

Genetical Genomics and the Transcriptional Connectome: *Building Better Hypotheses*

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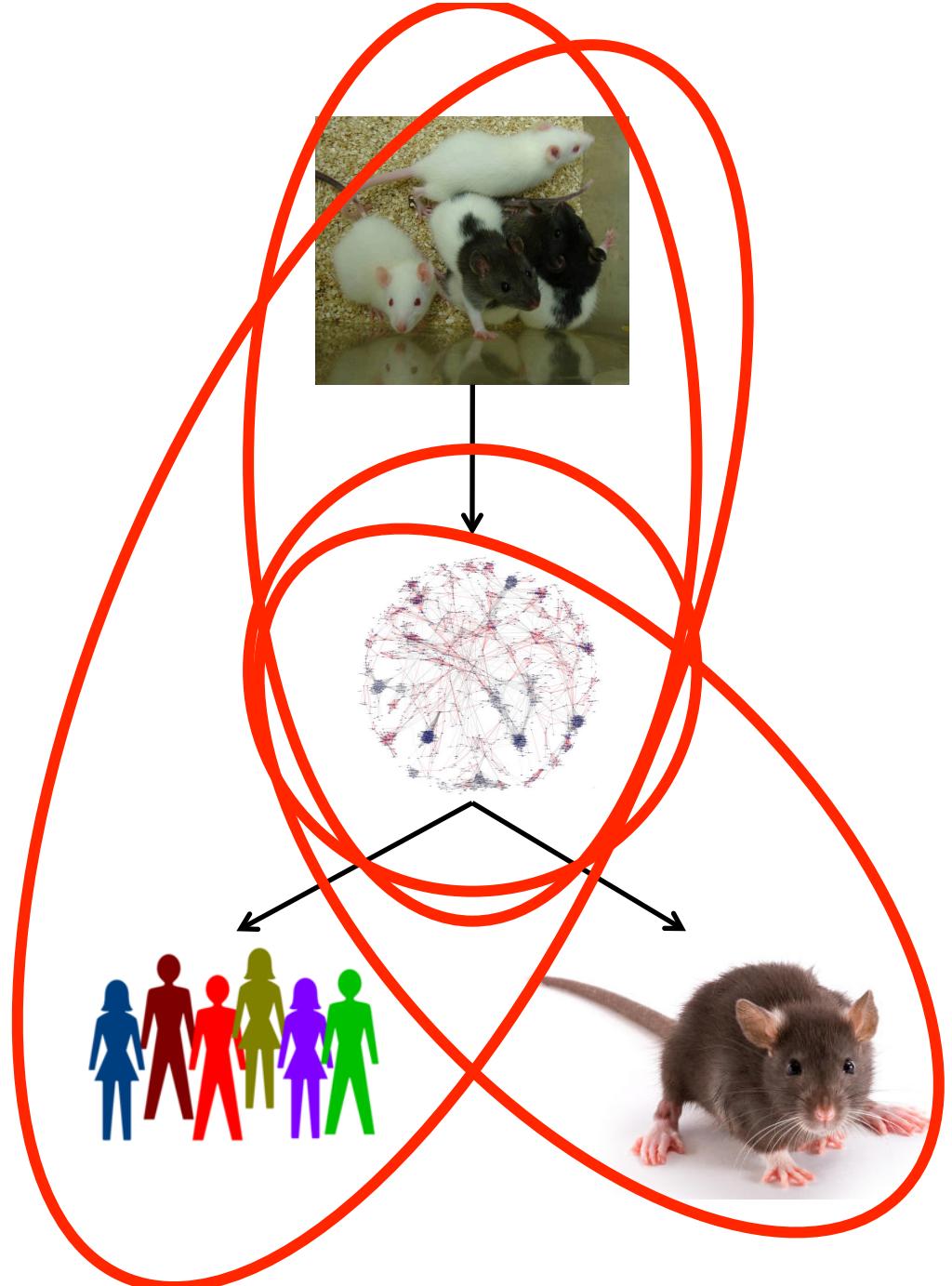
and

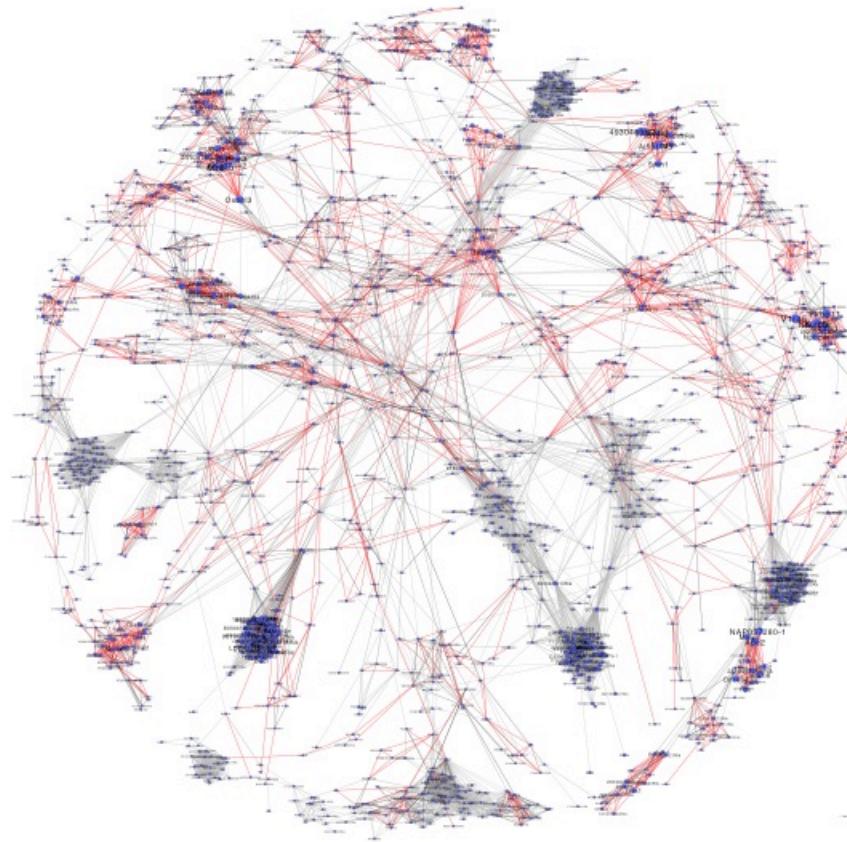
Department of Biostatistics and Informatics

Colorado School of Public Health

Outline

- Overview of the Transcriptional Connectome
- Generating and Sharing Baseline Connectome
- Prediction from Baseline Connectome
- Enhancing Human Genetic Studies with the Rodent Transcriptional Connectome





OVERVIEW OF TRANSCRIPTIONAL CONNECTOME

Example network image from www.john.ranola.org

Systems Genetics

“...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models” (Sauer et al., Science 2007).

“Good Enough Solutions”

Weiss et al (2012). “Good Enough Solutions” and the Genetics of Complex Disease. Circ Res 111:493-504.



http://evolution.berkeley.edu/evolibrary/article/mantisshrimp_01

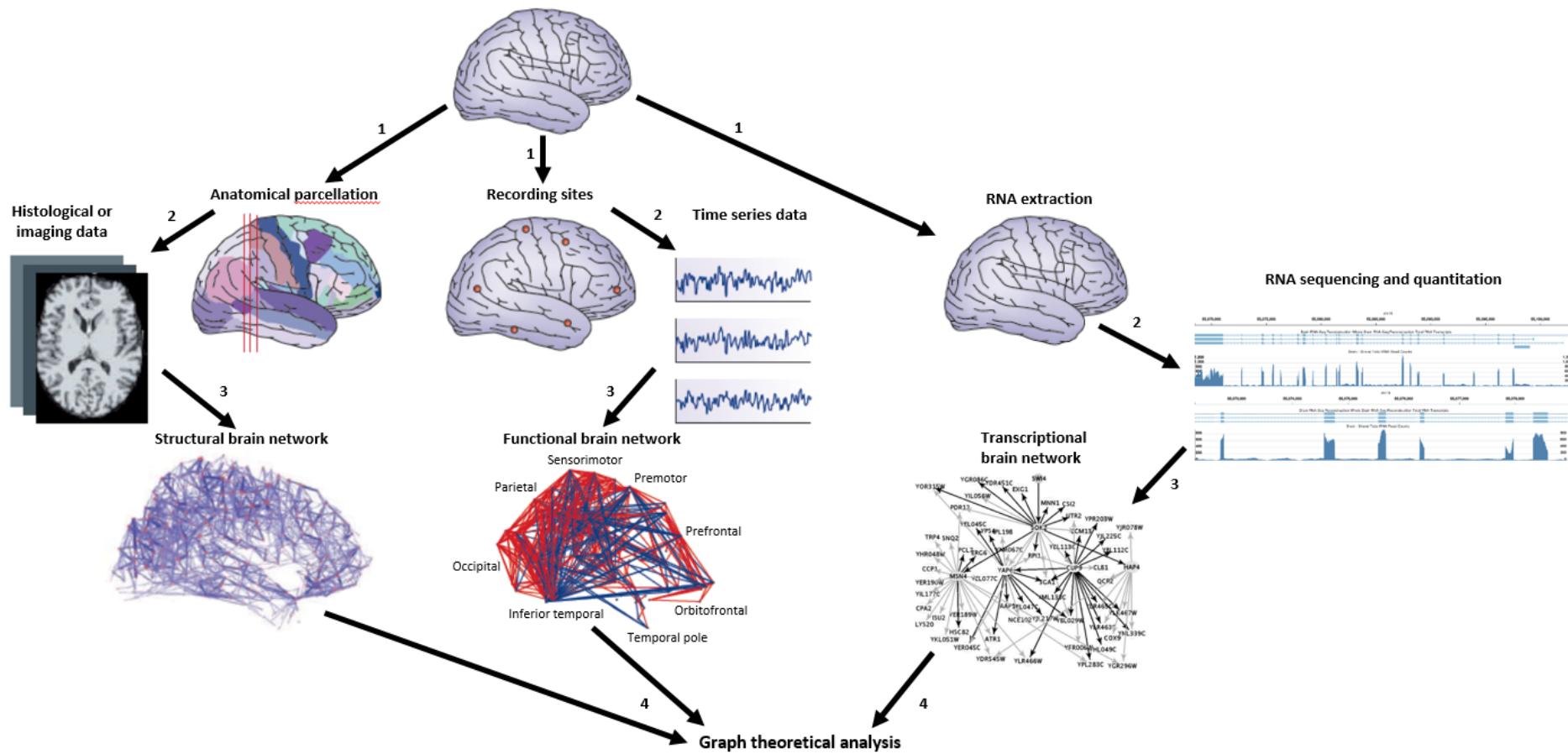
- Concept from evolutionary biology
- “in complex systems, many different combinations of the system’s parameters can produce a nearly identical output”

Good Enough Genetic/Genomic Solutions

- DNA sequence and RNA expression levels = ‘system parameters’
- Genetic diversity → differences in baseline systems
- Differences in baseline systems → differences in response to environmental variables

Can we statistically describe these baseline systems?

