Mouse phenotypes and disease genomics

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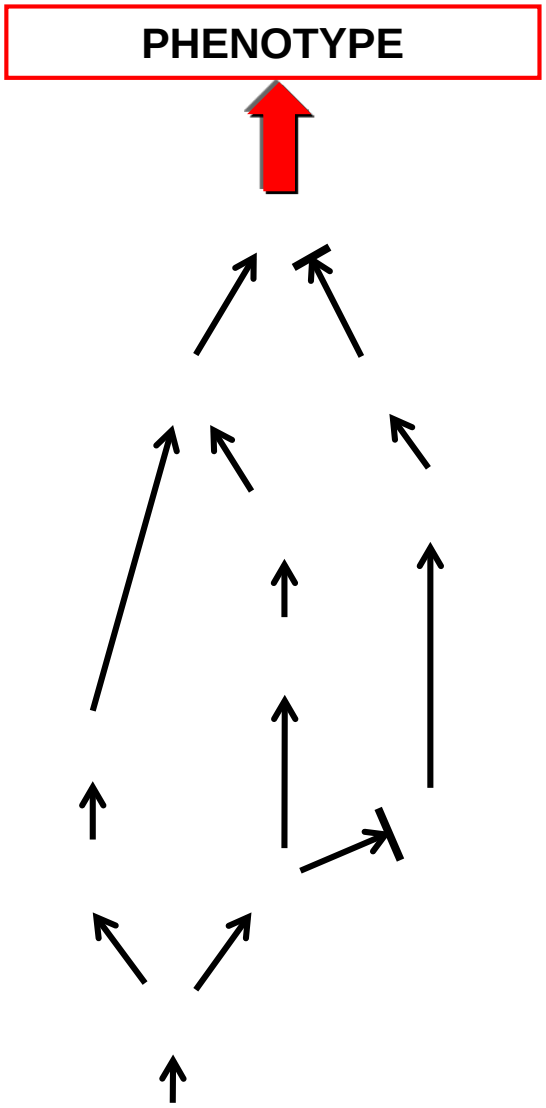
No conflicts of interest to declare

Why are dispersed loci involved in similar phenotypes?



