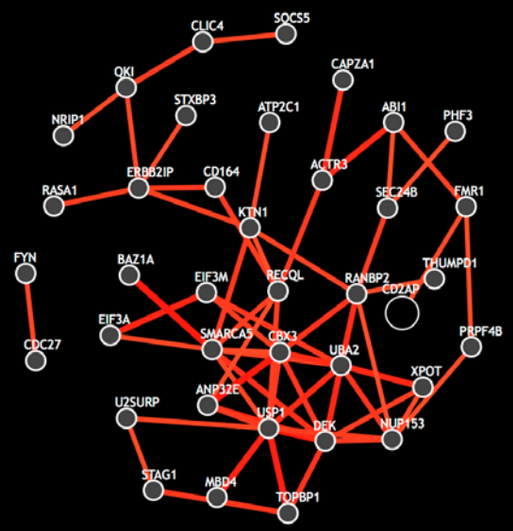
Machine learning classifier

2 Hierarchically integrated tissue-specific knowledge

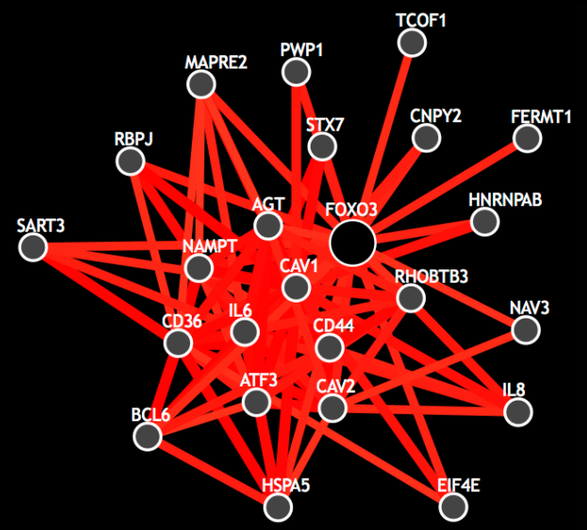




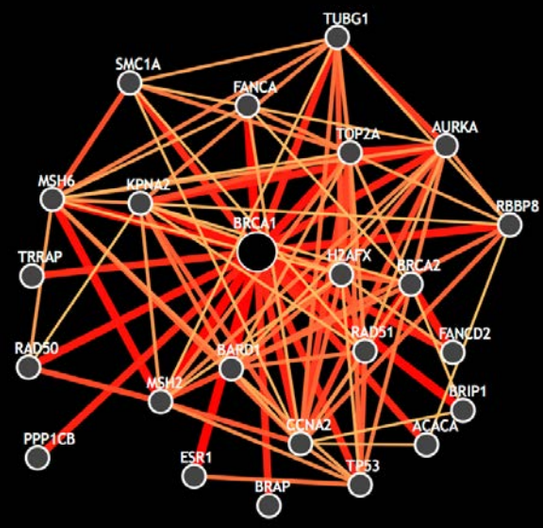
brain



kidney



blood vessel



muscle

144 Tissue-specific networks

Tissue networks can predict disease-relevant lineage-specific response

Computational Prediction

Top 20 functional neighbors of IL1B in the blood vessel network

Experimental Validation

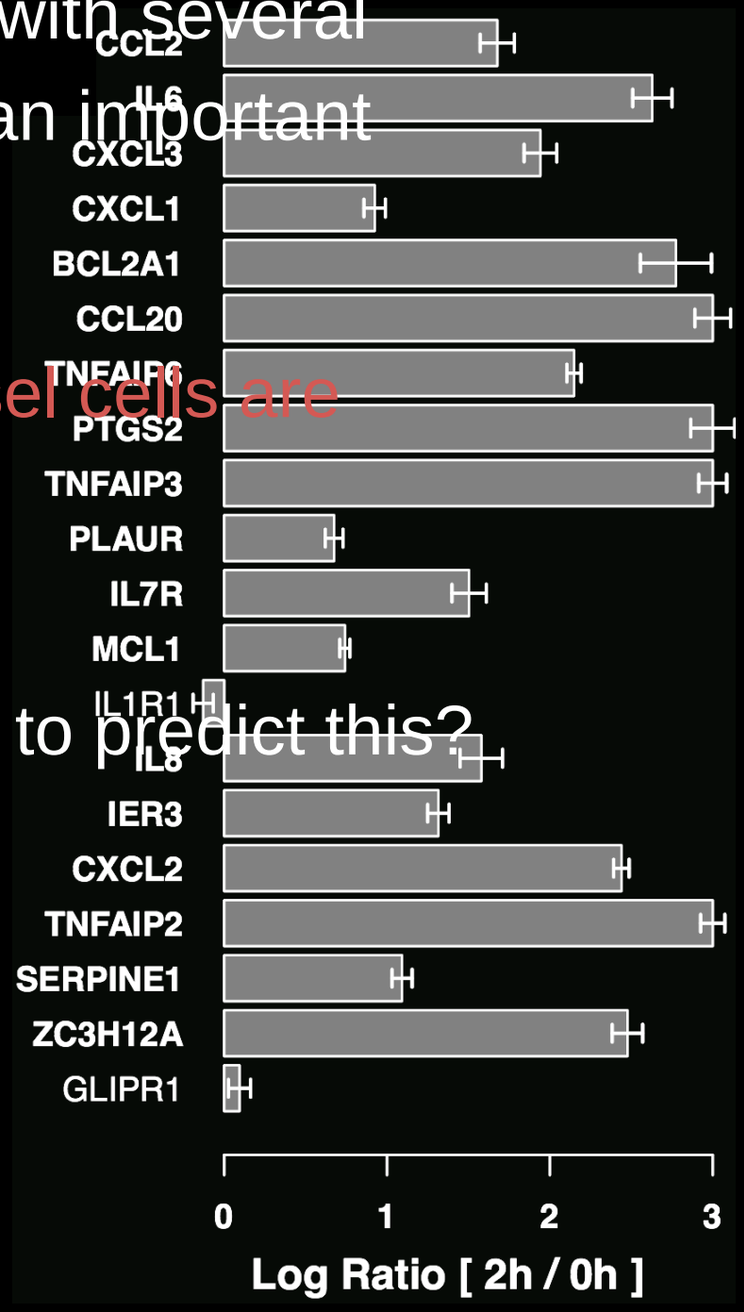
Transcriptional profiling of IL1B stimulation

Inflammation in blood vessel is associated with several cardiovascular diseases. Cytokine IL1B is an important mediator of inflammatory response.

Which genes will respond when blood vessel cells are stimulated with IL1B?

18/20 network neighbors respond to IL1B

p = 1.95e-23



The *blood vessel* network is the most accurate one in predicting IL1B response in blood vessel cells.