Brain Transcriptional Connectome

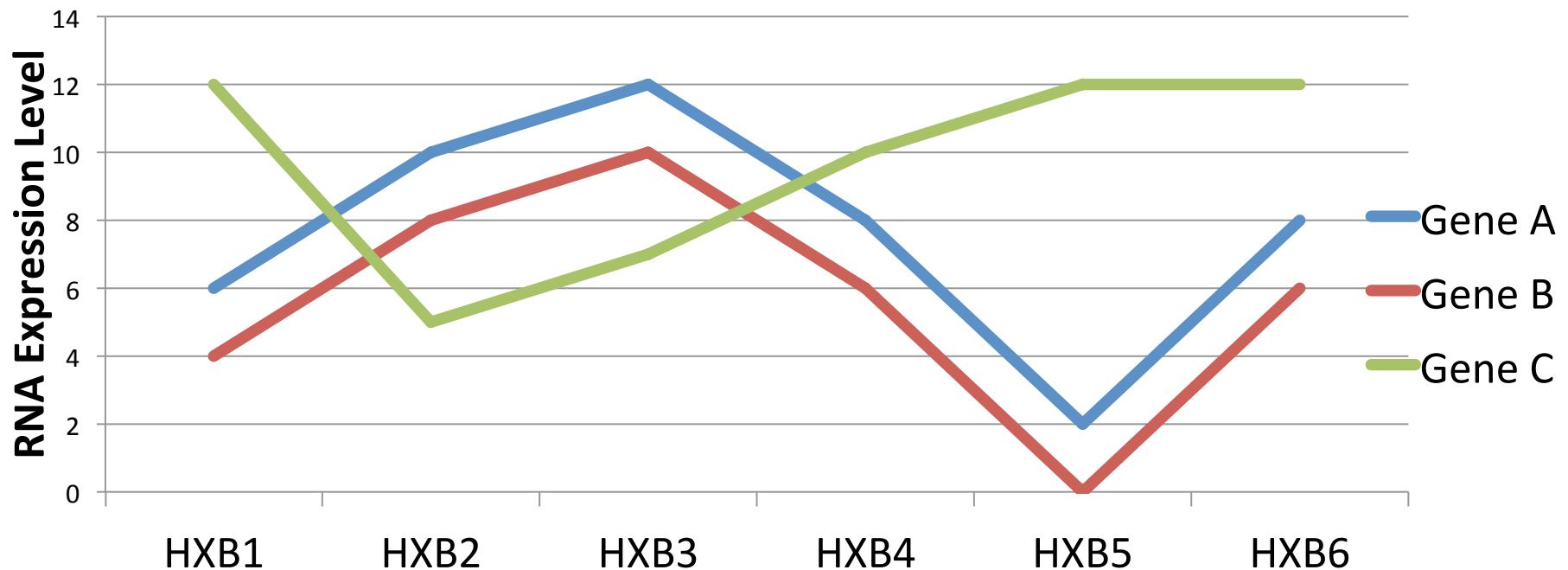


Why Study the RNA Dimension

Transcriptome links DNA and complex traits/diseases

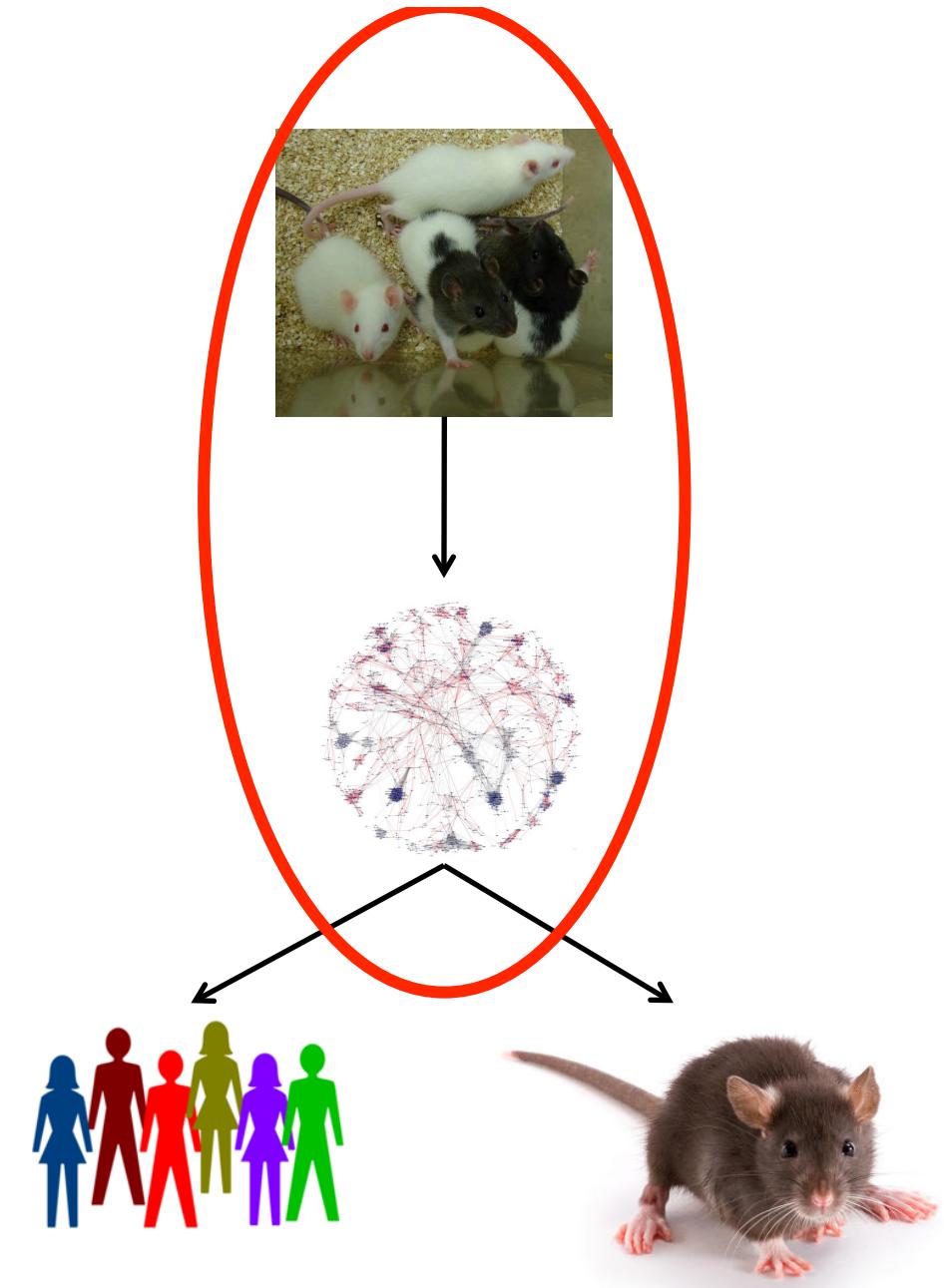
- A. One of the first quantitative links between DNA sequence and phenotype
- B. First step where DNA sequence and environment interact
- C. Implementation of graph theory at the transcript level provides insight into genetic/environmental interactions that are the basis for susceptibility to complex diseases.

Co-expression as a measure of the “connectome”



Theory – if the magnitude of RNA expression of two transcripts correlates over multiple “environments” (genomes), then the two transcripts are involved in similar biological processes

GENERATING AND SHARING BASELINE CONNECTOME



PhenoGen Informatics

The site for quantitative genetics of the transcriptome.



Boris Tabakoff, PhD
Principal
Investigator



Paula Hoffman, PhD
Principal
Investigator



Katerina Kechris,
PhD
Co-Investigator



Spencer Mahaffey,
ME
Computer
Programmer



Stephen Flink, PhD
Post-Doc



Lauren
Vanderlinden, MS
Biostatistician



Yinni Yu, MS
Lab Manager

RGAP: The heritable transcriptome and alcoholism (R24 AA013162 - NIH/NIAAA)

Laura Saba, PI (multiple PIs with Boris Tabakoff and Paula Hoffman)

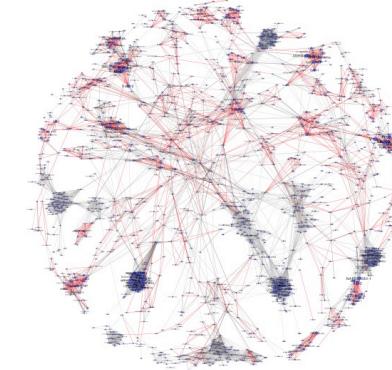
Role of sex and estrus cycle on baseline brain and liver transcriptional connectomes
(Competitive Supplement to R24 - NIH/NIAAA)

Boris Tabakoff, PI (Laura Saba, Co-I)

Current Goals for the PhenoGen Project

1. Baseline transcriptional connectomes

- Brain
- Liver
- Heart



2. Resource Distribution

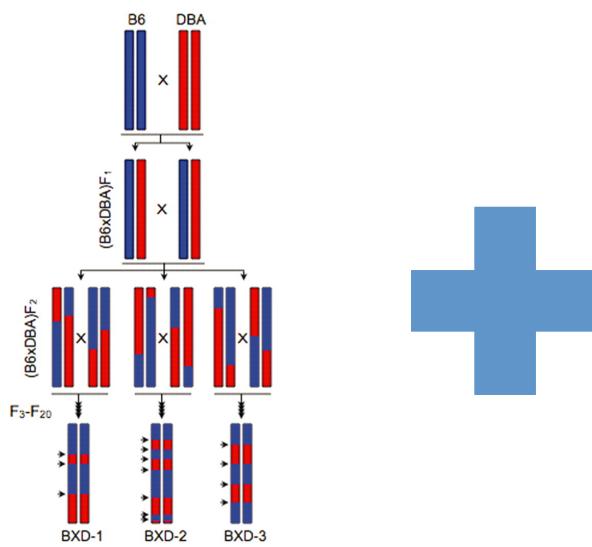


A screenshot of the PhenoGen Informatics website. The header includes links for Overview, General Data Browser, Microarray Gene Databases, Microarray Analysis Tools, Gene List Analysis Tools, QTL Tools, About, Help, and Login/Register. A sub-header says "Welcome to PhenoGen Informatics: The site for quantitative genetics of the transcriptome." A central feature is a circular navigation menu with links: What can we do with PhenoGen?, Gene List Analysis, Microarray Analysis, Genome / Transcription Data Browser, Download Data, QTL Analysis, General Info, Announce meets, and What's New. To the right, there is a sidebar for Announcements, a video player for the "Workshop Video/Slides 4/16/2015", and a message about adding GO term summary and mRNA expression data to the co-expression Network Analysis. At the bottom, there are sections for Acknowledgements, Funding, and a link to the "Recombinant Inbred Panels".