Comparing Patient Phenotypes - evidence

Patient 1

Phenotype A

Phenotype F

Phenotype N

Phenotype W

VS

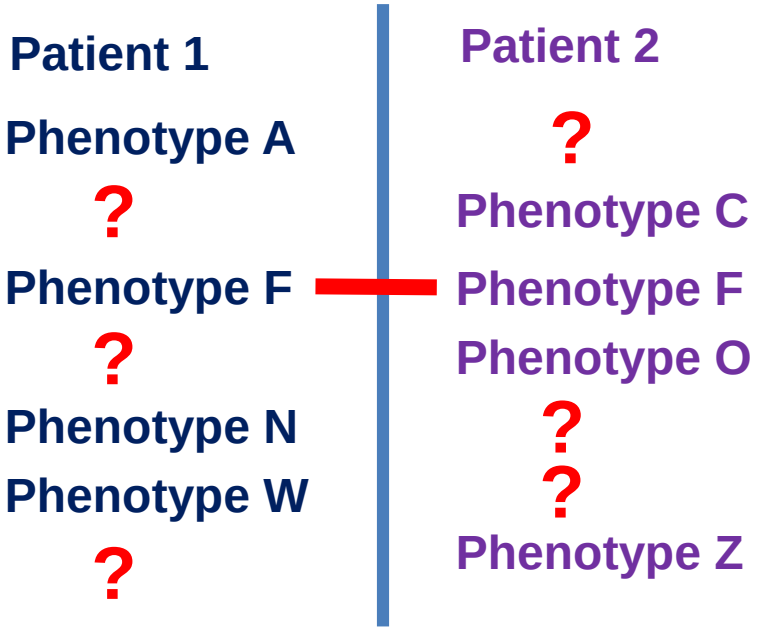
Patient 2

Phenotype C

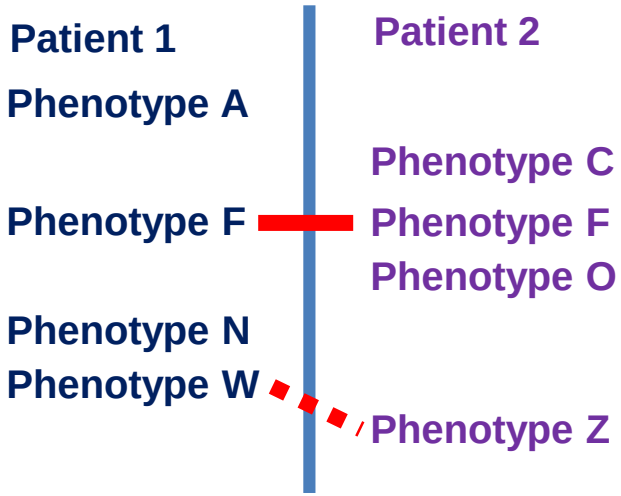
Phenotype F

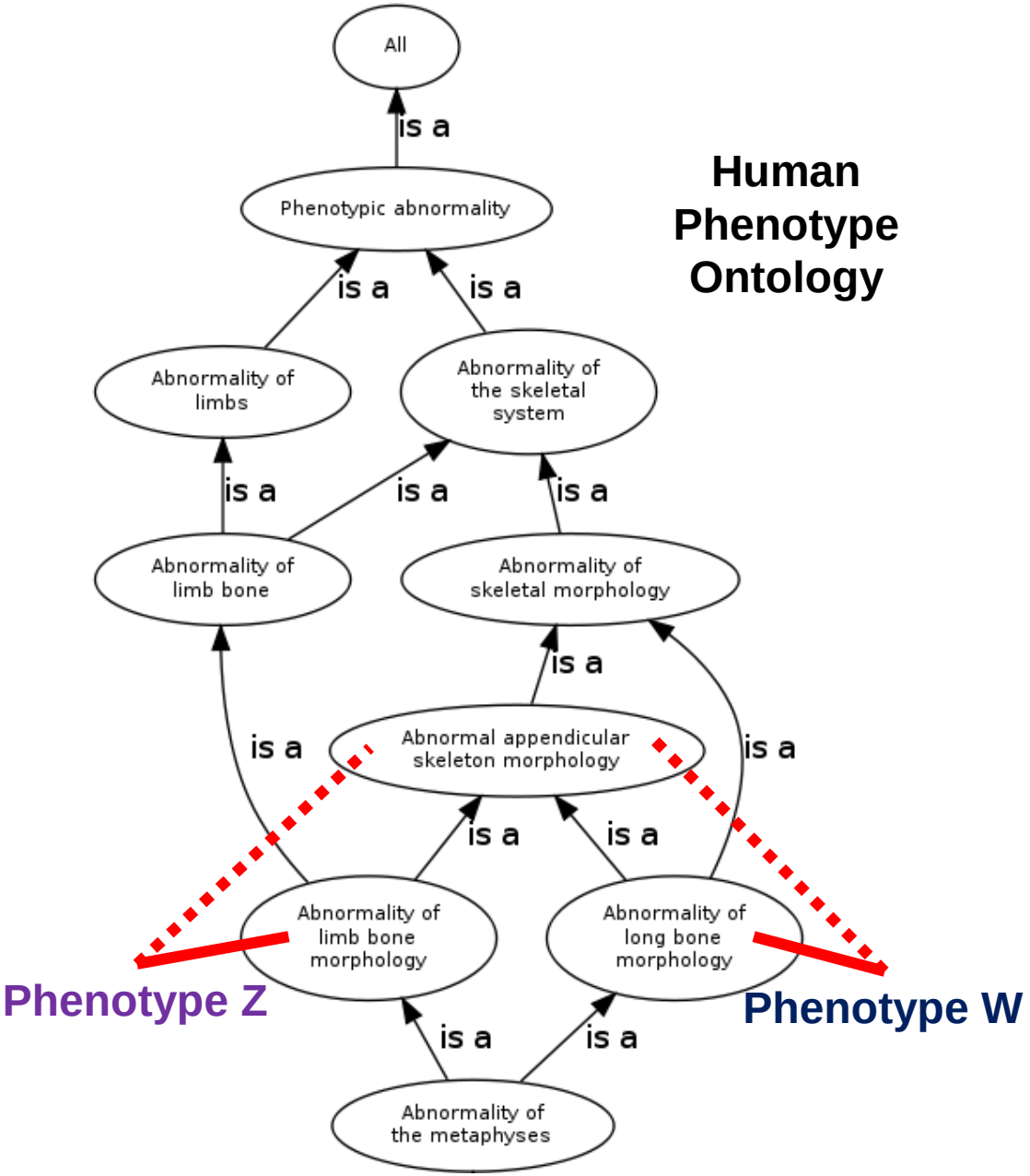
Phenotype O

Phenotype Z

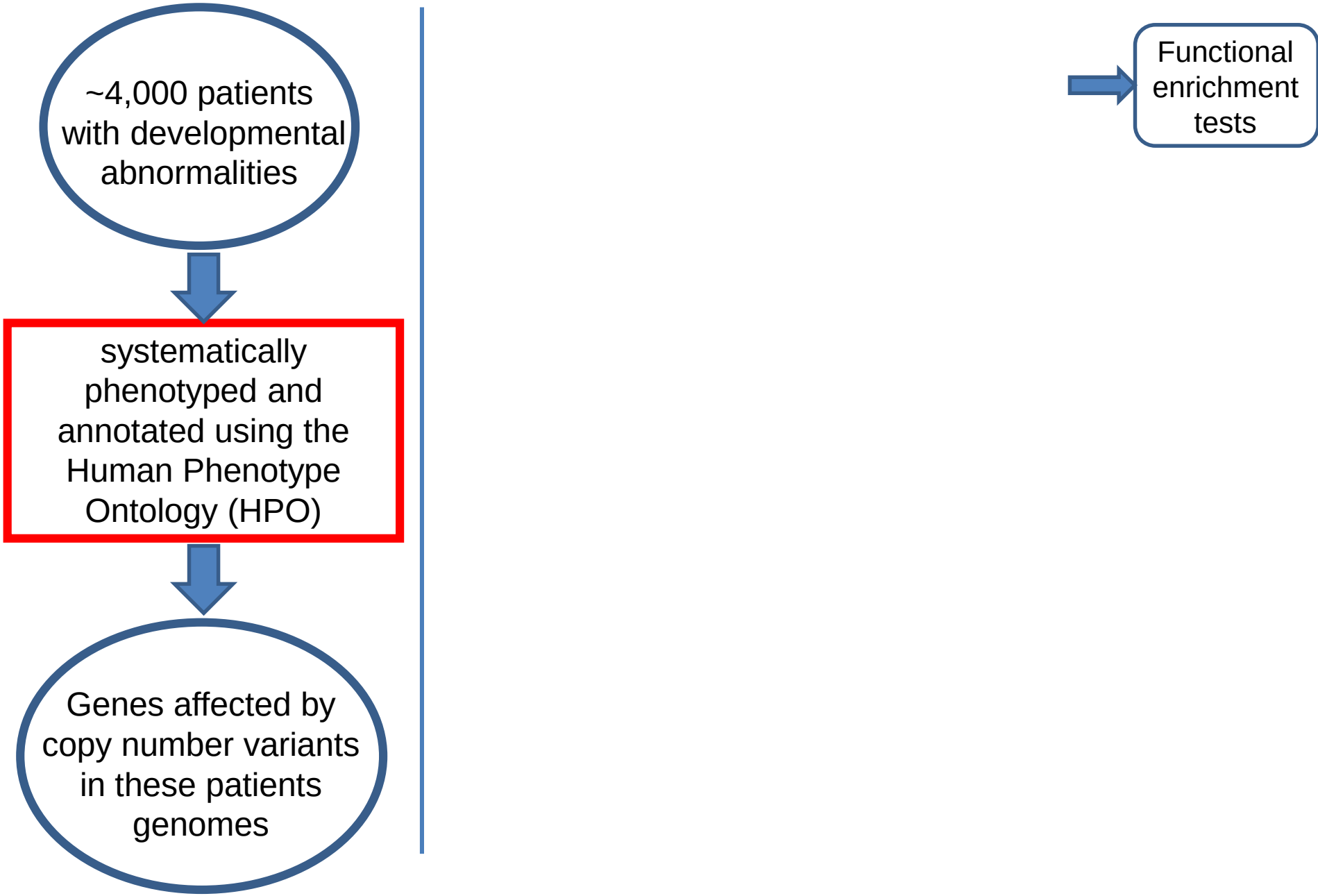


Comparing Patient Phenotypes - language

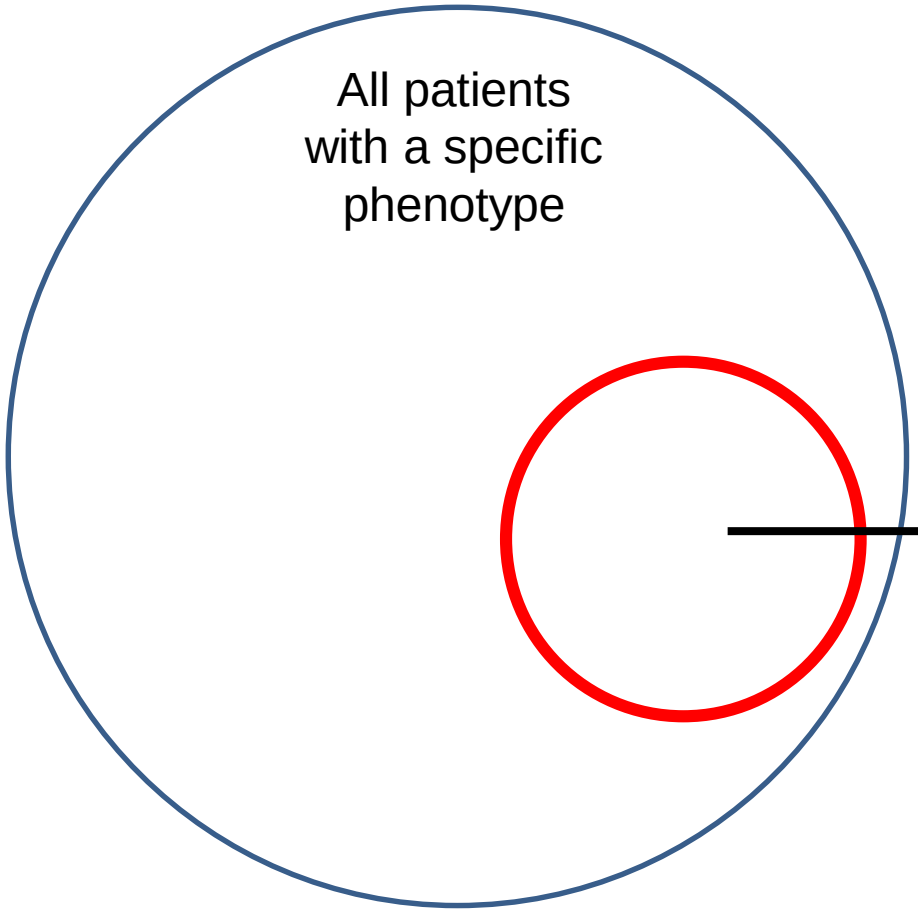




“Pathways” and convergent phenotypes



“Pathways” and convergent phenotypes



Patients with the specific phenotype whose variant genes form part of a particular “pathway”:

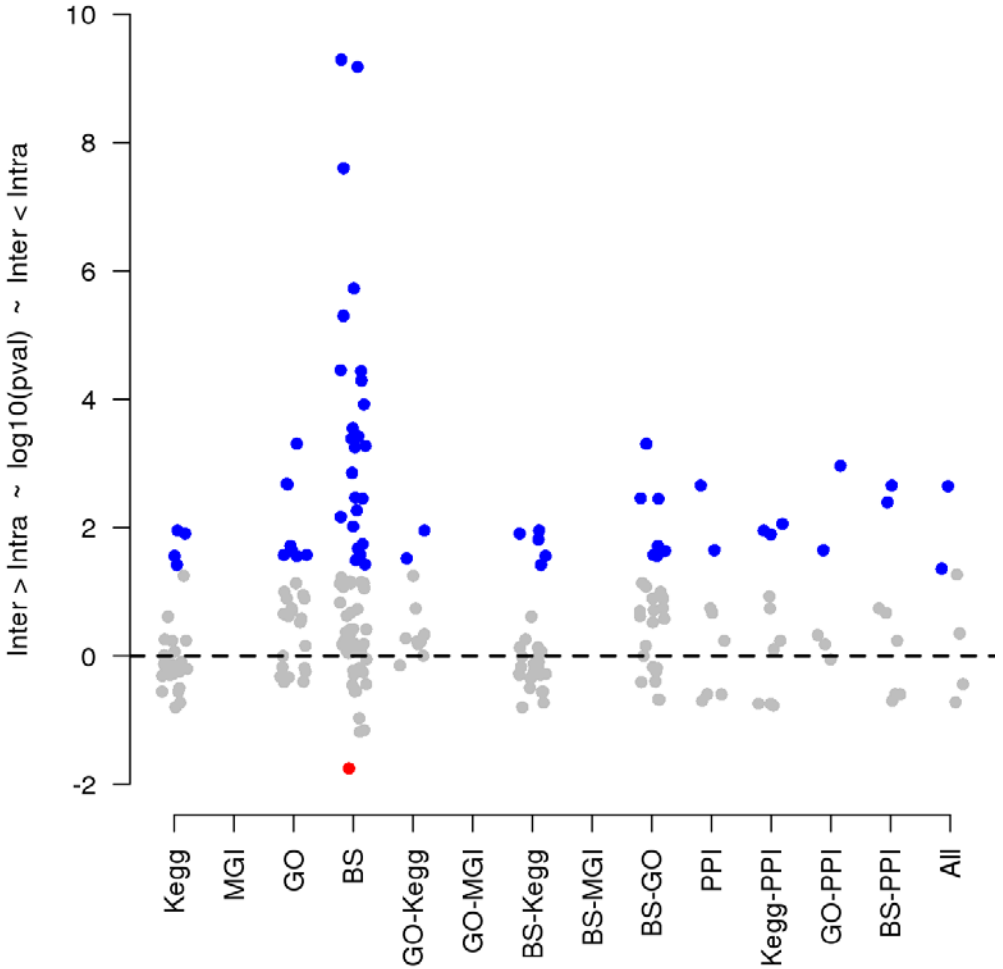
Q: Are these patients more phenotypically-similar?