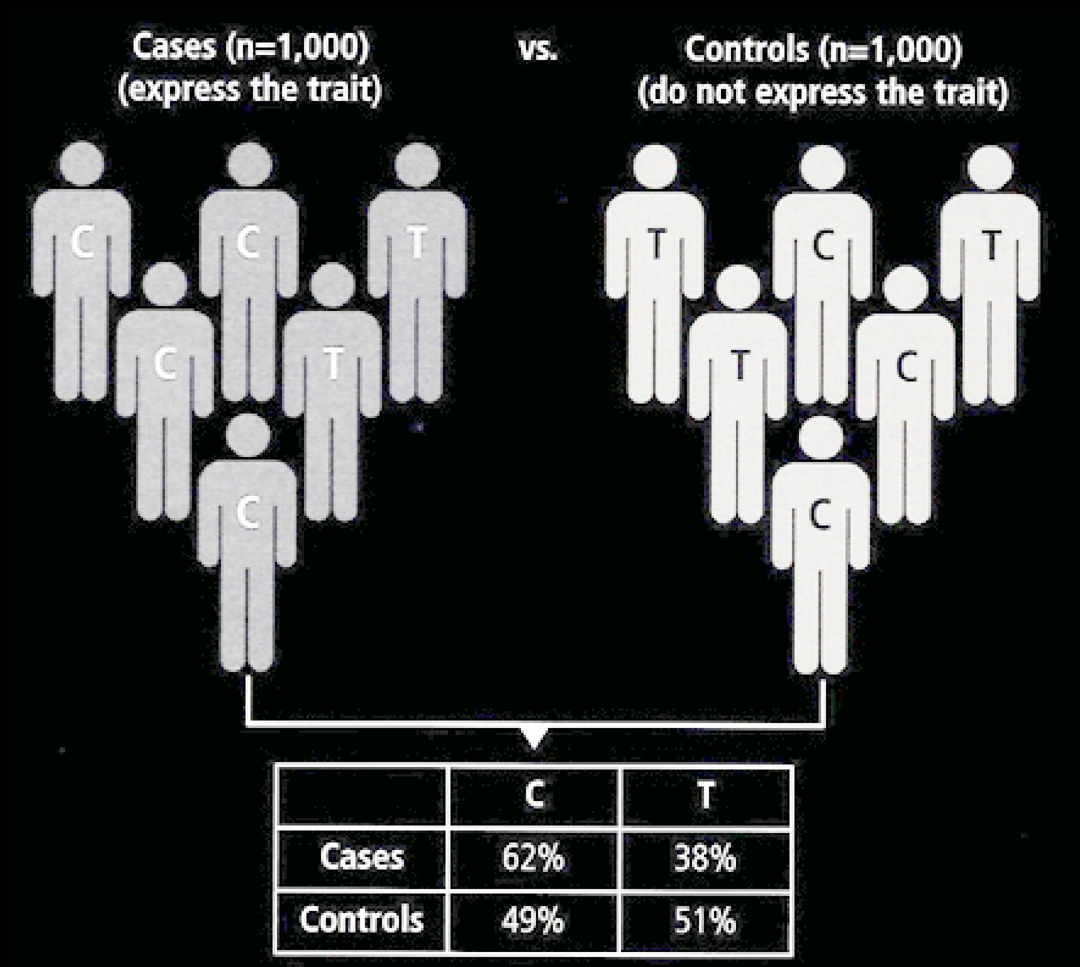
essel specific network to predict this?

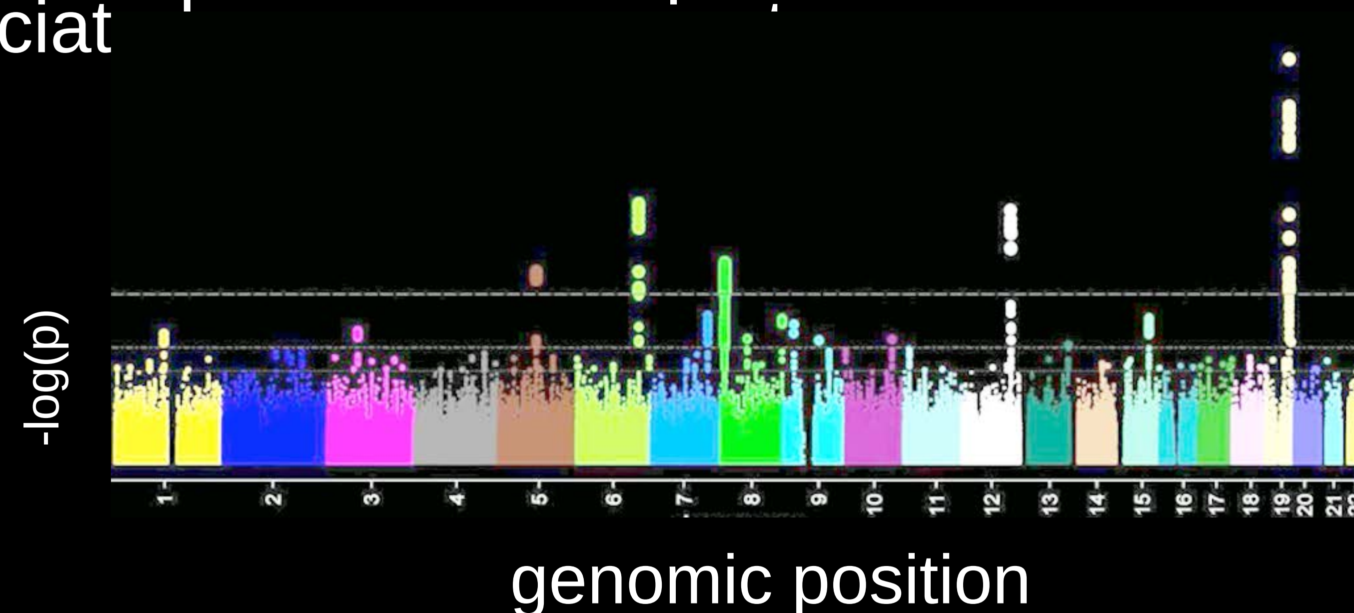
With Emanuela Ricciotti and Tilo Grosser

NetWAS: Network-based approach for reprioritizing GWAS results to identify disease genes and potential drug targets