THE POPULATION

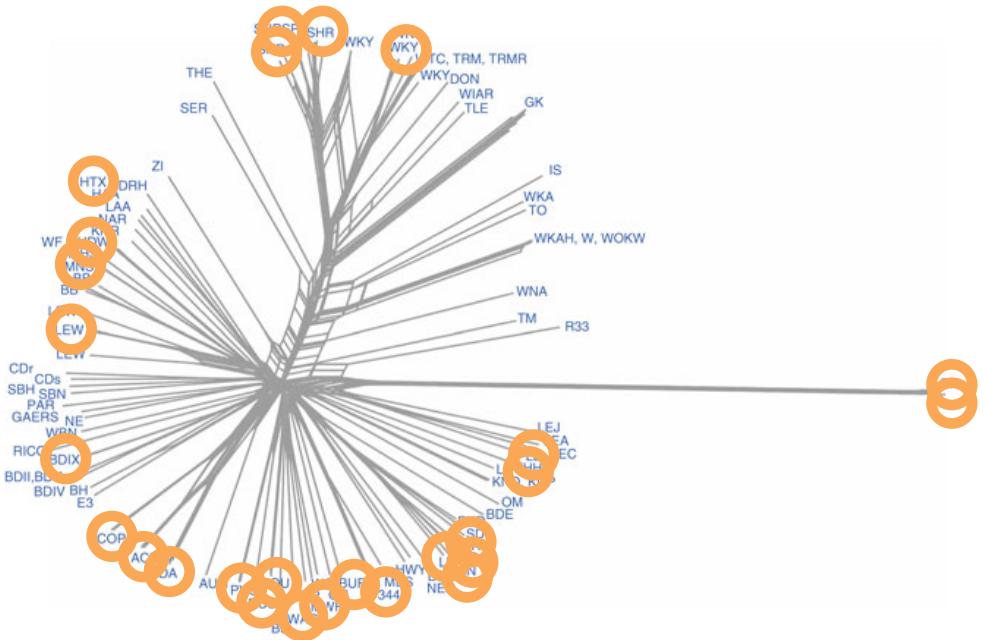
Rat Hybrid Diversity Panel

Population for Transcriptional Connectome



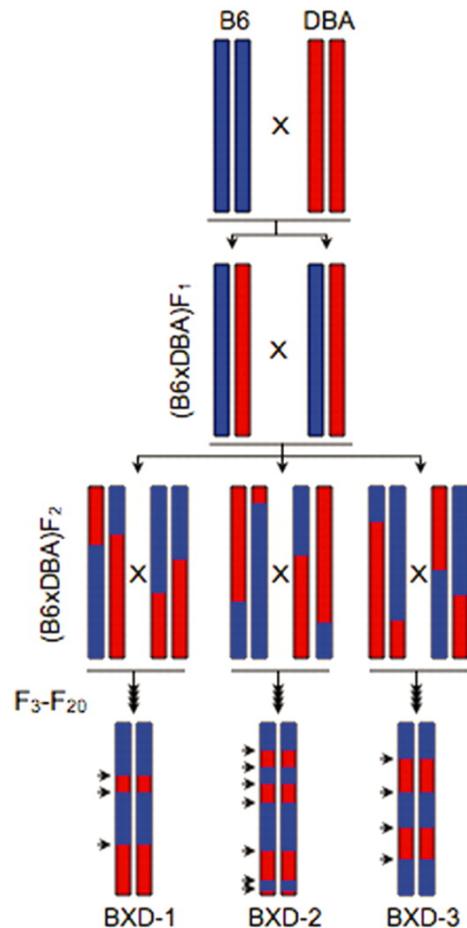
30 Recombinant
Inbred Strains

- Correlational power excellent
- Mapping power adequate
- Power to detect transcript variation (advantage using both inbred and recombinant)