Similarity in patients whose variant genes contribute to the same “pathway” term

phenotypically **similar** patients share term

Random

phenotypically **dissimilar** patients share term



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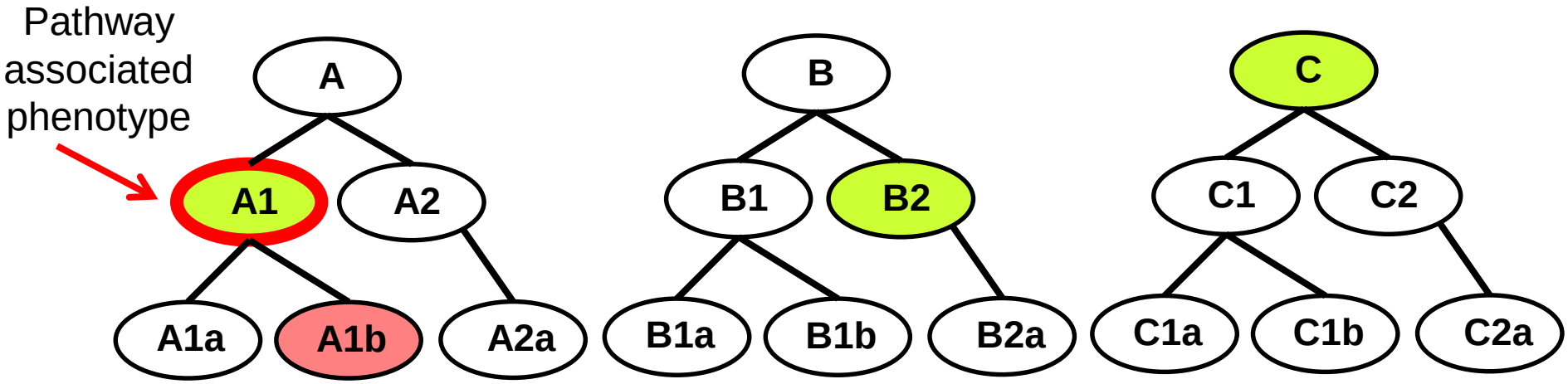
Same pathway = patients share a more specific phenotype?



Same "pathway" = more specific phenotype

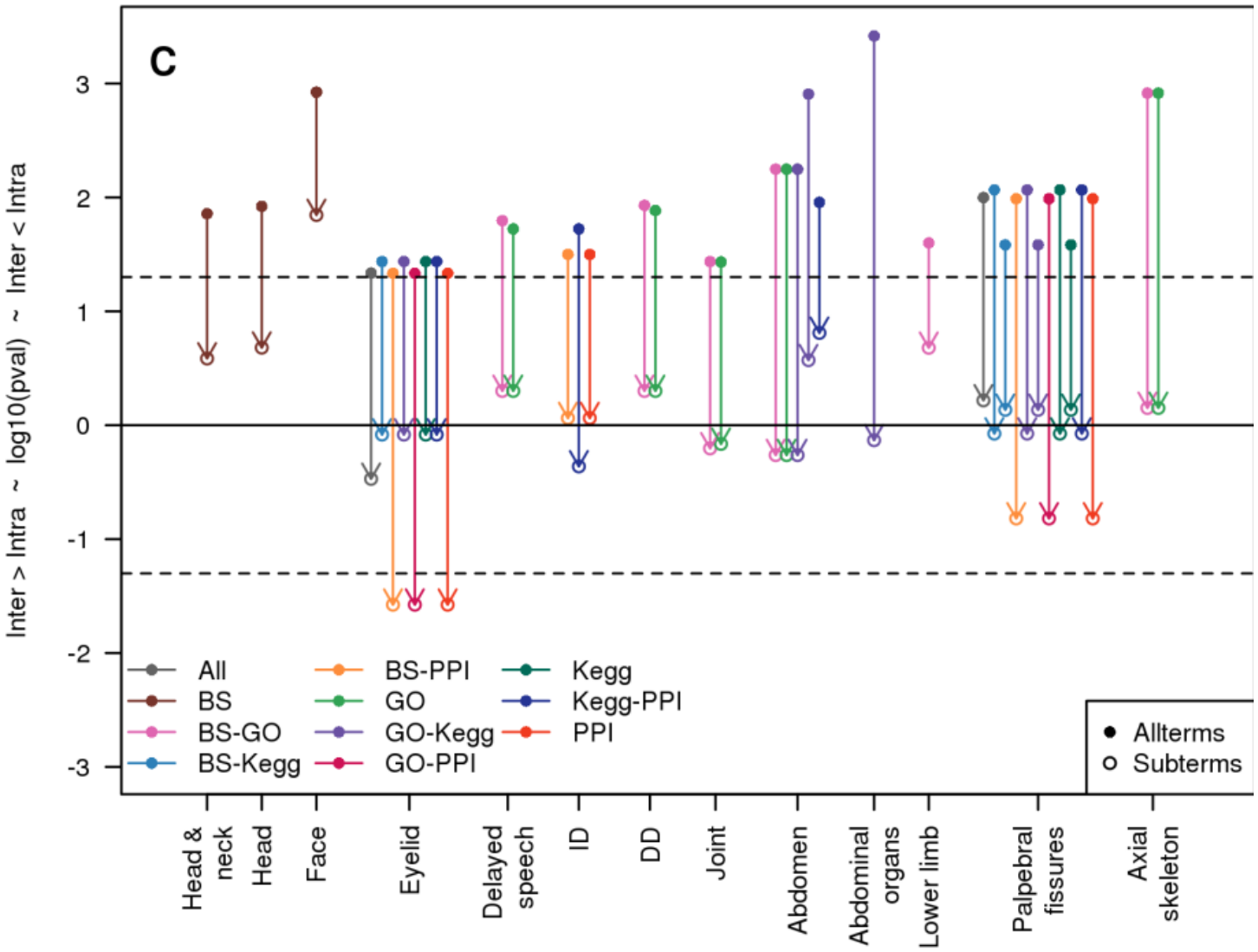
Same "pathway" = similar patterns of phenotypes