Genome-wide association study (GWAS) is a powerful approach

to catalogue trait-associat





Low statistical strength

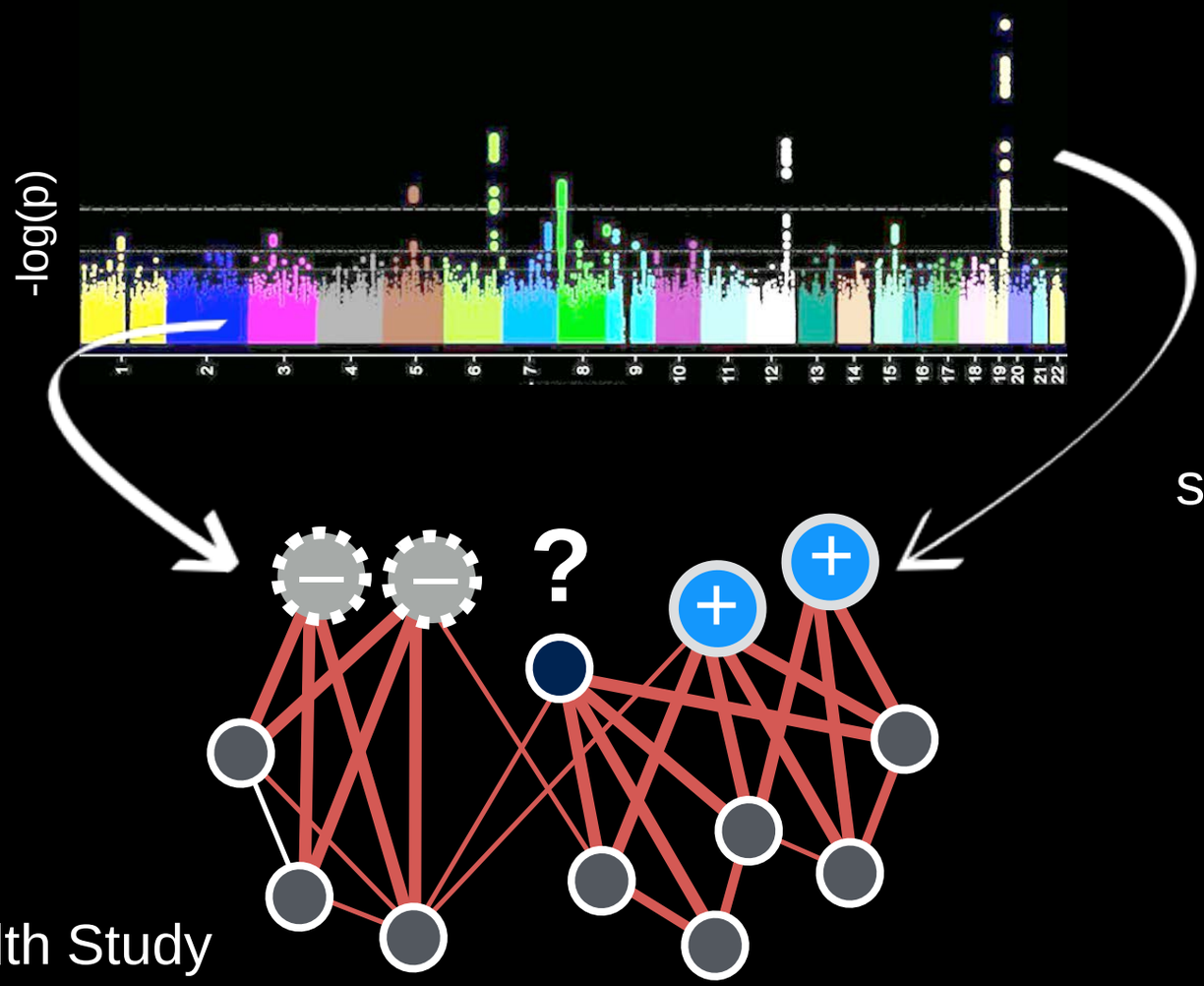
- Low frequency mutations
- Small effect sizes
- Epistasis

Can we improve GWAS results using tissue-specific networks?

Greene et al. ***Nature Genetics***, 2015

NetWAS: Network-based approach for reprioritizing GWAS results

Top GWAS hits for a disease – e.g. hypertension – are potentially enriched for disease genes



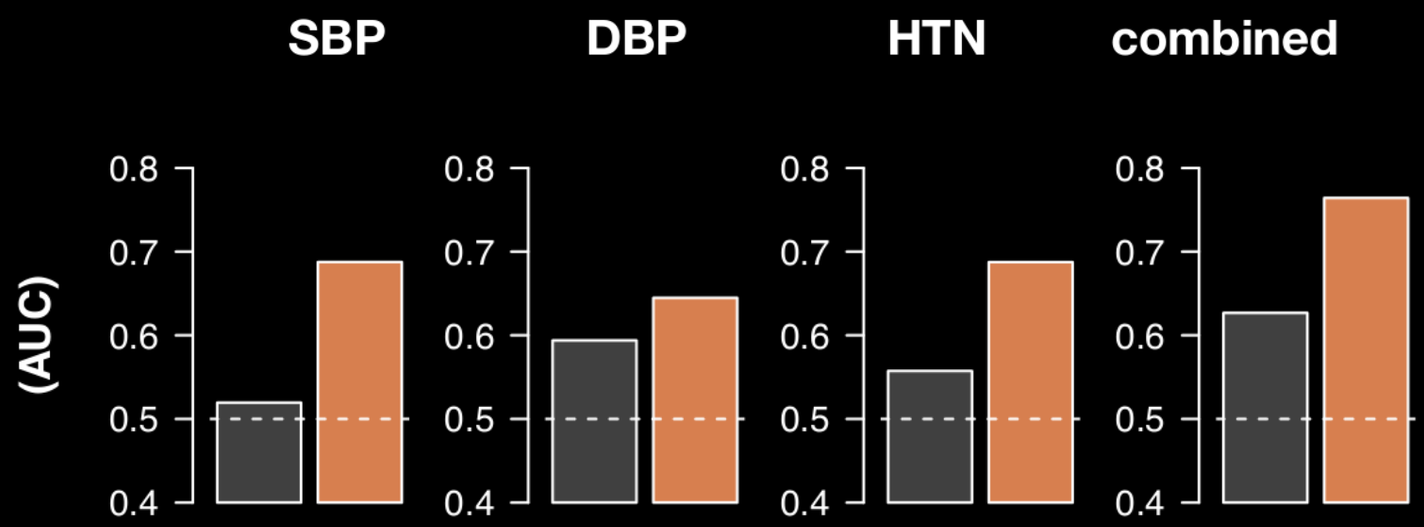
Case study

- Women’s Genome Health Study
- Three endpoints: systolic (SBP), diastolic blood pressure (DBP), and hypertension (HTN) diagnosis