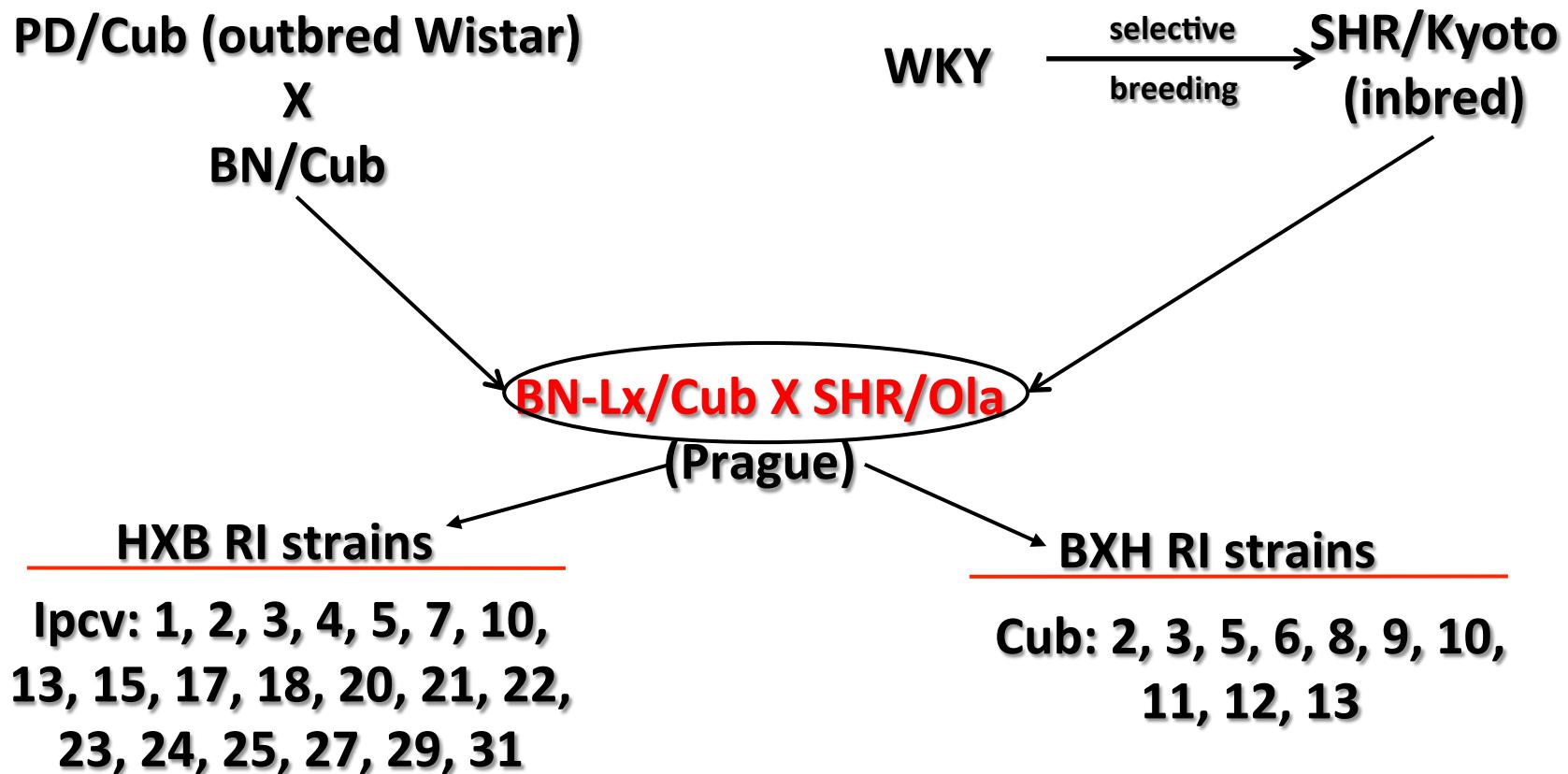
30 Classic Inbred
Strains

Recombinant Inbred Rodent Panel



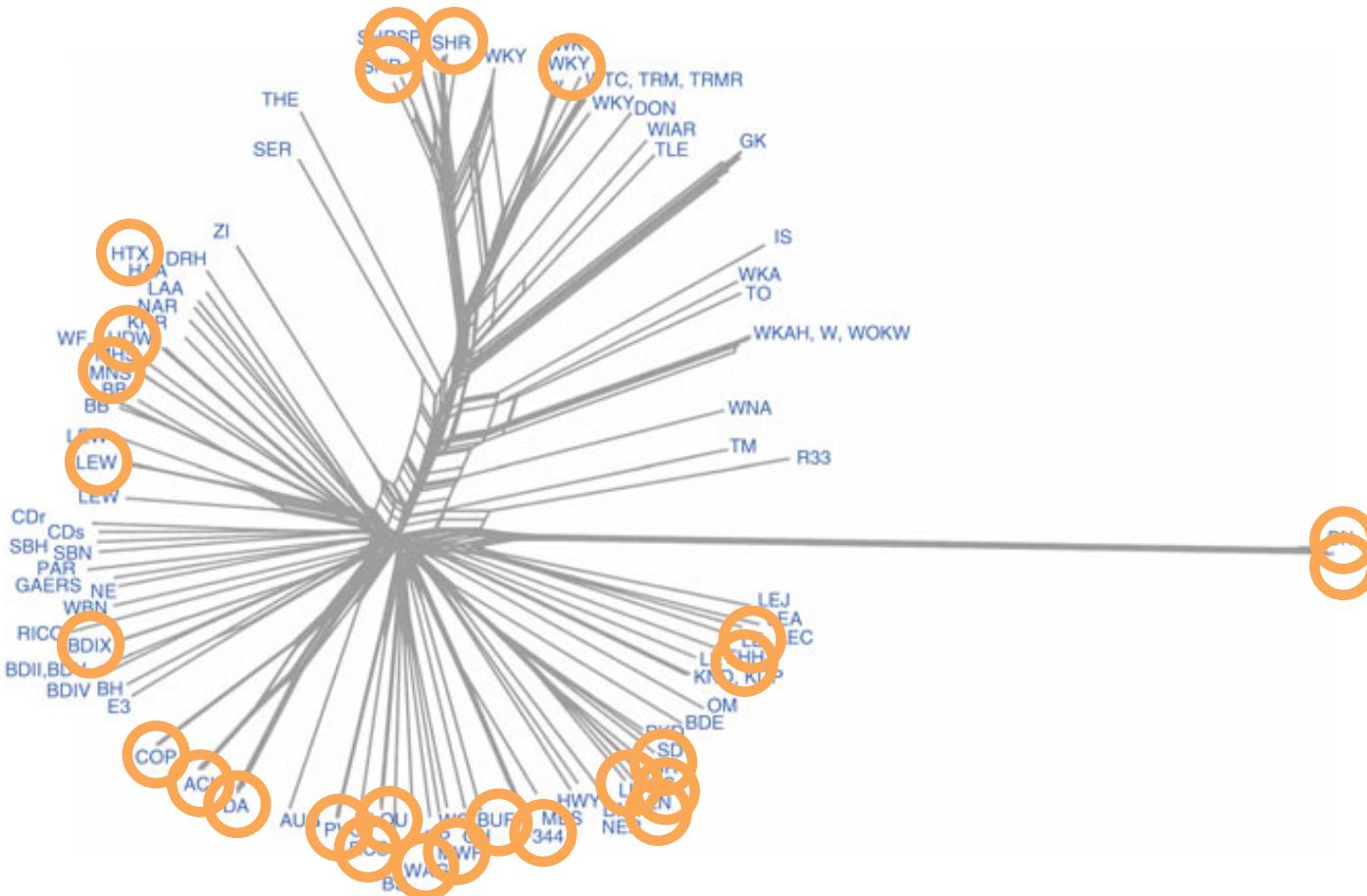
- Genetic identity is retained over generations
- Cumulative genetic and phenotype data across labs
- Ideal genetic controls for studying interventions/environmental effects

Origin of HXB/BXH RI Panel



- > 4,500,000 SNPs/indels between progenitors
 - Haplotype map generated

Genetic Relationship Between Inbred Strains



SNP and haplotype mapping for genetic analysis in the rat. The STAR Consortium*. Nature Genetics 40, 560-566 (2008)
PD, M520/N, and MR/N also added for a total of 30

Current Data – RNA-Seq

Strains	Tissue	Sex	Number of Biological Replicates Per Strain	Number of Paired-End Reads (rRNA-depleted total RNA)	Number of Paired-End Reads (polyA+ selected RNA)	Number of Single- End Reads (small RNA)
SHR and BNLx	brain	male	3	645 million	192 million	96 million
SHR and BNLx	brain	female	4	982 million	---	297 million
SHR and BNLx	liver	male	3	583 million	---	342 million
SHR and BNLx	heart	male	4	790 million	---	300 million
30 RI Strains	brain	male	1 to 2	7.3 billion	----	1.9 billion

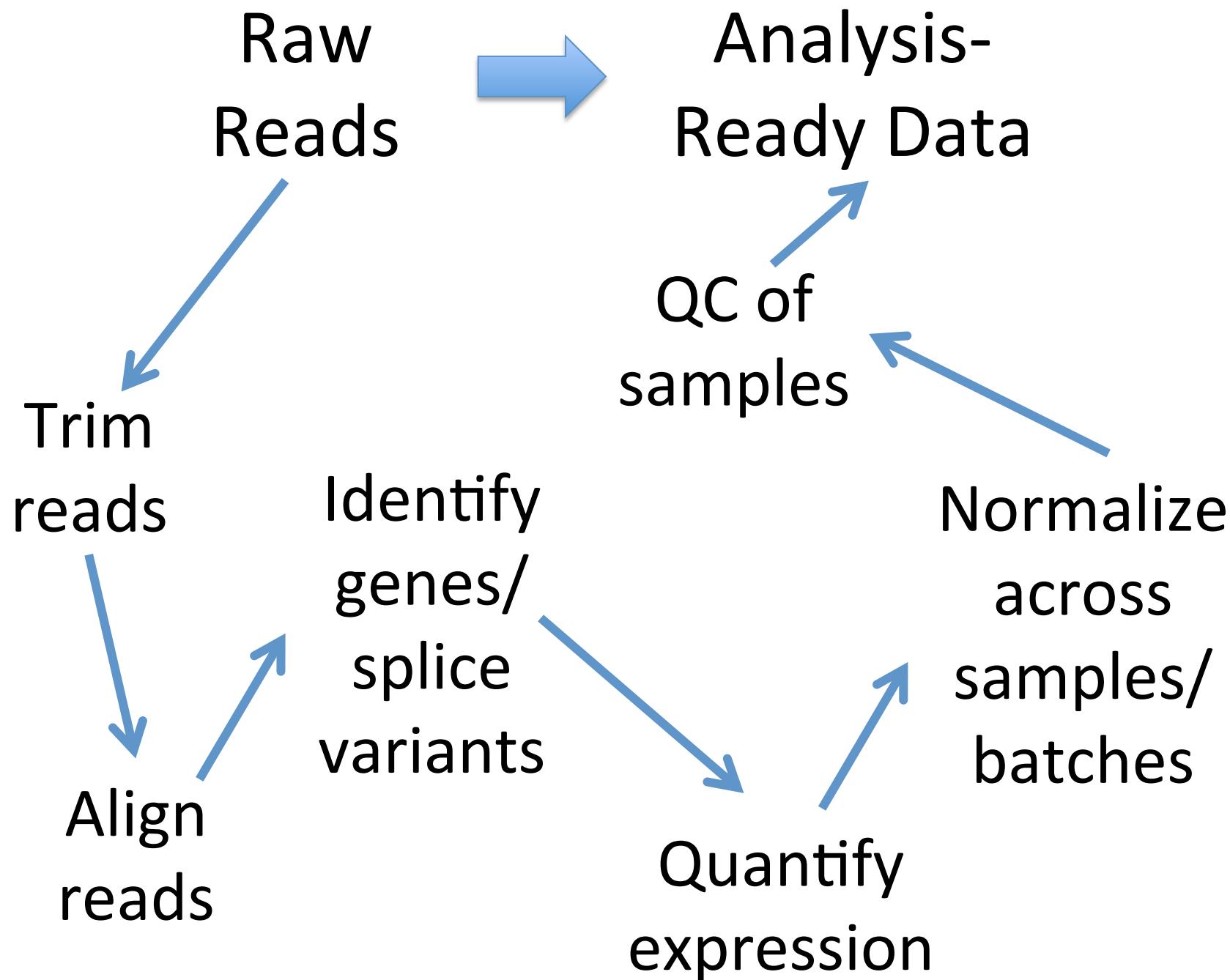
Current Data - Microarrays

Panel	Platform	Tissue	Number of Biological Replicates
21 HXB/BXH RI Strains	Exon Array	Brain	2 to 4
21 HXB/BXH RI Strains	Exon Array	Liver	2 to 4
21 HXB/BXH RI Strains	Exon Array	Heart	2 to 4
21 HXB/BXH RI Strains	Exon Array	Brown Adipose	2 to 4
60 LXS Mouse RI Strains	Exon Array	Brain	6
30 BXD Mouse RI Strains	3' Array	Brain	4 to 7
26 Inbred Mouse Strains	3' Array	Brain	4 to 6

Working to Complete Data Acquisition

Strains	Tissue	Sex	Number of Biological Replicates Per Strain	Number of Paired-End Reads (rRNA-depleted total RNA)	Number of Single- End Reads (small RNA)
30 Classic Inbred Strains	brain	Male	4	36 trillion	11.0 billion
30 RI Strains	brain	Male	4	36 trillion	11.0 billion
30 Classic Inbred Strains	liver	Male	4	36 trillion	11.0 billion
30 RI Strains	liver	Male	4	36 trillion	11.0 billion

THE ROLE OF STATISTICS/ INFORMATICS



Weighted Gene Co-Expression Network Analysis (WGCNA)

Why Not Just Use Correlation?

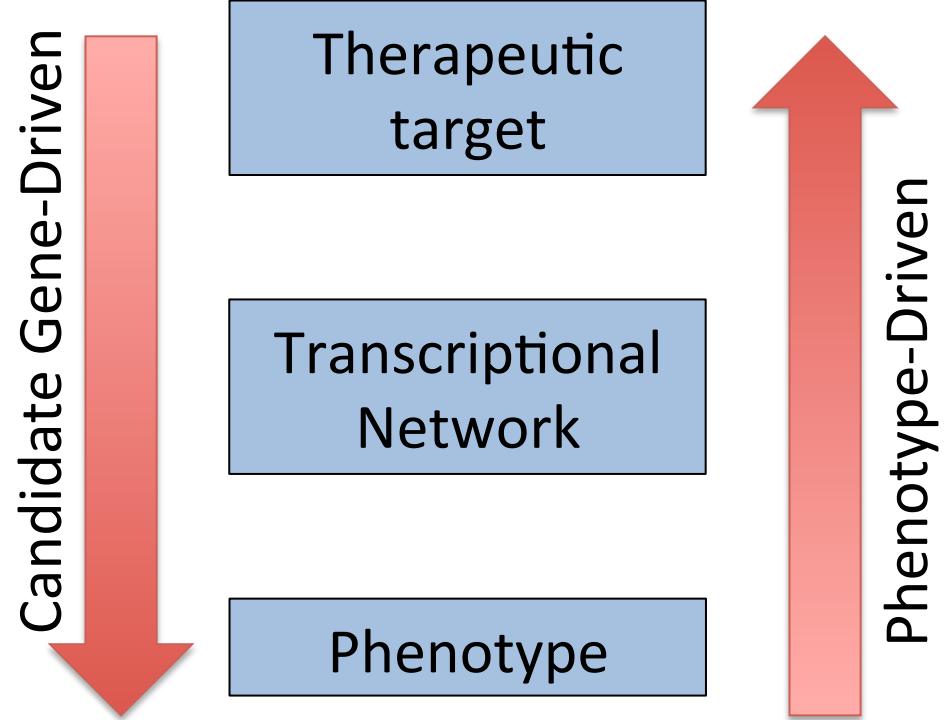
1. Simple correlation does not give connectivity.
2. How are we measuring co-expression?
 - Scale-Free Network
 - Network has few highly connected genes rather than each gene have similar connectivity
 - **Biologically motivated**, fewer highly connected genes means that a system is more robust to failure of any one gene
3. How do we get a **robust** measure of connectivity for identifying modules?
 - Topological Overlap Measure
 - Includes a measure of how many “friends” two genes have in common
 - Protects against spurious correlations among genes

Zhang, B., & Horvath, S. (2005). A general framework for weighted gene co-expression network analysis. *Statistical Applications in Genetics and Molecular Biology*, 4, Article17.