Patients whose variant genes contribute to the same "pathway" term – All phenotypes vs narrow phenotypes

phenotypically **similar** patients share term

Random

phenotypically **dissimilar** patients share term



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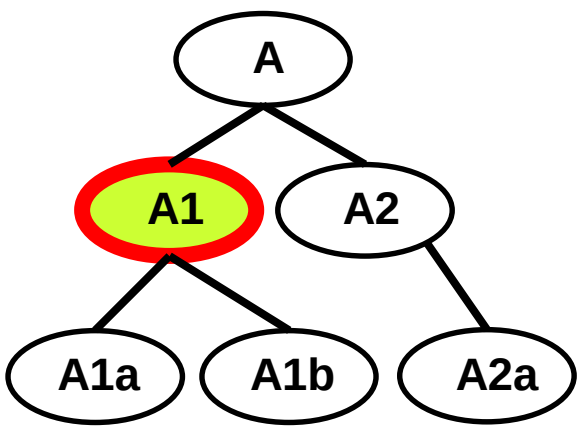
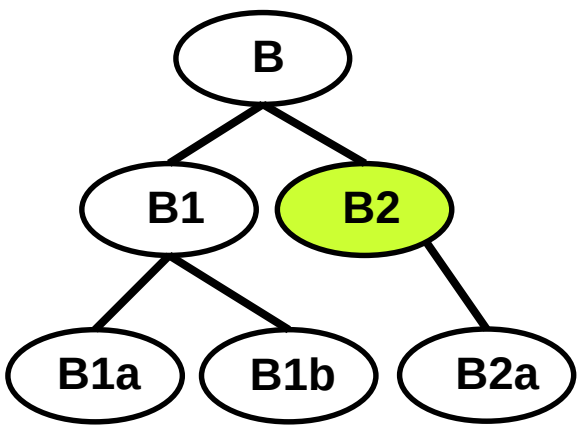
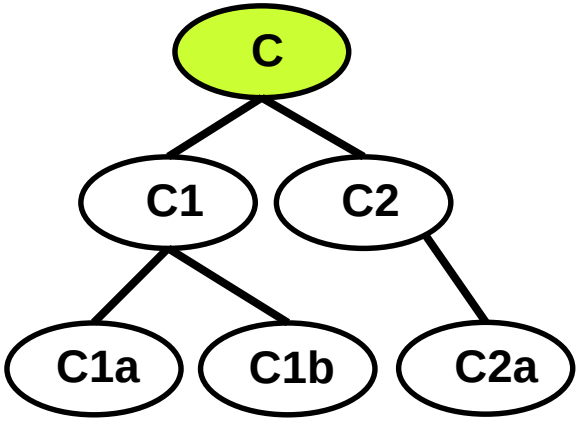
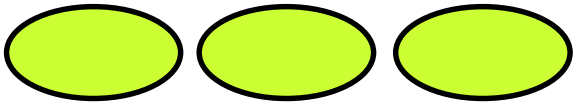
Same pathway = same pattern of phenotypes







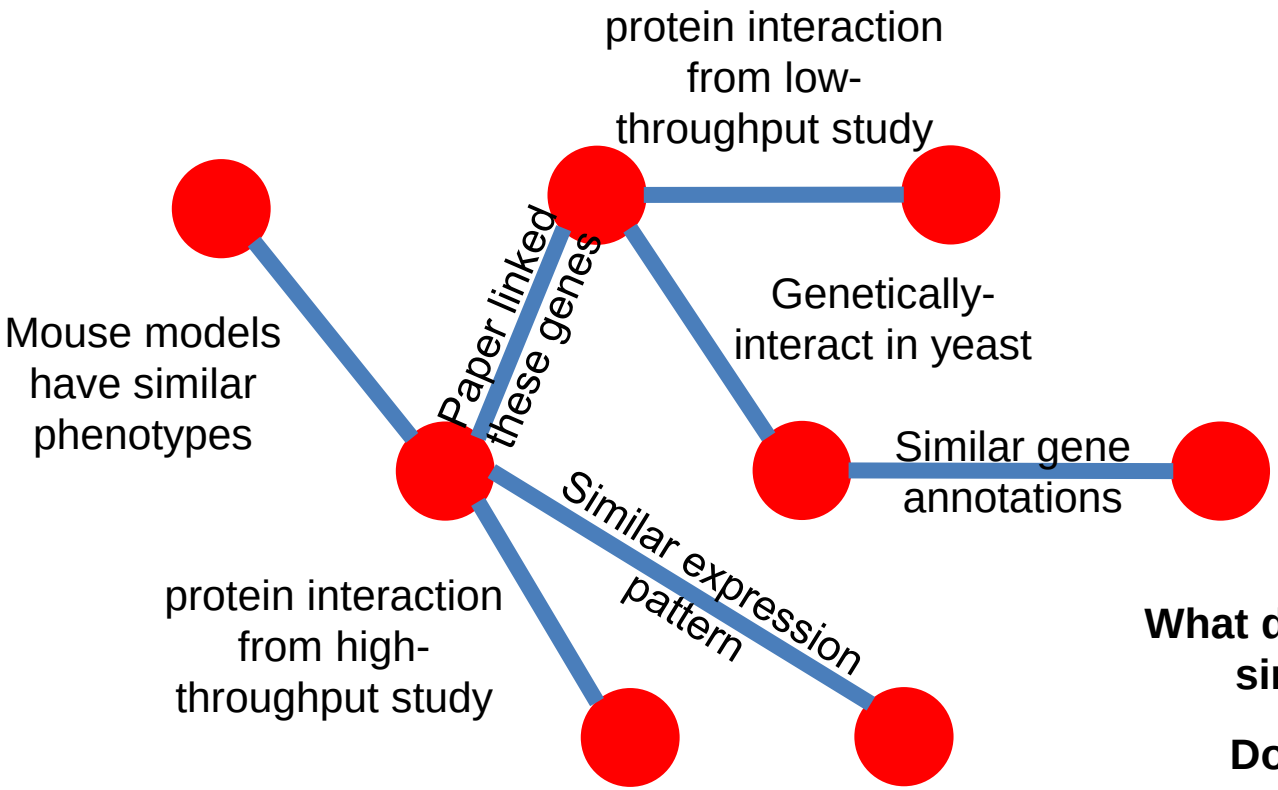


Same “pathway” = similar patterns of phenotype

Take homes

1. Patients whose variants disrupt the same “pathway” share a broad range of phenotypic similarities

Functionally-linking genes through orthogonal data sources

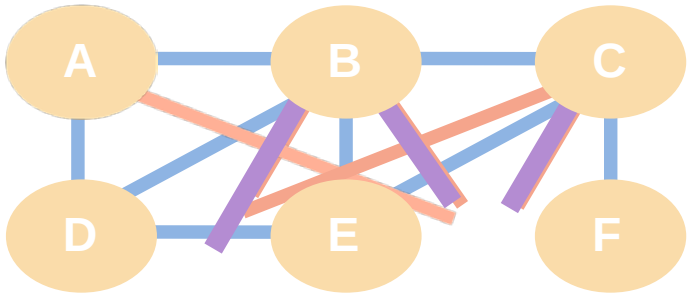


What does functionally-similar mean?

Do I trust these experiments equally?

What is the chance of seeing this by random?

Functional-linkage networks: Integration of functional genomics resources to identify human disease genes