NetWAS: Network-based approach for reprioritizing GWAS results

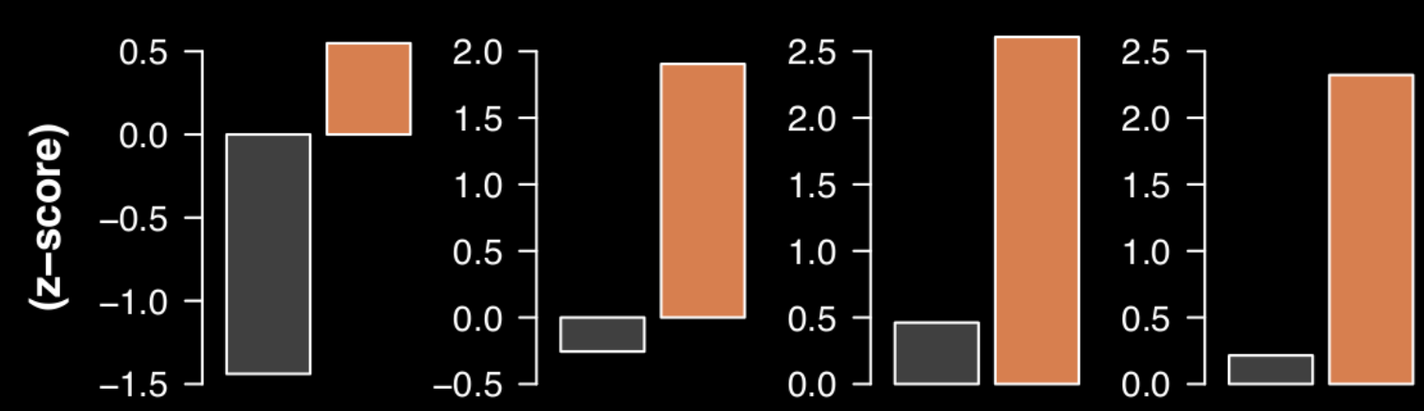
Phenotypic

Hypertension disease-genes from OMIM



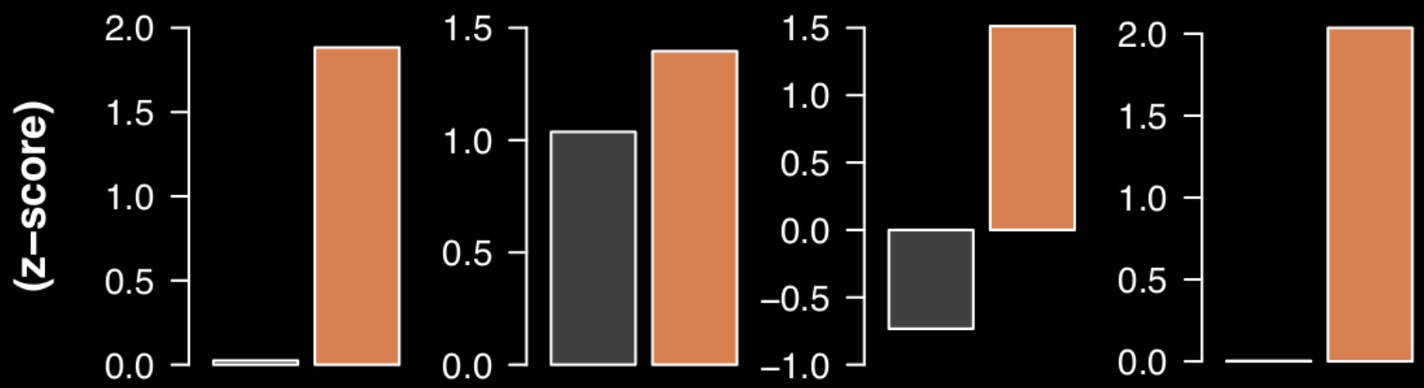
Functional

Blood pressure regulatory genes from GO

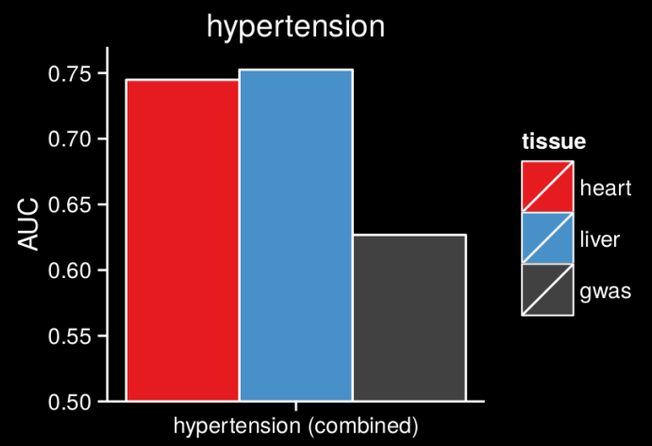


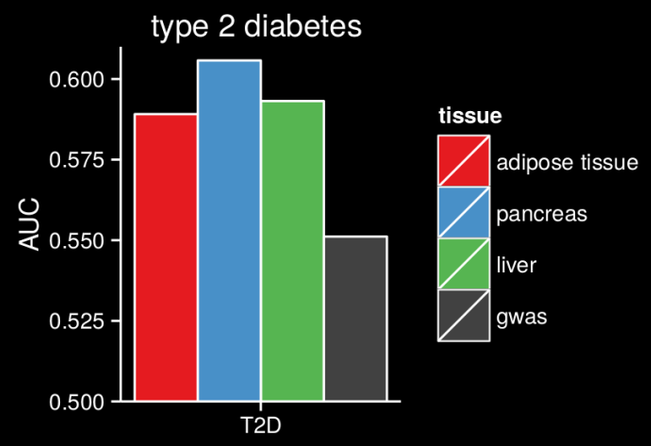
Therapeutic

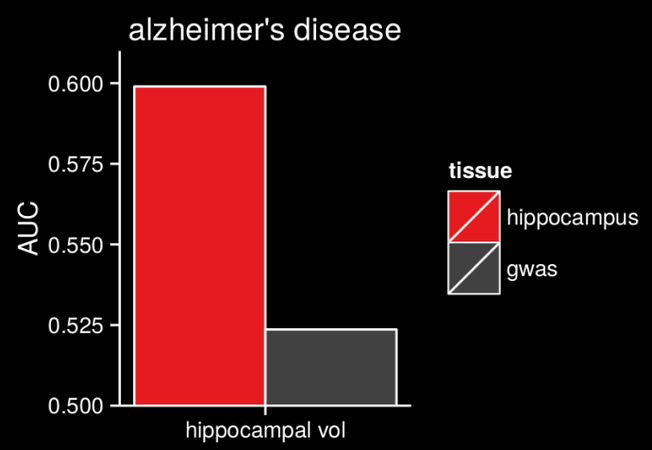
Antihypertensive drug-targets from DrugBank

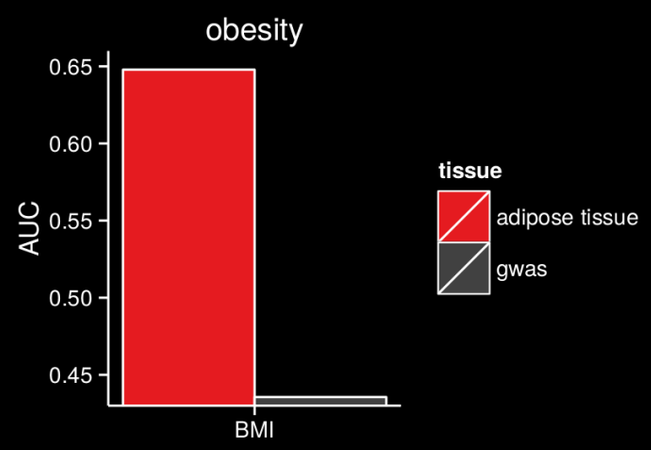


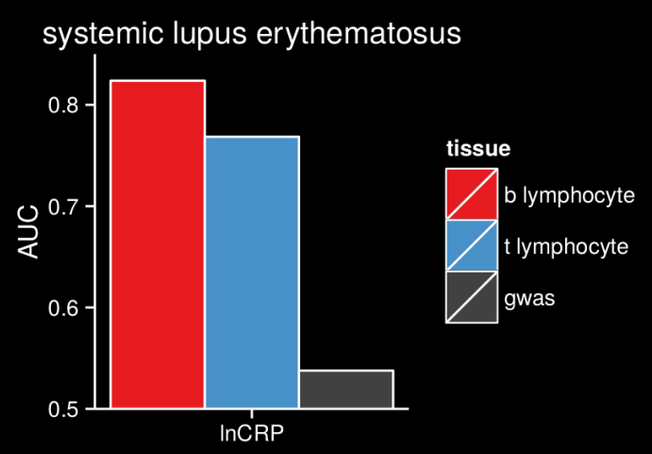
NetWAS: Network-based approach for reprioritizing GWAS results