SHARING THE BASELINE CONNECTOME

Two Primary Approaches To Accessing the Transcriptional Connectome on PhenoGen

1. **Candidate gene-driven** analysis of biological/genetic context
2. **Phenotype-driven** genome-wide analysis for candidate genetic pathways for predisposition to disease



CANDIDATE GENE-DRIVEN APPROACH

Pharmacologic Targets for Alcohol Dependence

Start with gene product of interest and learn about its network partners and pathways.

e.g., Naltrexone and the mu-opioid receptor

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 38, No. 12
December 2014

Effects of Naltrexone on Neural and Subjective Response to Alcohol in Treatment-Seeking Alcohol-Dependent Patients

Primavera A. Spagnolo, Vijay A. Ramchandani, Melanie L. Schwandt, Lishu Zhang,
Sara K. Blaine, Julie M. Uzal, Kristie A. Diamond, Monte J. Philips, David T. George,
Reza Momenan*, and Markus Heilig*

Neuropsychopharmacology (2003) 28, 1546–1552
© 2003 Nature Publishing Group All rights reserved 0893-133X/03 \$25.00
www.neuropsychopharmacology.org

A Functional Polymorphism of the μ -Opioid Receptor Gene is Associated with Naltrexone Response in Alcohol-Dependent Patients

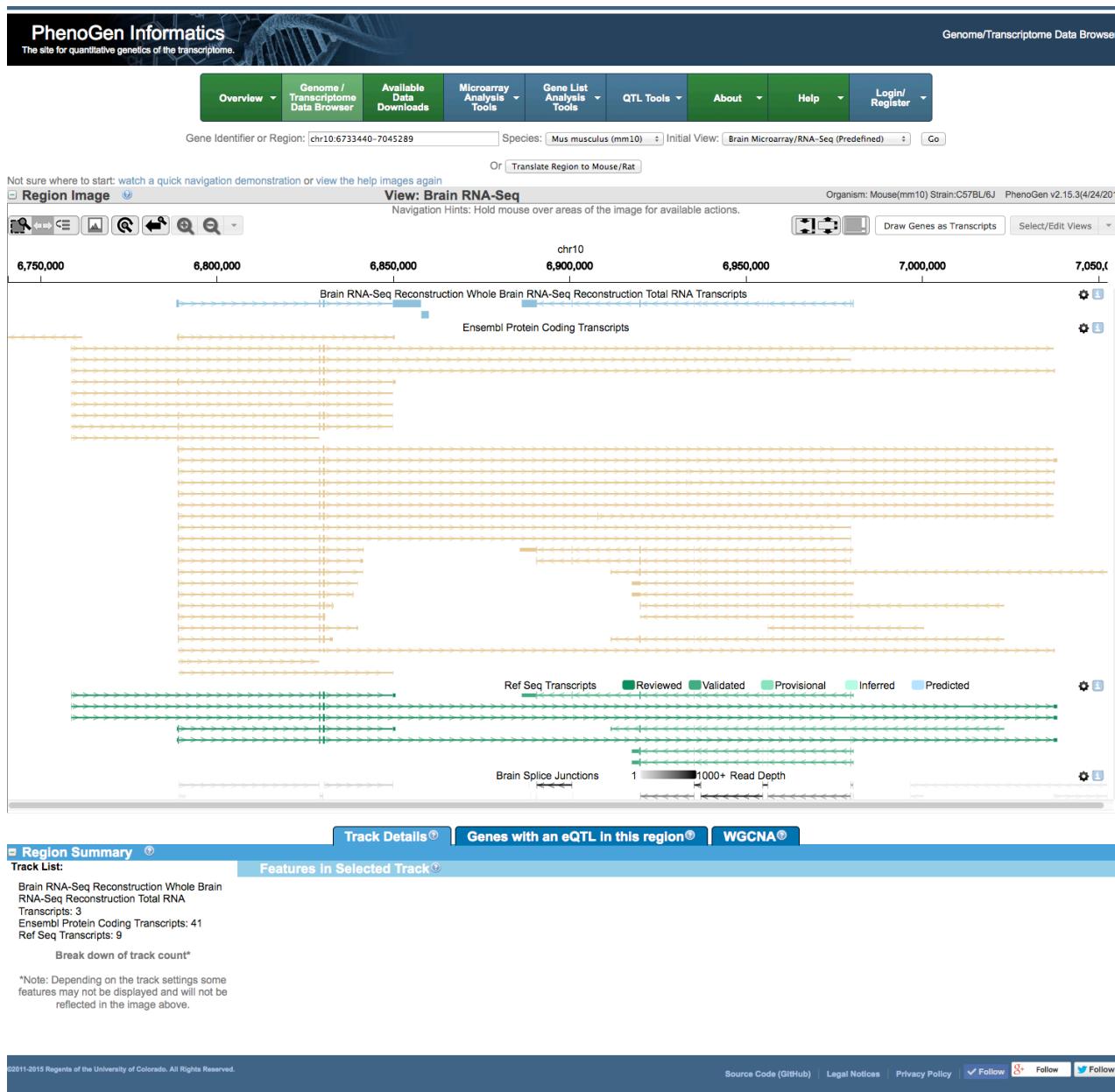
ORIGINAL ARTICLE

An Evaluation of μ -Opioid Receptor (*OPRM1*) as a Predictor of Naltrexone Response in the Treatment of Alcohol Dependence

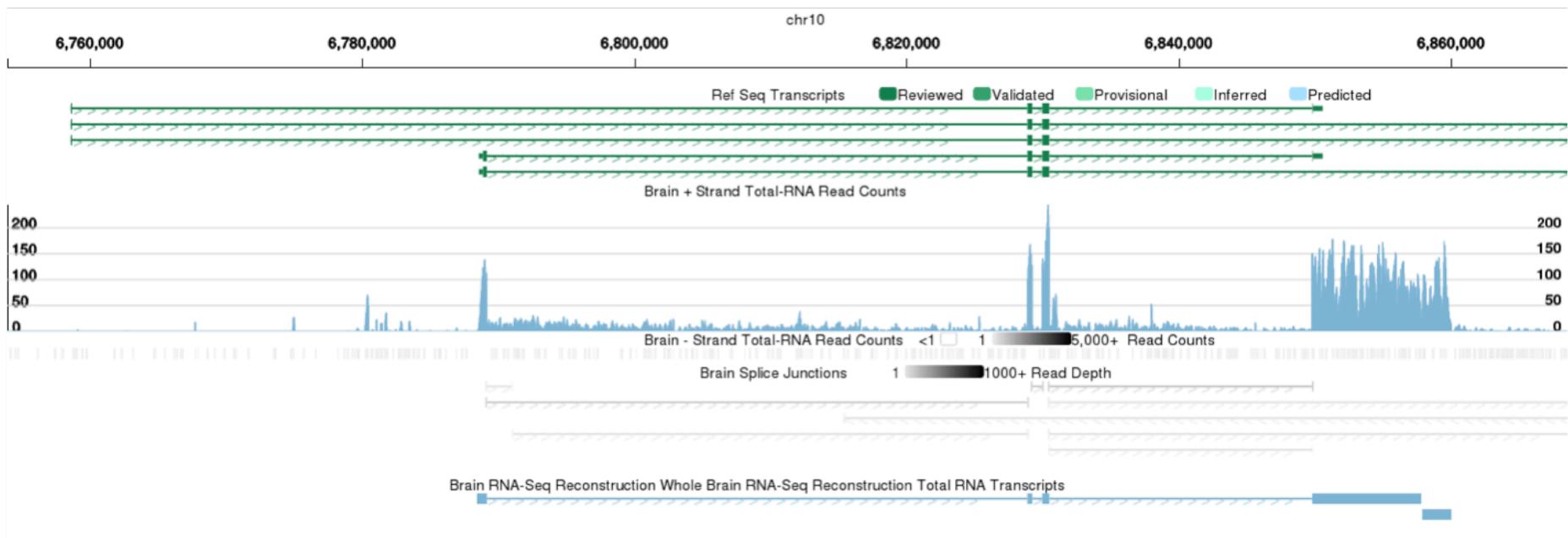
Results From the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study

Raymond F. Anton, MD; Gabor Oroszi, MD, PhD; Stephanie O'Malley, PhD; David Couper, PhD;
Robert Swift, MD, PhD; Helen Pettinati, PhD; David Goldman, MD