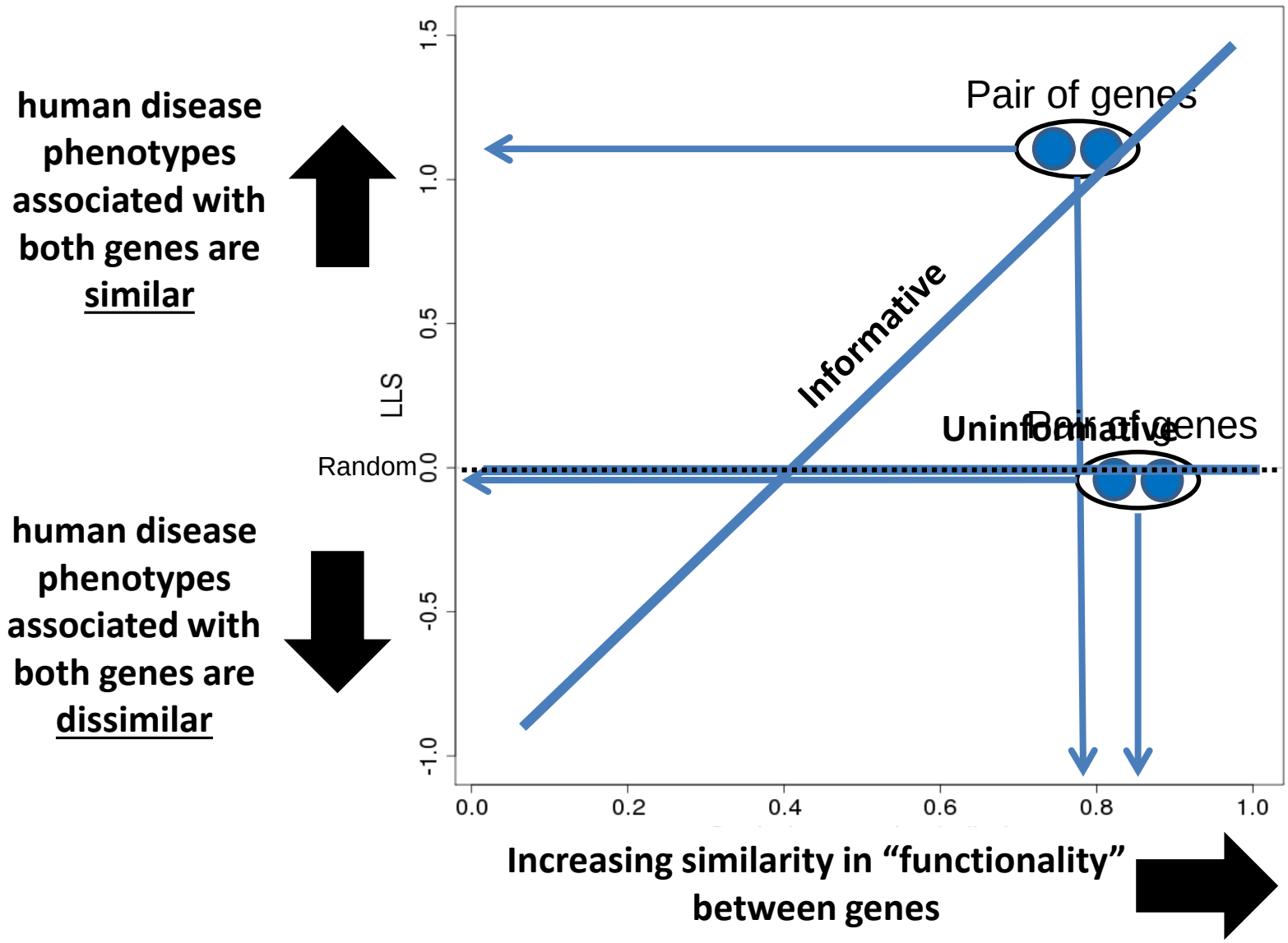
a gene

Protein interaction

gene co-expression

integrated

Predicting human phenotypic associations



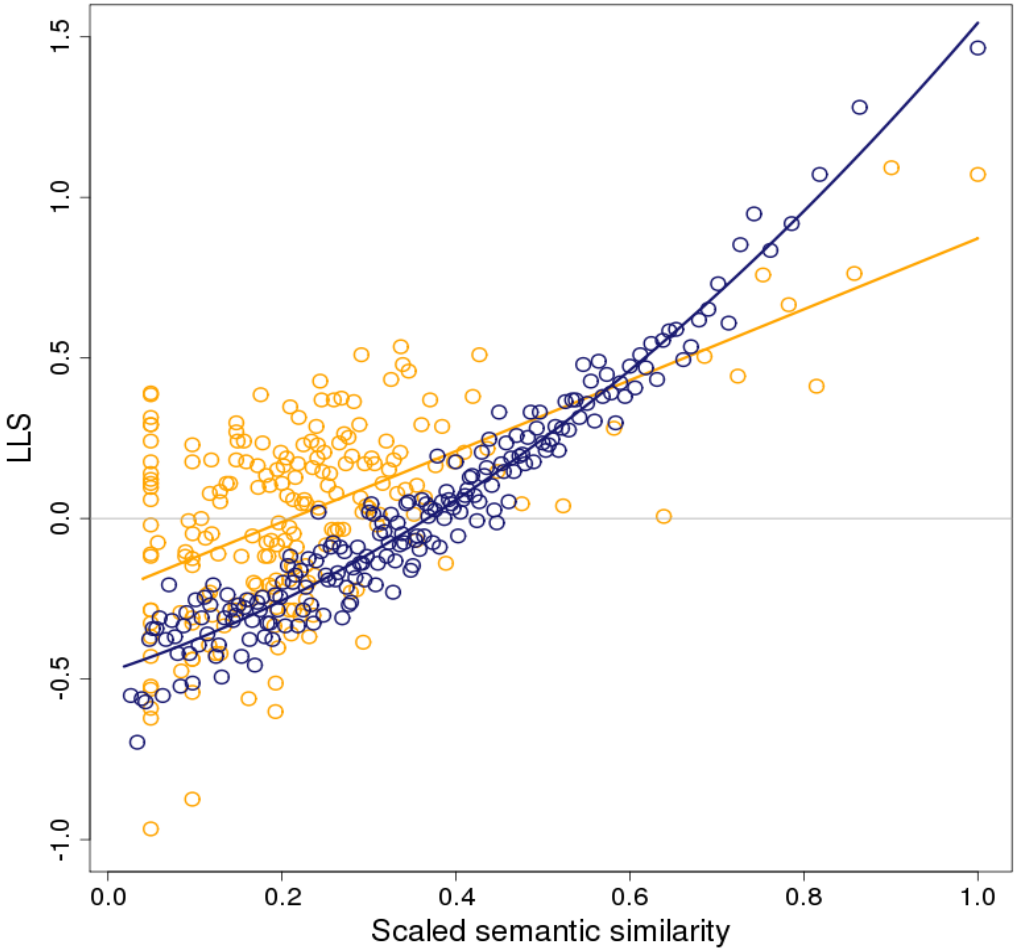
The value of mouse phenotypic data (MGI) compared to Gene Ontology (GO) annotations

Predict they are

Ability to predict whether 2 genes are involved in the same disorder

Know nothing

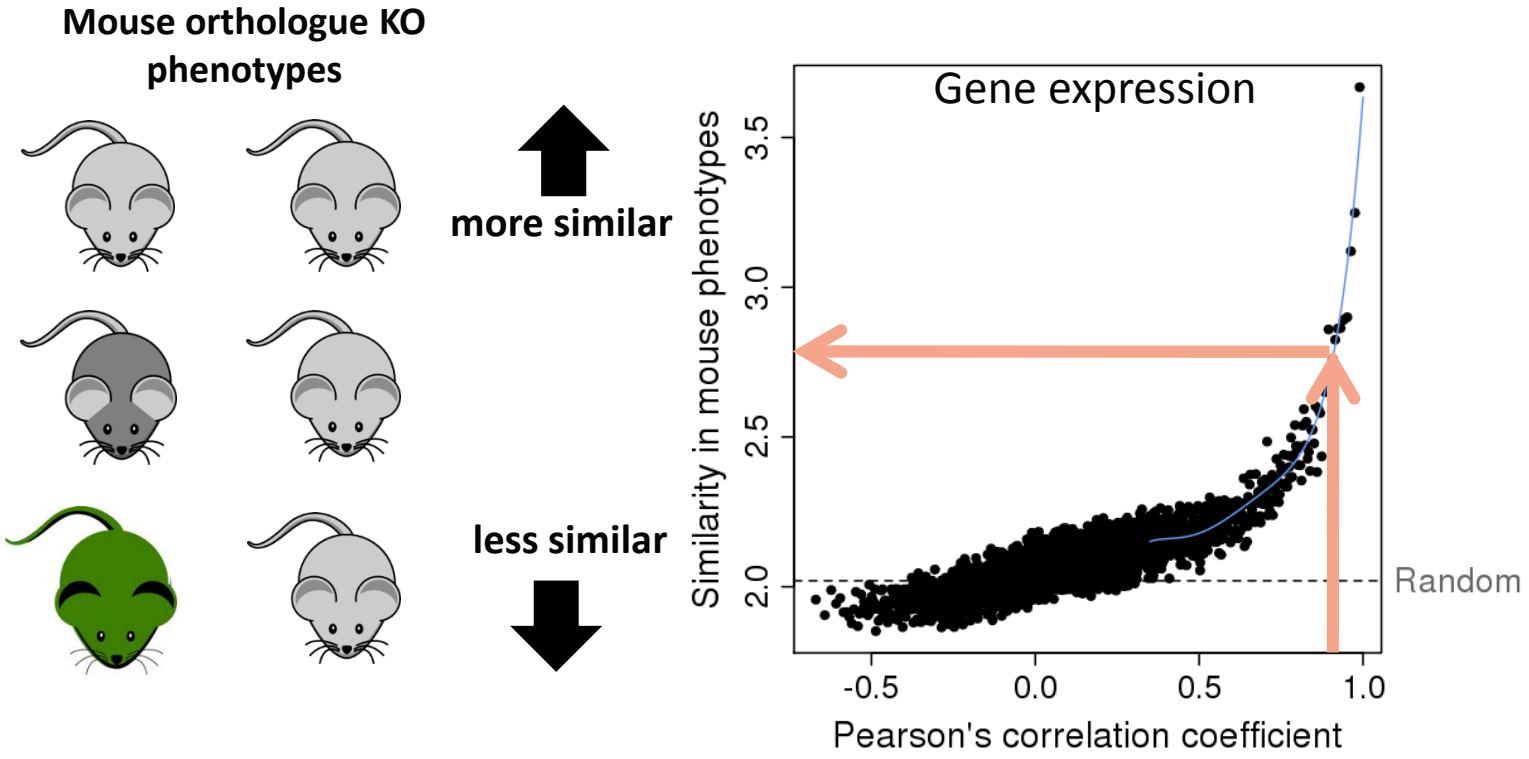
Predict they are not



Increasing similarity in functional annotation (either GO or MGI) between genes

Weighting functional information

The data types are assessed and weighted according to how well they predict shared mouse phenotypes