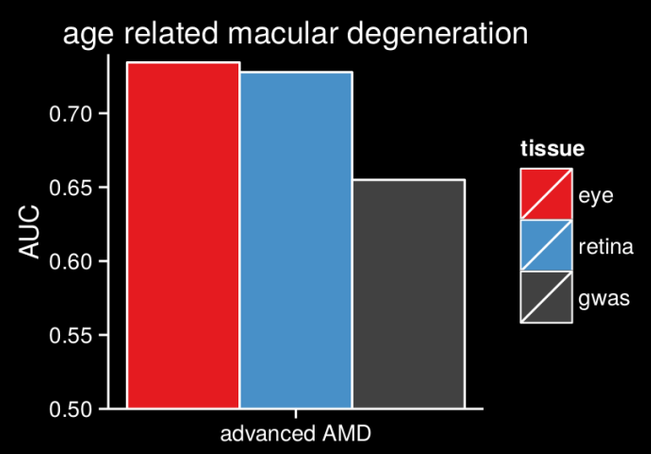






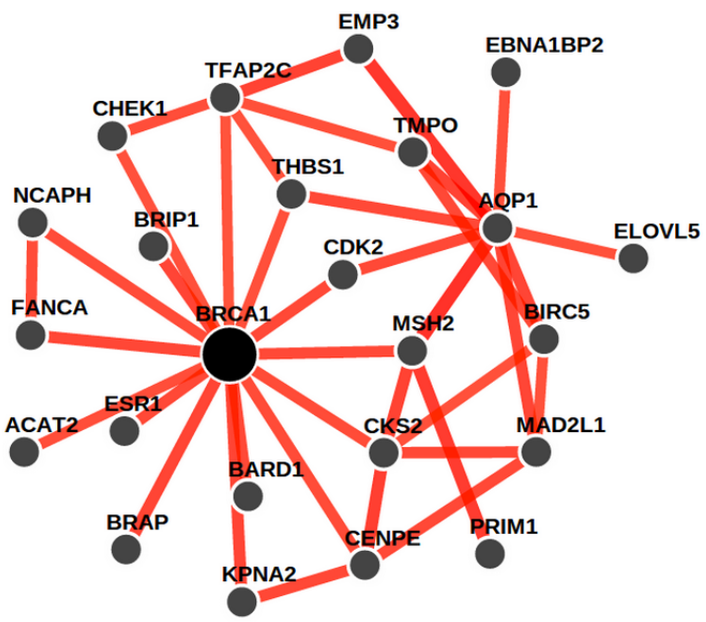






NetWAS: Network-based approach for reprioritizing GWAS results

GIANT | NetWAS Analysis | Download | Data | About | History | My Gene Sets (Tribe Login)



giant.princeton.edu

GIANT

Genome-scale Integrated Analysis of gene Networks in Tissues

Tissue: None selected

LEF1 ×

Search

Tissue-specific Interactions

GIANT leverages a tissue-specific gold standard to automatically up-weight datasets relevant to a tissue from a large data compendium of diverse tissues and cell-types. The resulting functional networks accurately capture tissue-specific functional interactions.

Multi-tissue Analysis

Beyond questions pertaining to the role of single genes in single tissues, GIANT also enables examination of changes in gene function across tissues on a broad scale. Users can compare a gene's functional interaction in different tissues by selecting the relevant tissues in the dropdown menu.

NetWAS Analysis

GIANT can effectively reprioritize functional associations from a genome-wide association study (GWAS) and potentially identify additional disease-associated genes. The approach, named NetWAS, can be applied to any GWAS study, and does not require that the phenotype or disease have any known associated genes.

The challenges of studying human disease or “model systems to the rescue”

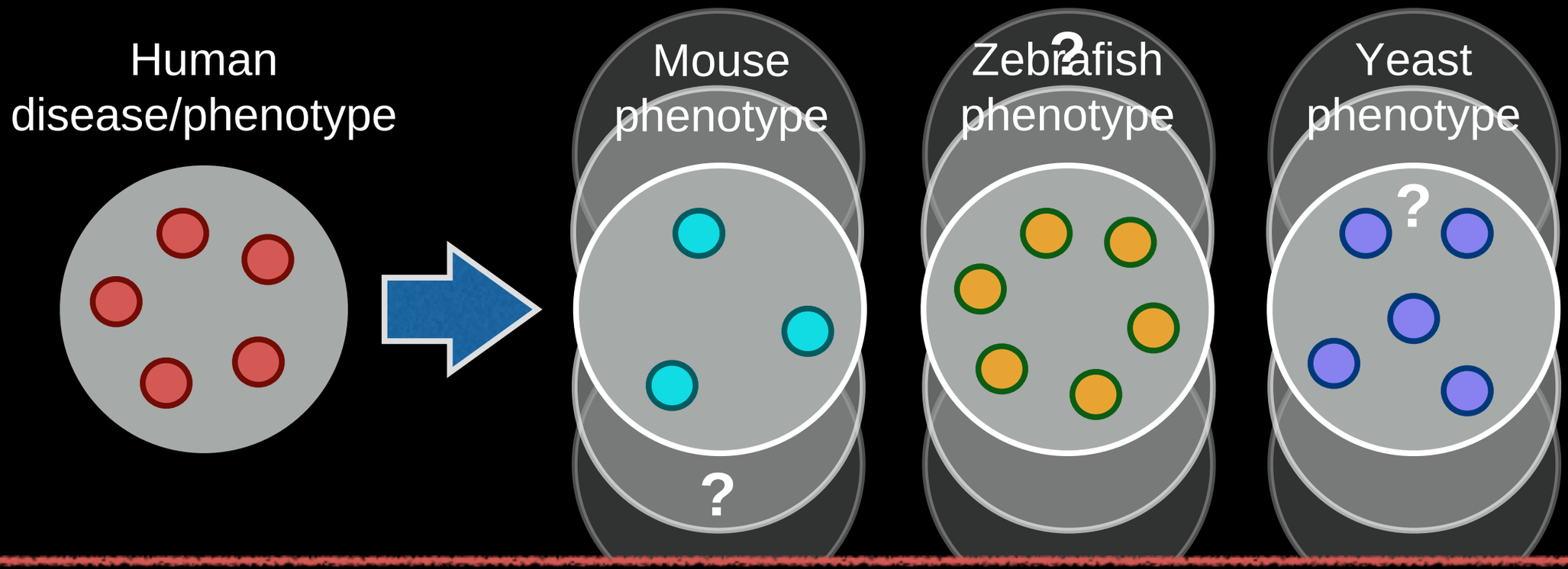
Most human diseases are molecularly under-characterized

1. The genes/mechanisms are poorly understood
2. Performing specific genetic experiments is very hard

There are excellent model systems out there

1. Each model organism/system best suited for studying different diseases/processes/aspects
2. Genetics is a lot more tractable
3. There are already genotype-phenotype data available in primates, mouse, zebrafish, worm, fly, yeast (and cell lines)

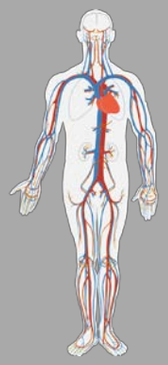
Which system to use - that is the question!