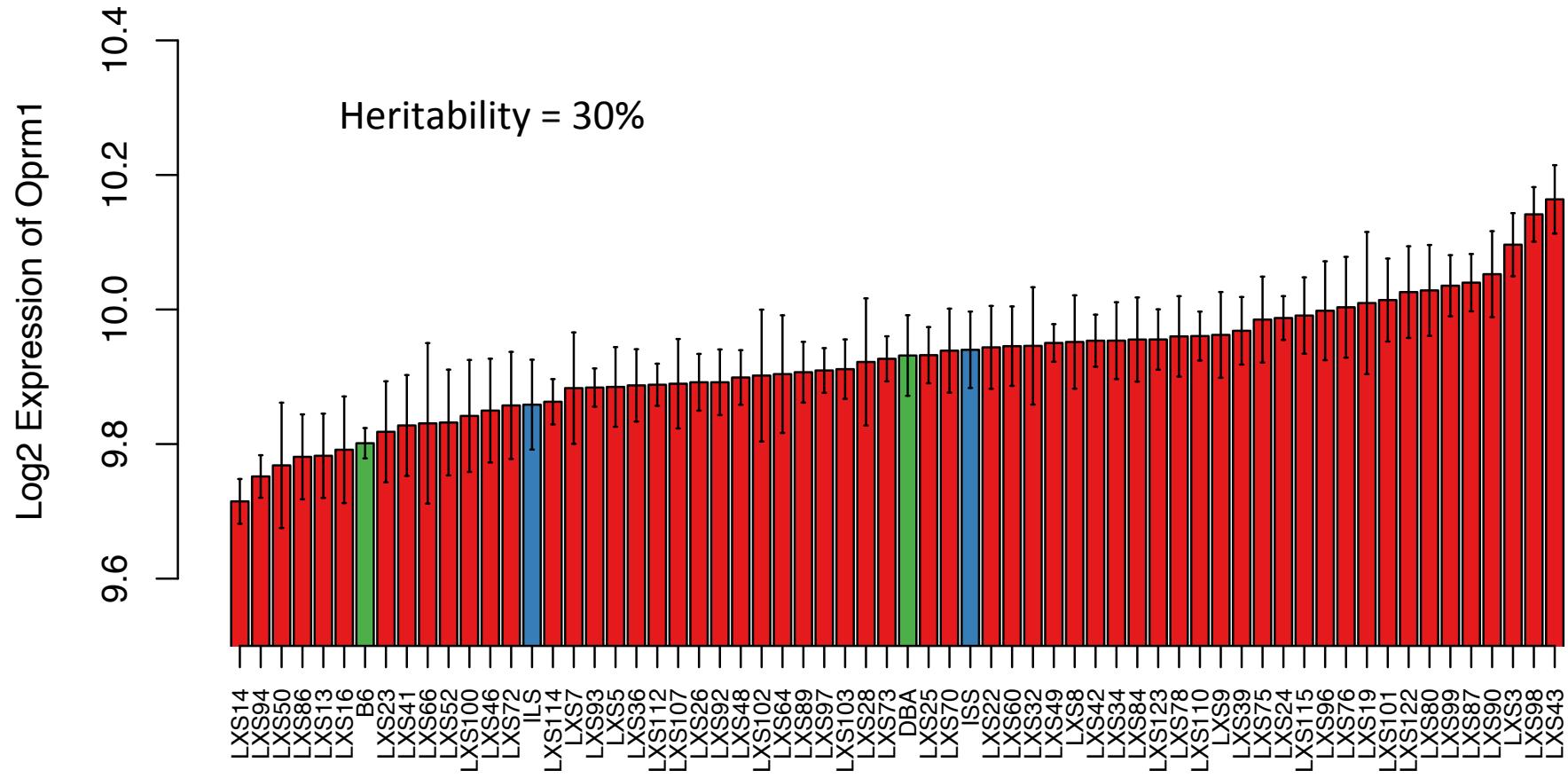
Oprm1 on PhenoGen



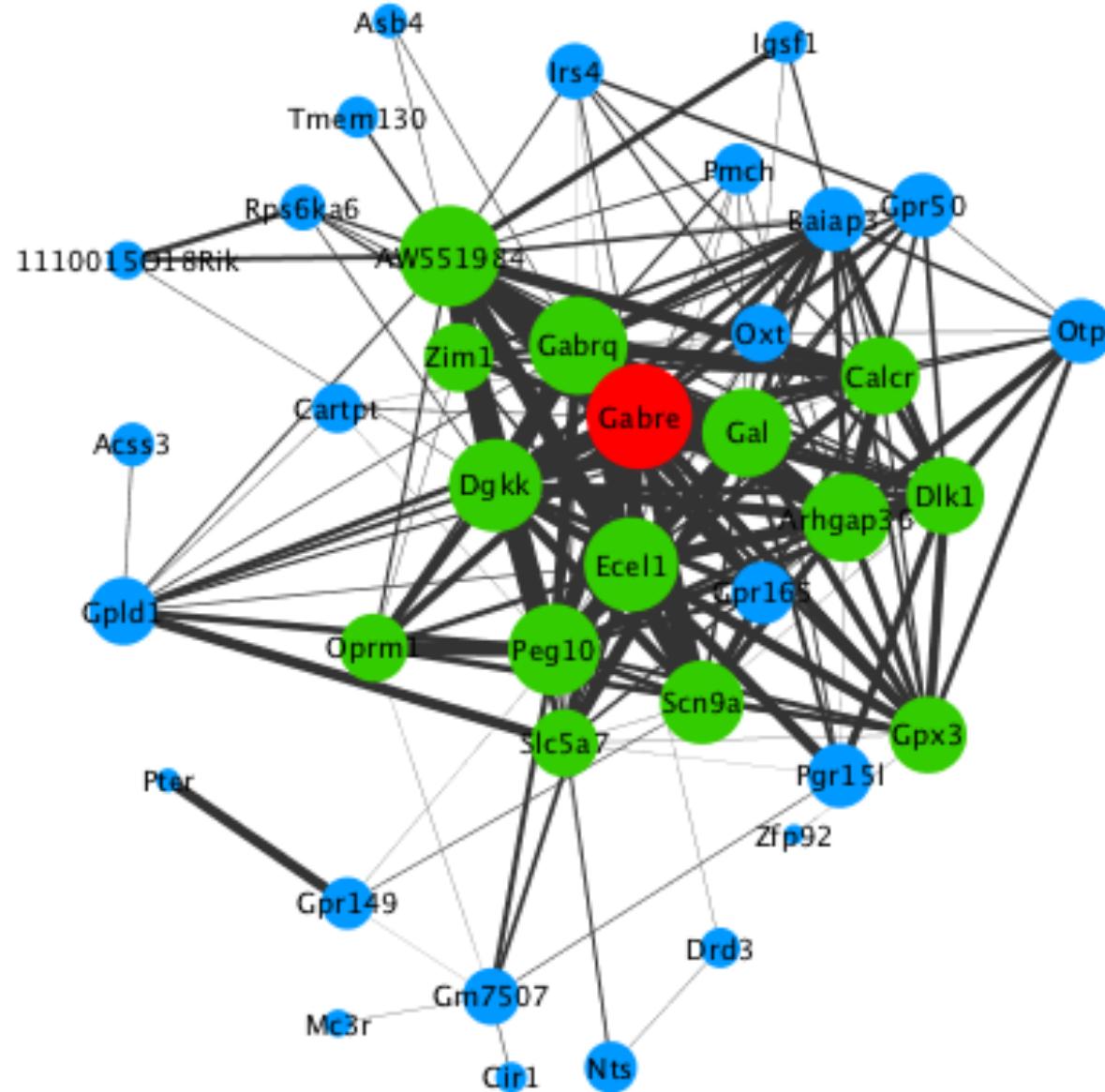
Oprm1 on PhenoGen



Distribution of Oprm1 Expression in Brain Across LXS Panel



Brain Network Module With Oprm1



Functional Enrichment in Oprm1's Module

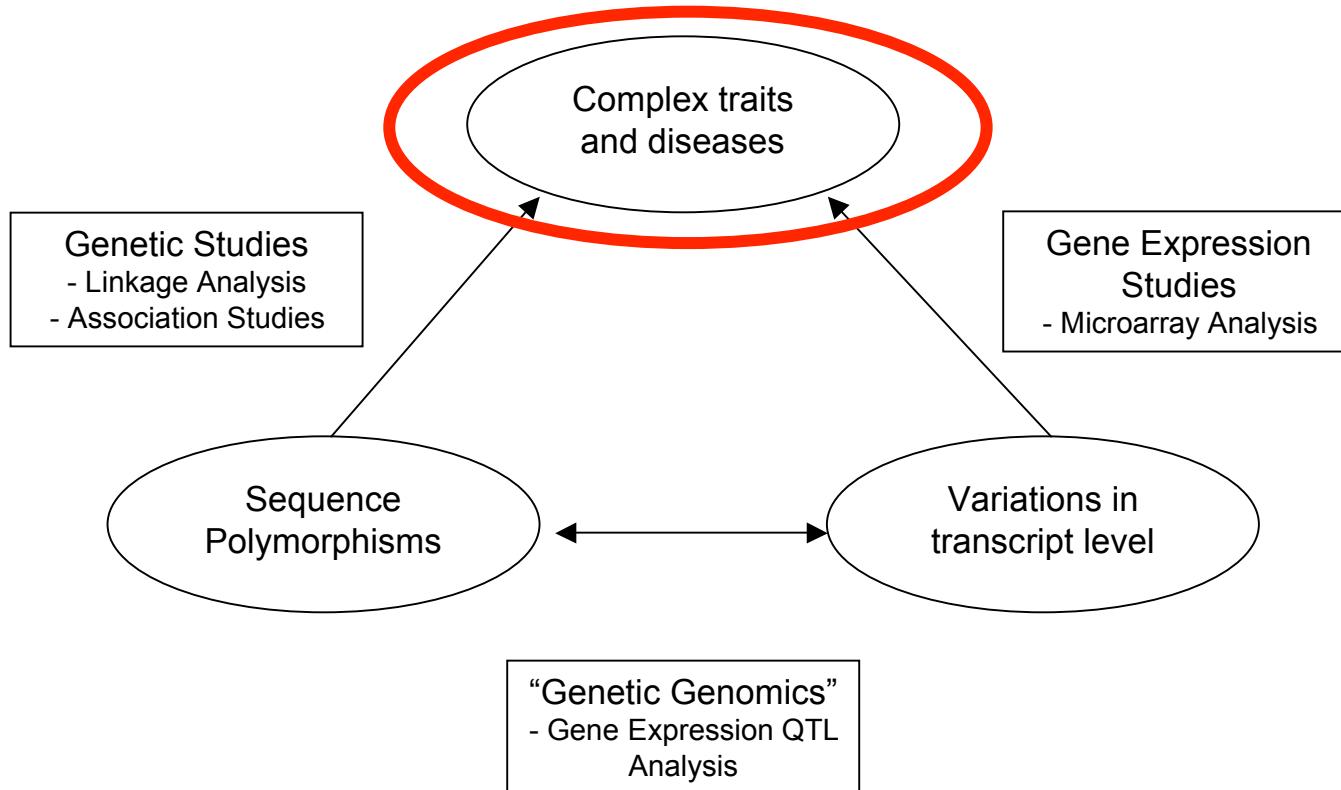
- Enriched Gene Ontology Categories (FDR<0.05; >5 fold enrichment)
 - **Molecular Functions**
 - Neuropeptide hormone activity (5 genes)
 - Neuropeptide receptor binding (3 genes)
 - Melanocortin receptor binding (2 genes)
 - **Biological Processes**
 - Neuropeptide signaling pathway (7 genes)
 - G-protein coupled receptor signaling pathway (15 genes)
 - Synaptic transmission (8 genes)
 - Behavior (11 genes)