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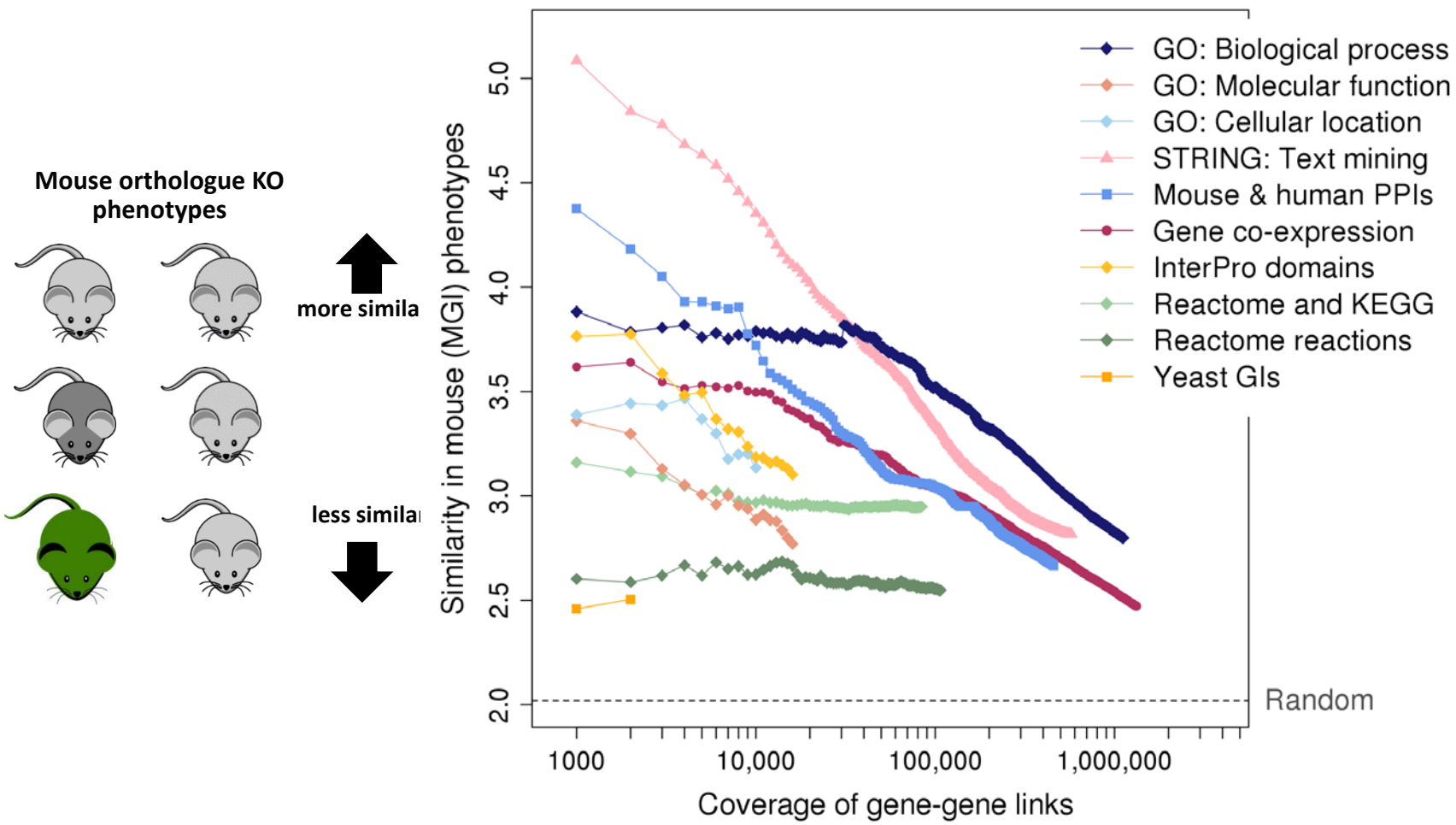
Comparison of functional data sources



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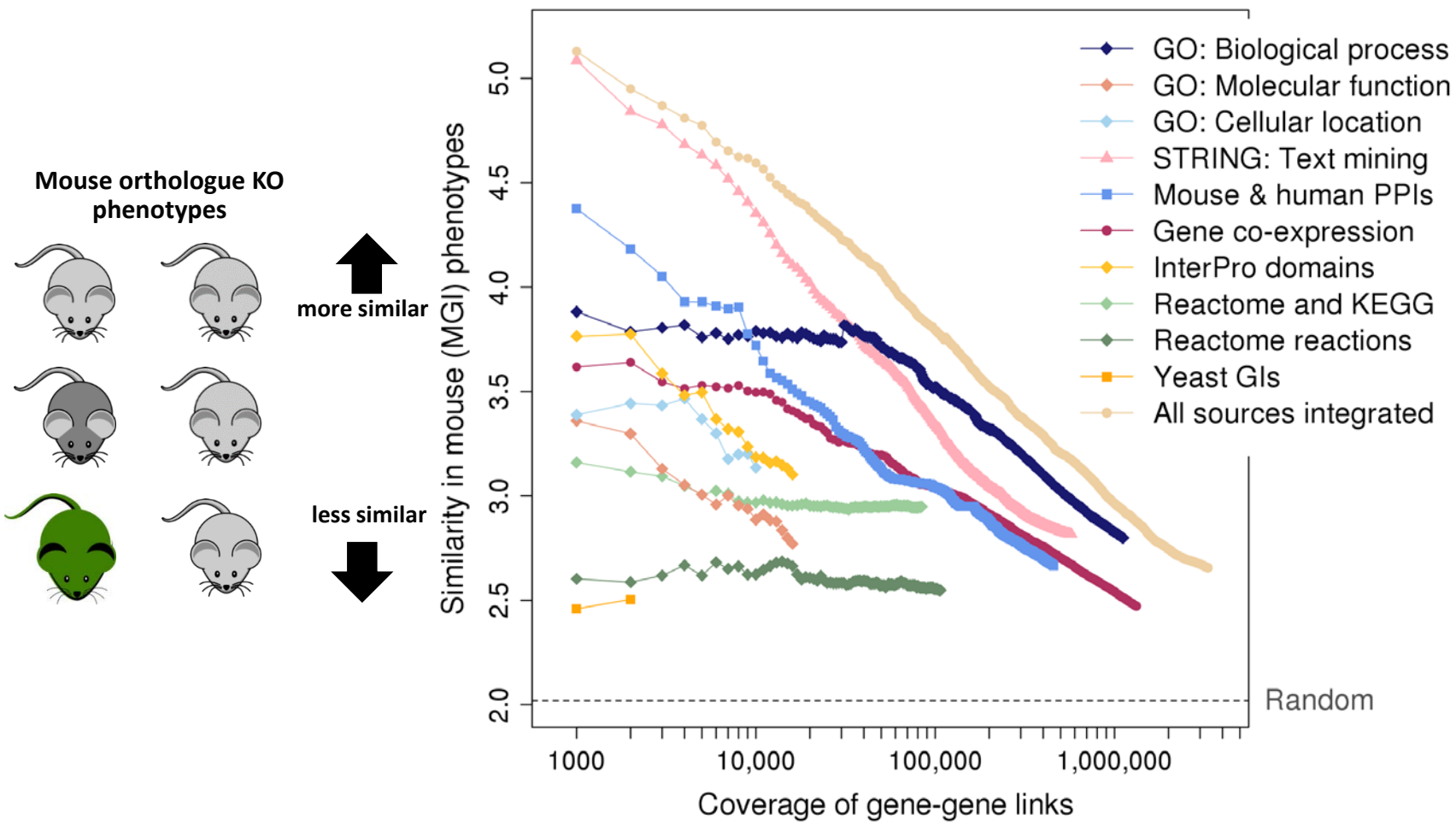
Frank Honti