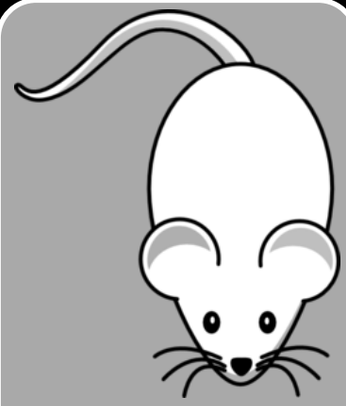
Mapping diseases and phenotypes is challenging:

1. Diseases and phenotypes often poorly understood at the molecular level (e.g. gene-phenotype associations very incomplete)
2. Many-to-many relationships between genetic mutations and observable phenotypes
3. Even semantically similar phenotypes are differently assayed, recorded, and annotated across organisms

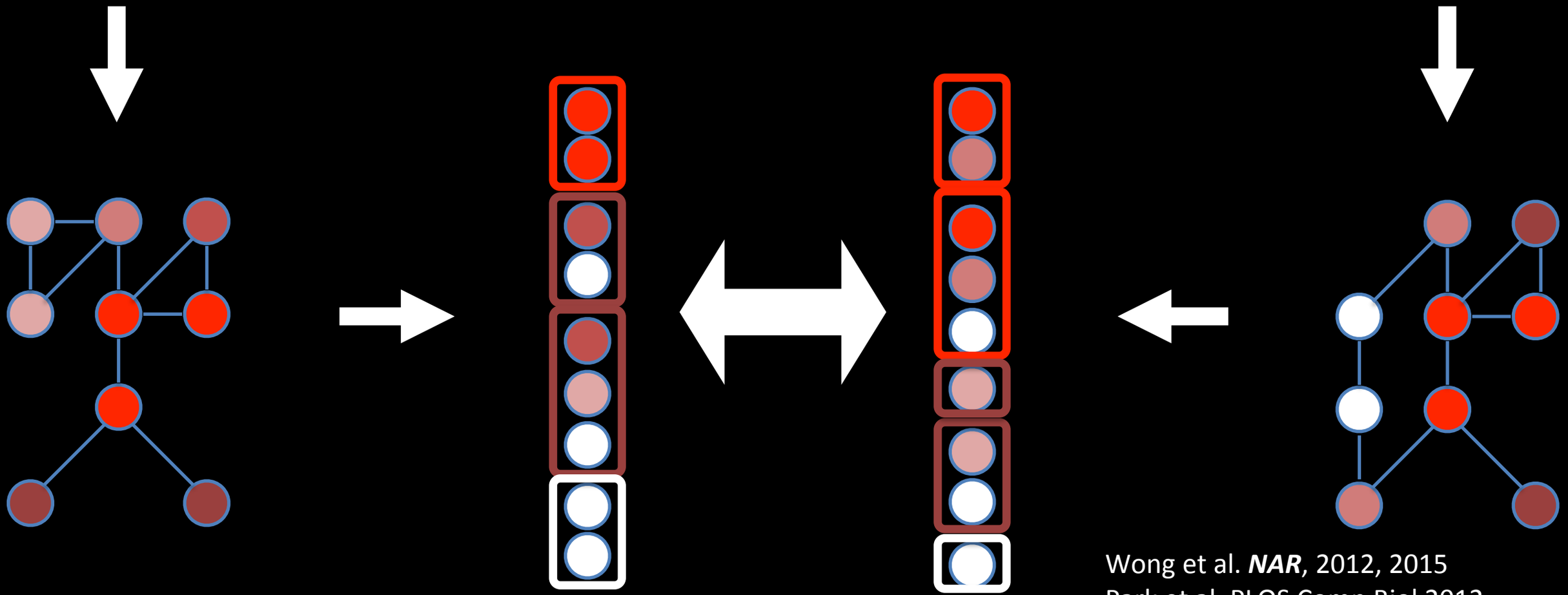
Linking human disease to model phenotypes on the molecular level