Conclusions

- Using PhenoGen, we were able to:
 1. Identify which isoform is expressed in mouse brain
 2. Establish that expression levels of Oprm1 are influenced by genetics
 3. Relate Oprm1 co-expression to shared biological function
 - identify particular G-protein subunits that Oprm1 is related to in the baseline connectome
 4. Identify Oprm1 ‘nearest neighbors’ for further knowledge base analyses

PHENOTYPE DRIVEN APPROACH

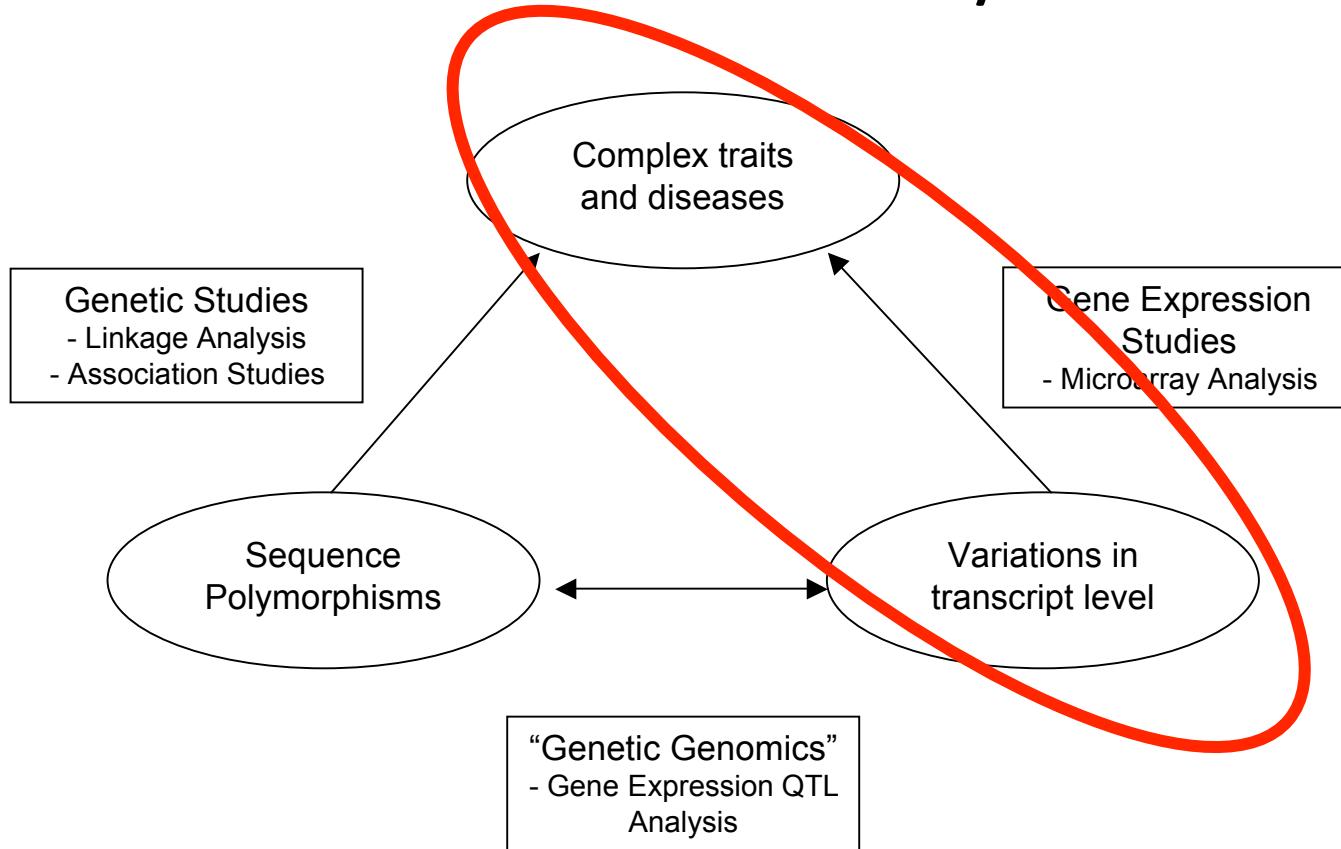
Candidate Modules from Genetical Genomics/Phenomics Approach



1. Identify a quantitative, heritable, polygenic phenotype with the potential for quantitative transcriptional influence

Image copied from Saba et al, The Marriage of Phenomics and Genetical Genomics: A Systems Approach to Complex Trait Analysis. In Systems Biology in Psychiatric Research: From High-Throughput Data to Mathematical Modeling, edited by Tetter F, Winterer G, Gebicke-Haerter PG, and Mendoza E. Wiley-VCH 2010.

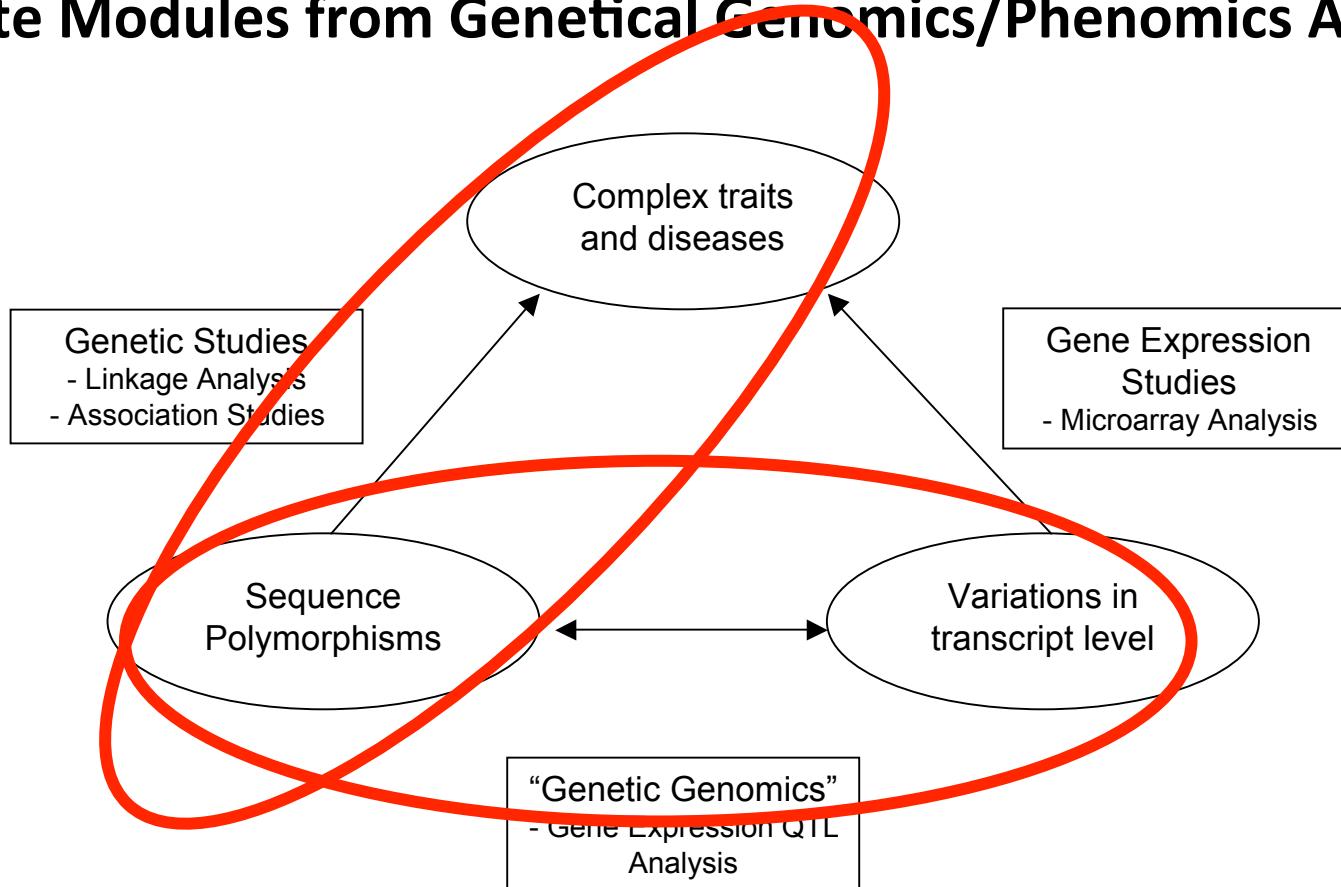
Candidate Modules from Genetical Genomics/Phenomics Approach



2. Identify co-expression modules that are correlated with the complex trait

Image copied from Saba et al, The Marriage of Phenomics and Genetical Genomics: A Systems Approach to Complex Trait Analysis. In Systems Biology in Psychiatric Research: From High-Throughput Data to Mathematical Modeling, edited by Tetter F, Winterer G, Gebicke-Haerter PG, and Mendoza E. Wiley-VCH 2010.

Candidate Modules from Genetical Genomics/Phenomics Approach



3. Limit to co-expression modules that are whose expression is influenced from the same region that influences the complex trait

Image copied from Saba et al, The Marriage of Phenomics and Genetical Genomics: A Systems Approach to Complex Trait Analysis. In Systems Biology in Psychiatric Research: From High-Throughput Data to Mathematical Modeling, edited by Tetter F, Winterer G, Gebicke-Haerter PG, and Mendoza E. Wiley-VCH 2010.