Comparison of functional data sources



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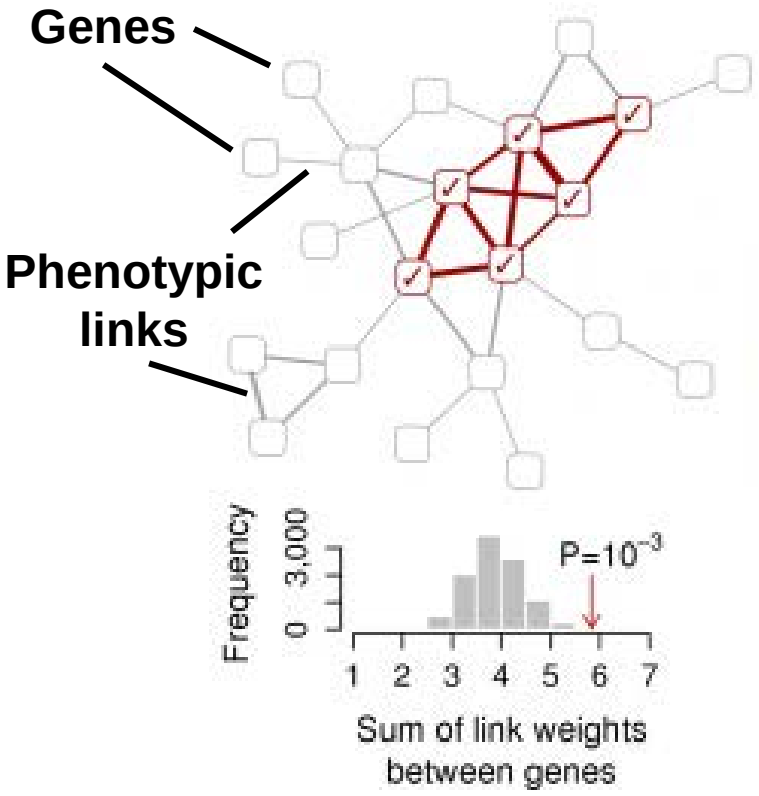
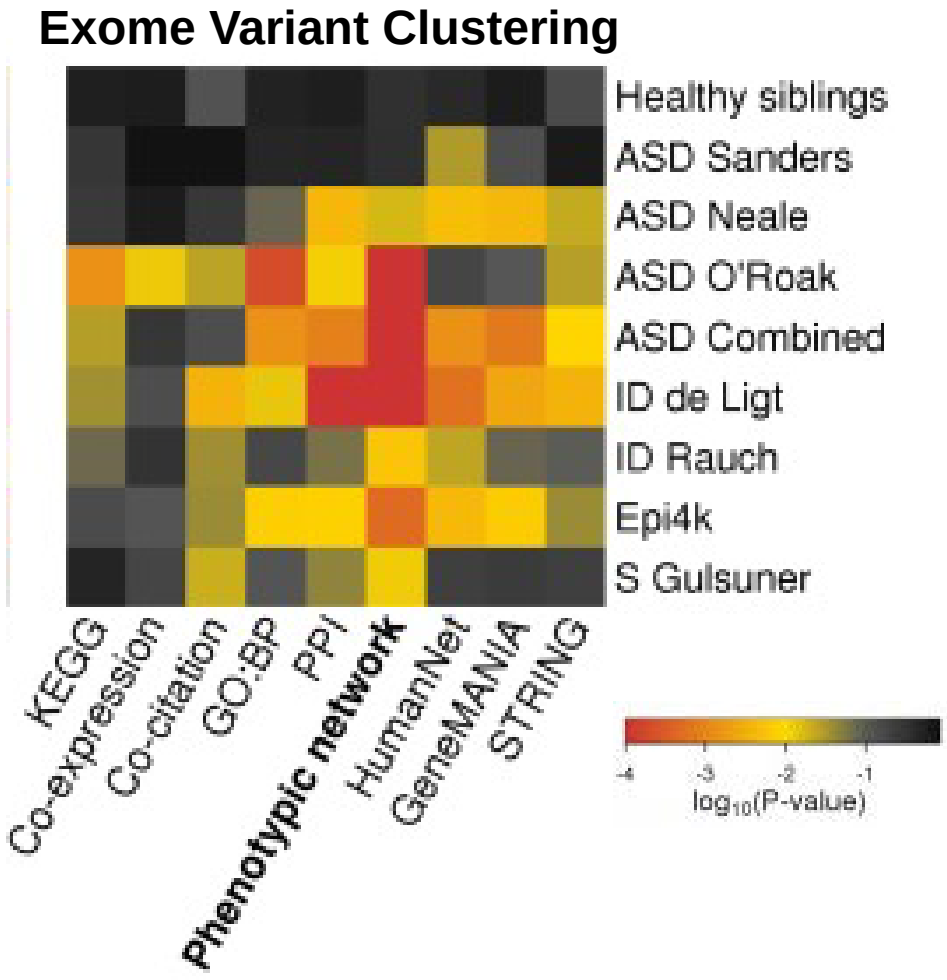
Phenotypic-linkage networks





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Frank Honti

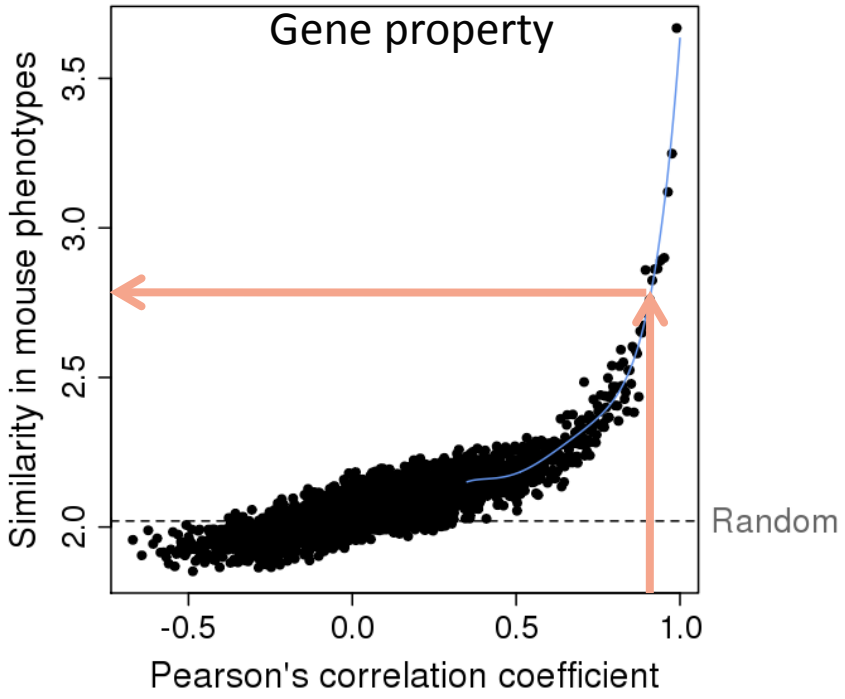
Disorder-specific networks – tuning data to specific disorders

Type 2 Diabetes relevant phenotypes

MP:0005379	endocrine/exocrine gland phenotype
MP:0005376	homeostasis/metabolism phenotype
MP:0005375	adipose tissue phenotype

more similar diabetes-relevant phenotypes

less similar diabetes-relevant phenotypes



Cynthia Sandor

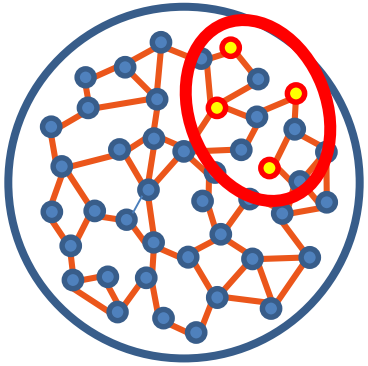
Clustering T2D exome variants from 12,884