Disease-associated genes

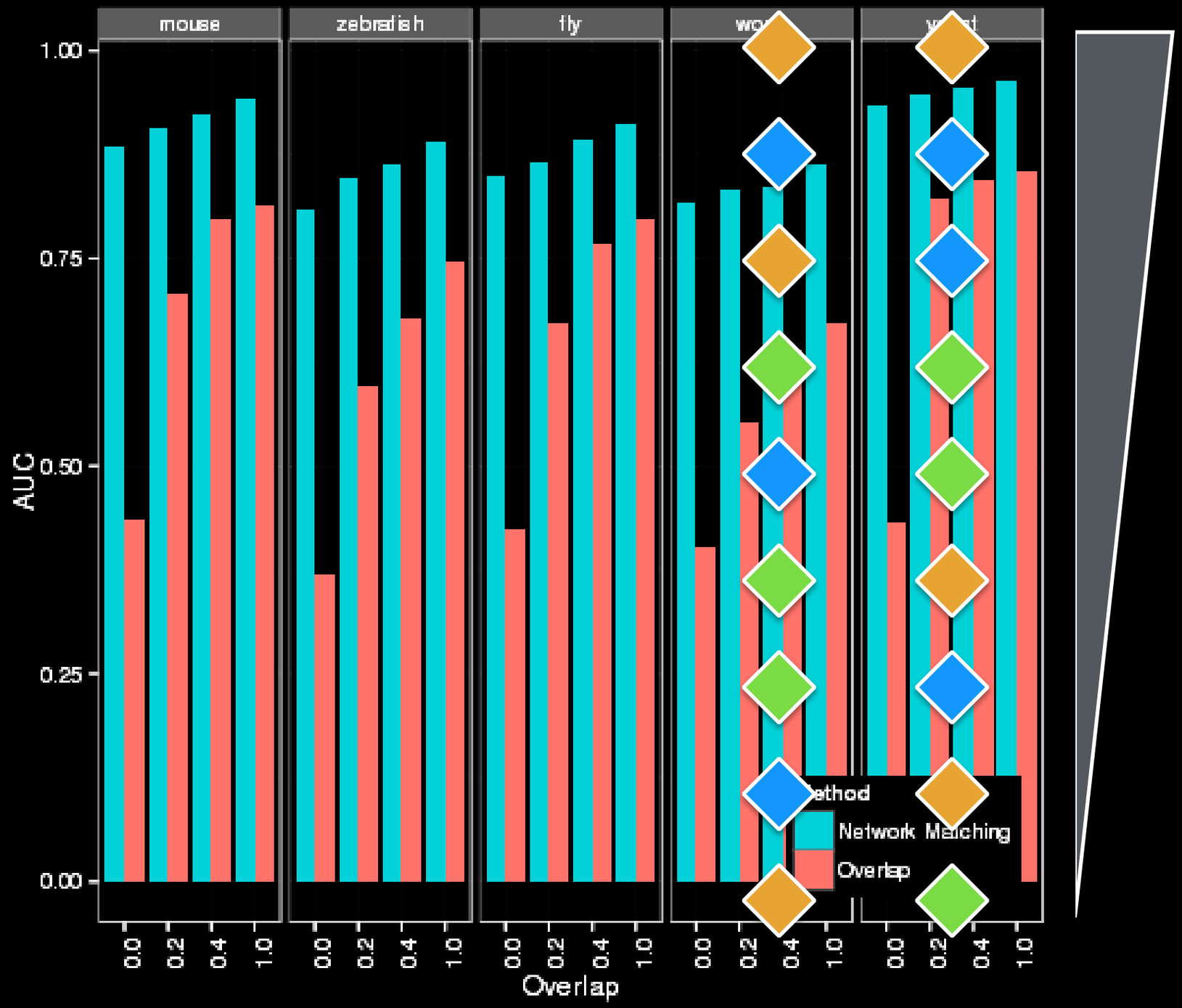


Phenotype-associated genes



Wong et al. ***NAR***, 2012, 2015
Park et al. PLOS Comp Biol 2012

How do we evaluate this approach?

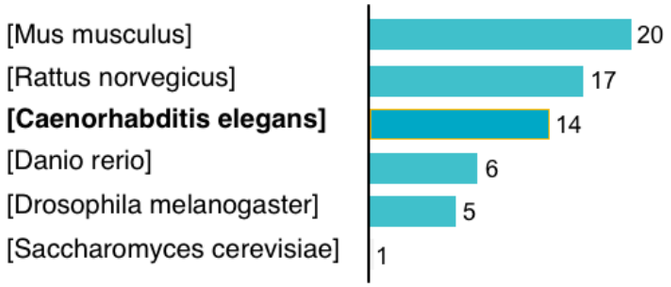


1. Network-based score
2. Overlap-based score

Parkinson's Disease

A synucleinopathy that has a basis in degeneration of the central nervous system that often impairs motor skills, speech, and other functions. Parkinson disease was first described by James Parkinson in 1817. It is the second most common neurodegenerative disorder after Alzheimer disease, affecting approximately 1% of the population over age 50 (Polymeropoulos et al.1996).

Related Phenotypes



phenotype	z-score
cell division polarity variant	4.1989
nucleolus variant	3.7339
embryonic polarity variant	3.7112
thermotolerance reduced	3.6479
reduced levels of glutathione	3.5633
spindle position orientation defective early emb.	3.4605
sluggish	1.9749

next | last

Parkinson's Disease - [Homo sapiens]

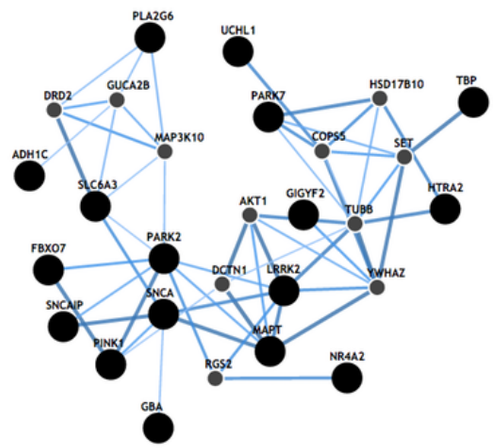
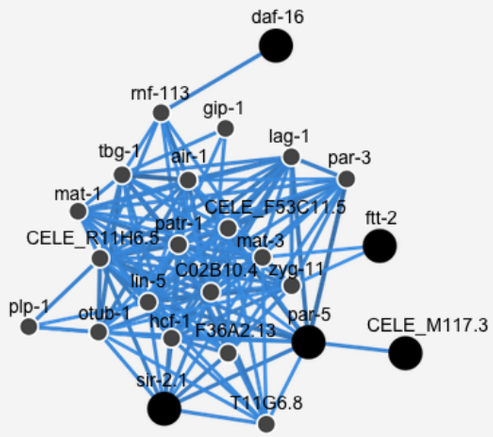


table / network

0.1 1.0

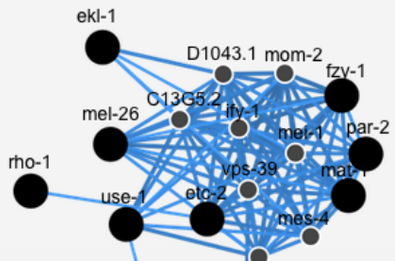
Edge Confidence

Reduced levels of glutathione



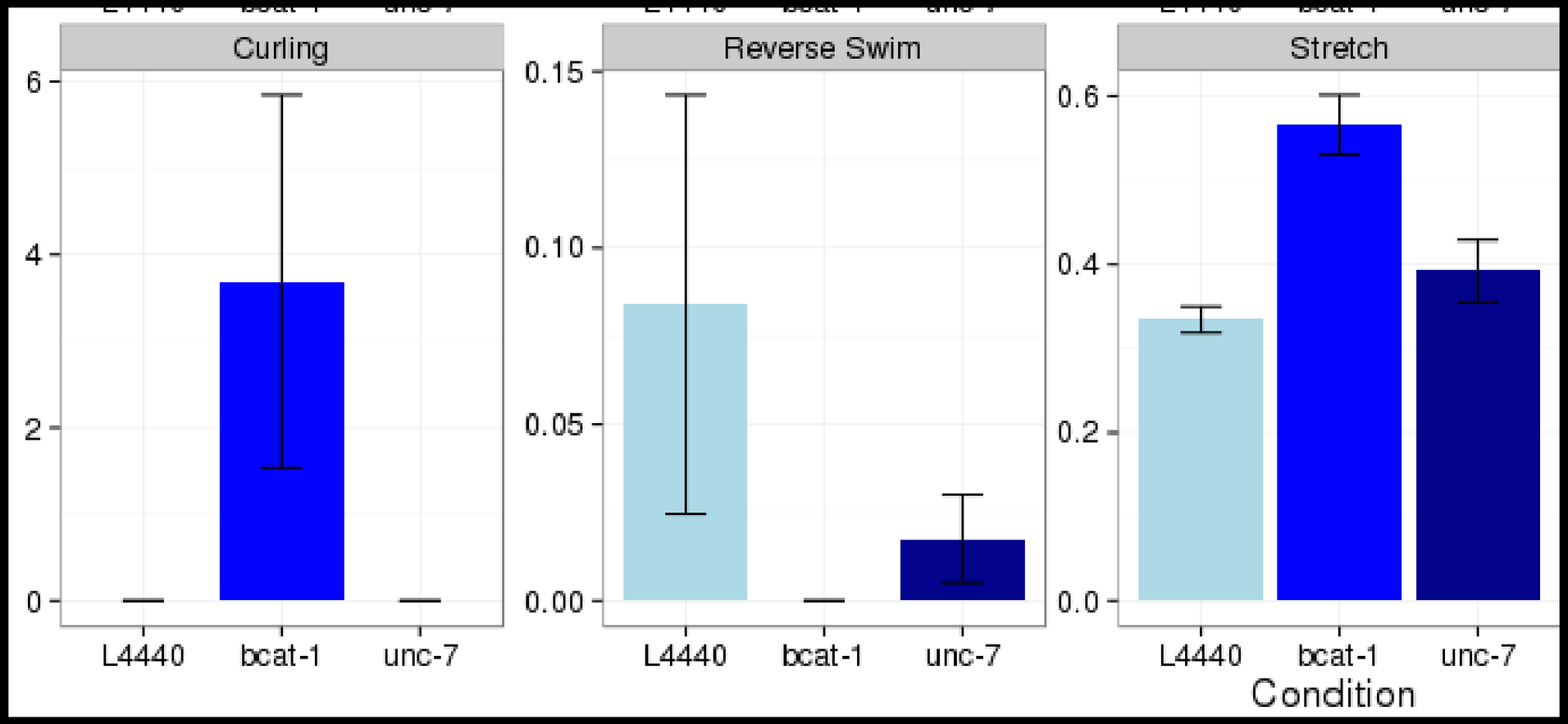
[C. elegans]

Spindle position orientation defective



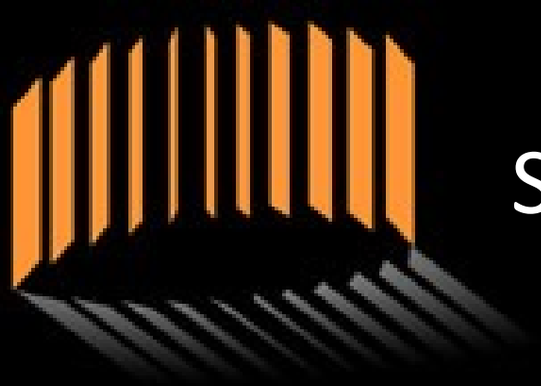
With Kara Dolinski group (Princeton)

Candidate genes for Parkinson's disease in *C. elegans*



- Candidate genes for Parkinsons predicted based on worm dopaminergic neuron network and human GWAS studies
- example: age-dependent motility defect in BCAT-1 (predominant branched-chain aminotransferase in the nervous system)
- inhibited by neuronal drug gabapentin (GABA analog)

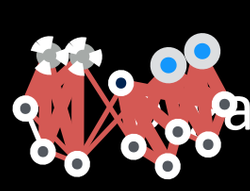
With Coleen Murphy's group (Princeton)



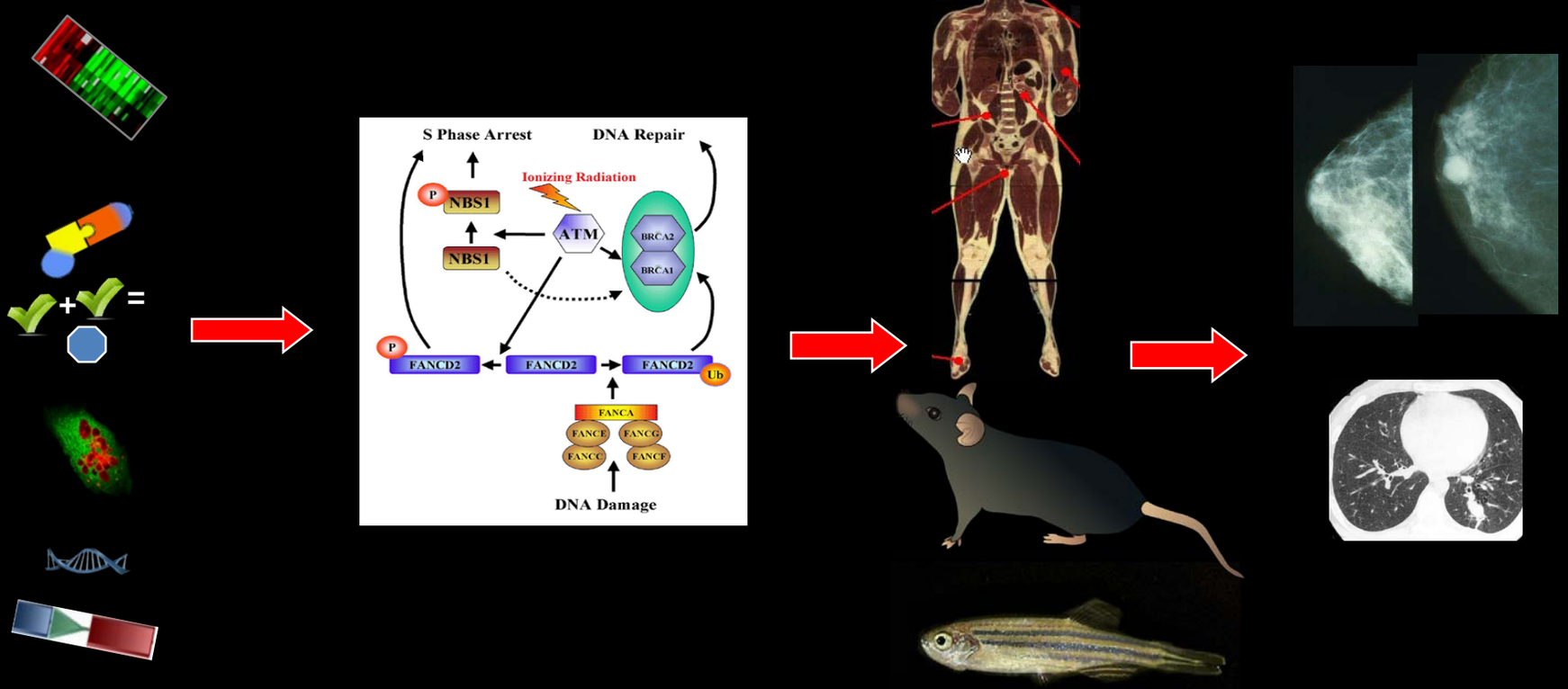
Summary: tissue-specific genome-scale view of human biology and disease

A general method can perform tissue-specific data integration into functional works

Tissue-specific networks are complementary to quantitative genetics and can disease associations and reprioritize GWAS hits



Human diseases and pathways can be linked to best model systems through anism-specific functional networks



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* David Hess (@ USantaClara)
* Matthew Hibbs (@JAX)
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* Edo Airoldi (@ Harvard)
* Lars Bongo (@ U Tromso)
* Casey Greene (@ Dartmouth)
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