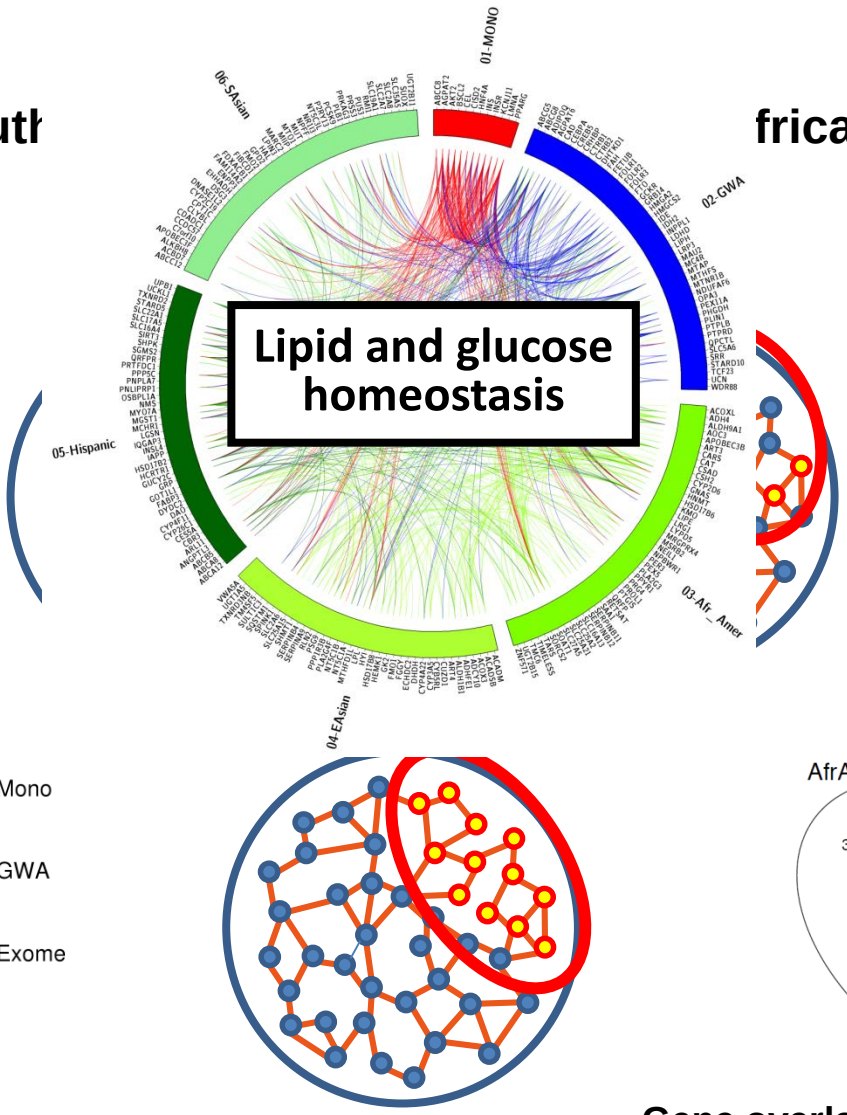
5 ethnic samples: South

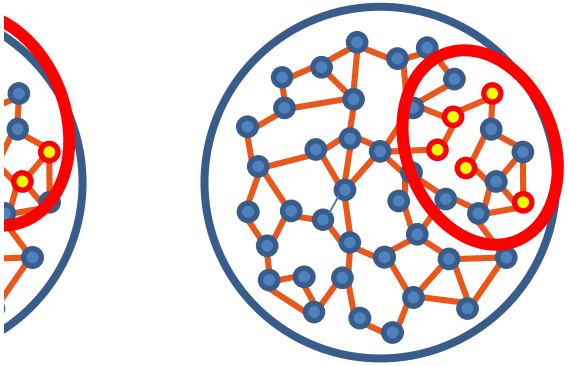
frican American, European

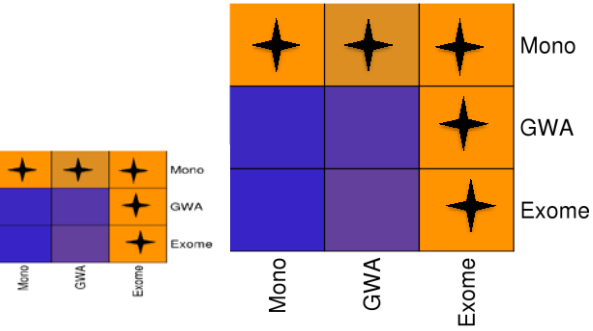
South Asian

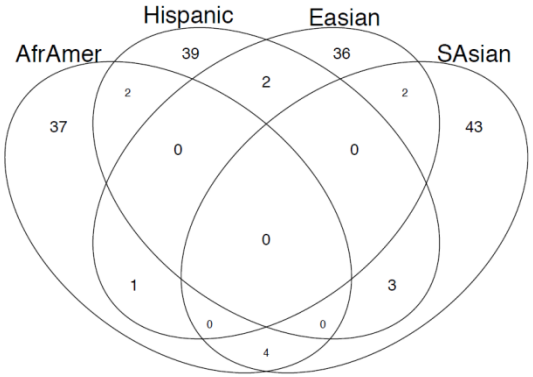
African American











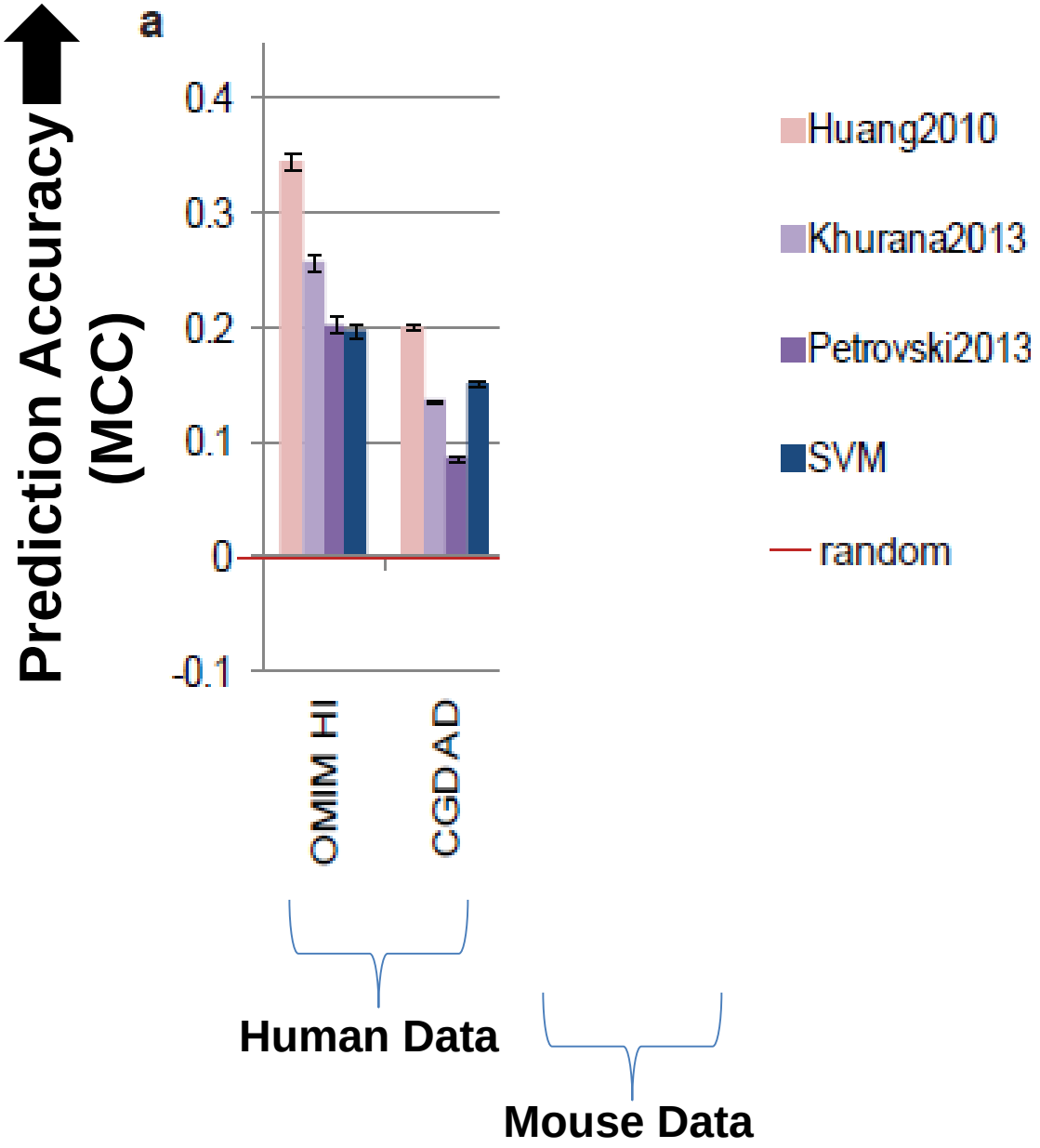
Gene overlap between exome variant sets

Take homes

1. Patients whose variants disrupt the same "pathway" share a broad range of phenotypic similarities

2. Use the mouse phenotypic data to evaluate other functional data, especially for particular phenotypes of interest

Study Bias in haploinsufficiency prediction



Steinberg *et al*, NAR,

Take homes

1. Patients whose variants disrupt the same “pathway” share a broad range of phenotypic similarities

2. Use the mouse phenotypic data to evaluate other functional data, especially for particular phenotypes of interest

3. We need less studied genes phenotyped to help our estimates of variant deleteriousness

Disease Genomics Programme, FGU, Oxford University

Webber Group


Stuart Grice


Avi Taylor


Cynthia Sandor


Steph Millin


Tallulah Andrews


Viola Volpato


Frank Wessely


Kieran Campbell


Katarina Vrcelj


Julia Steinberg

Diabetes exomes in collaboration with Mark McCarthy;
Nijmegen CNVs with Bert DeVries