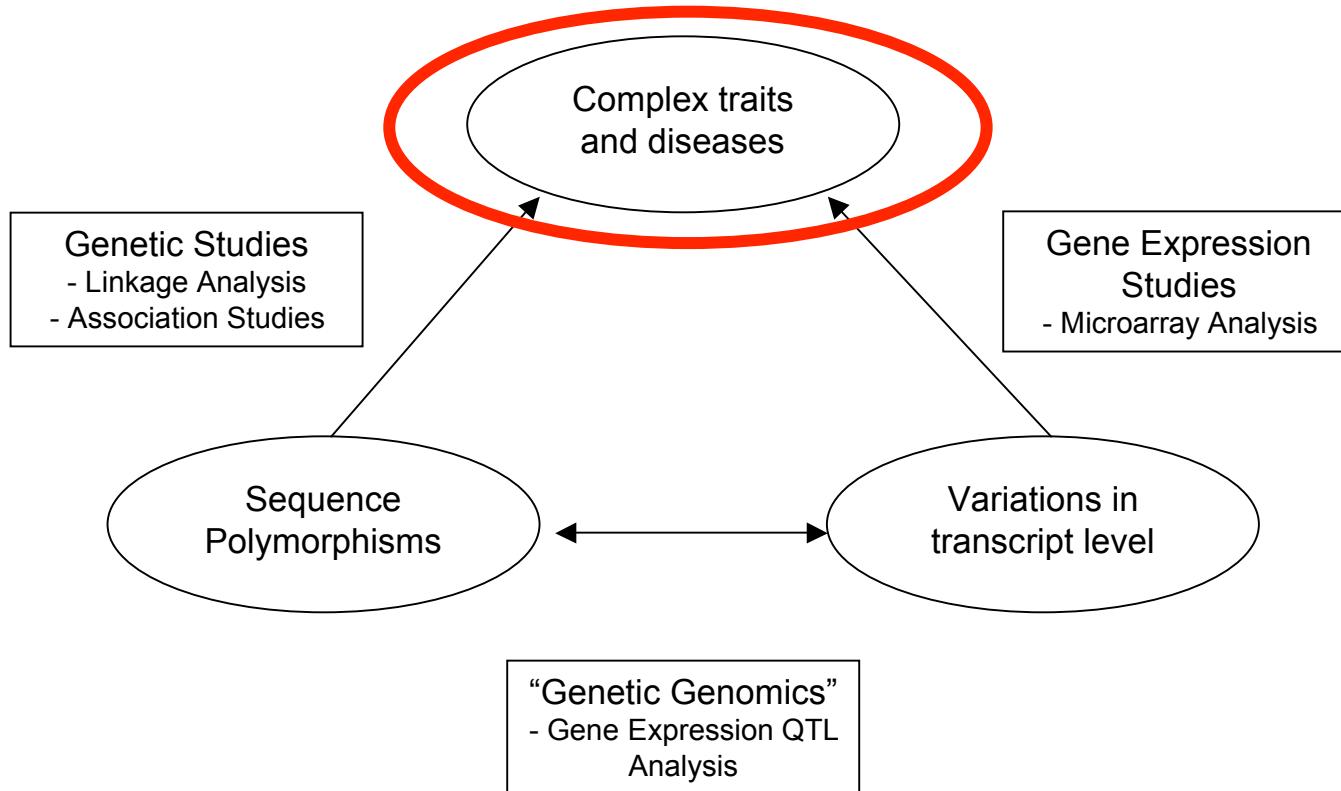
Genetics and Alcohol Consumption

- etiologic essential
- strong genetic influence
- complex polygenic trait



<http://lets-go-to-the-movies.tumblr.com/tagged/Bridesmaids/page/4>

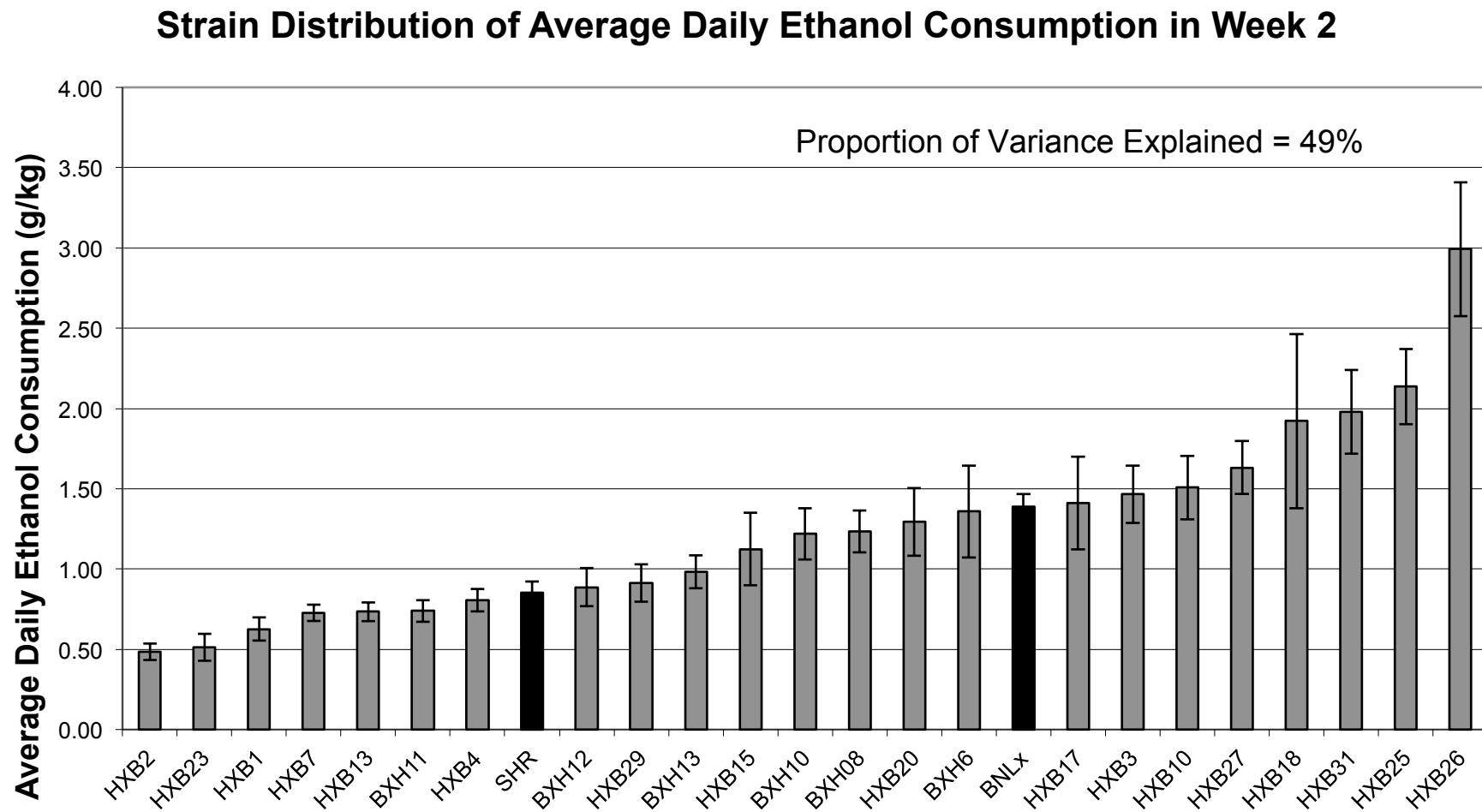
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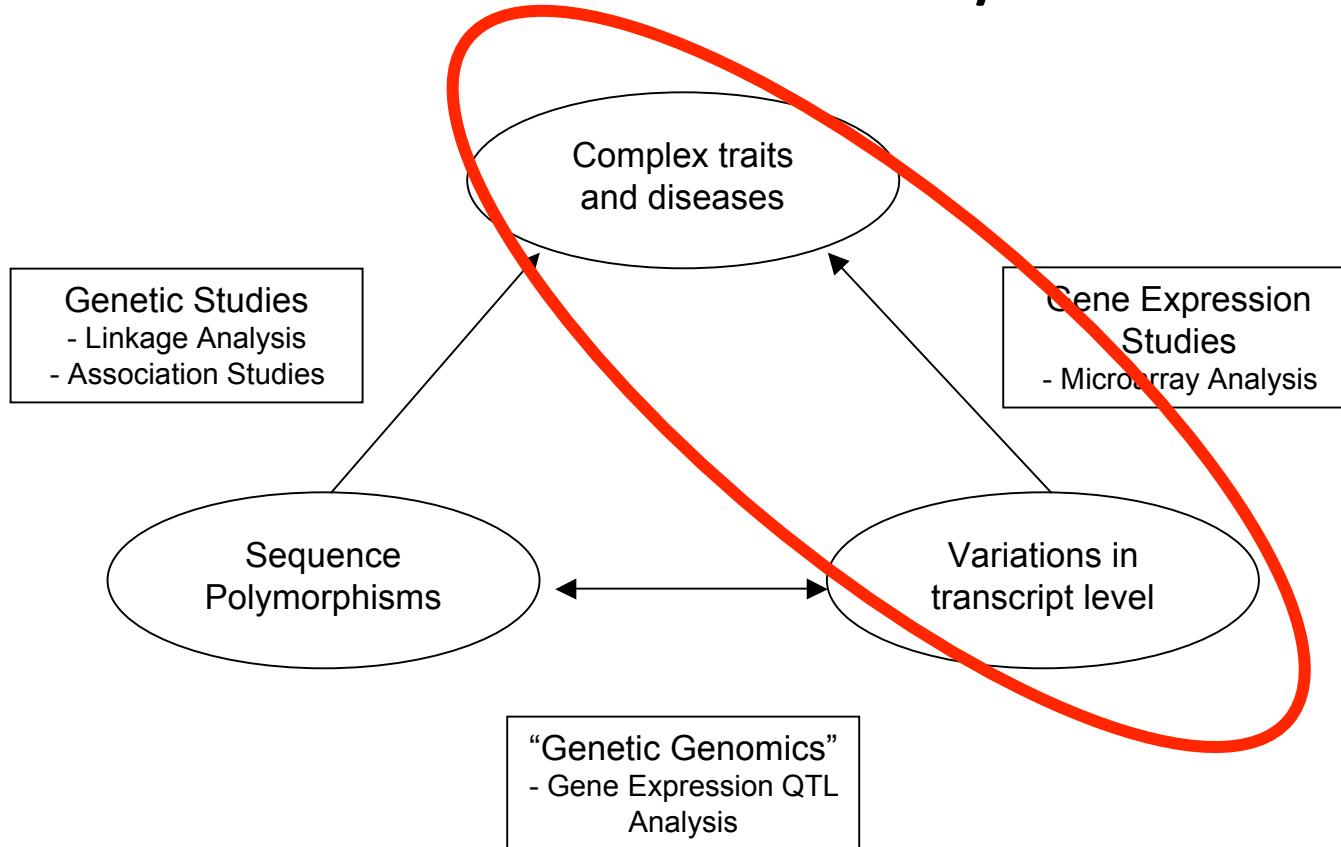
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Alcohol Consumption Across HXB/BXH RI Panel



Copied From Tabakoff B, Saba L et al 2009. BMC Biol. 7:170

Candidate Modules from Genetical Genomics/Phenomics Approach

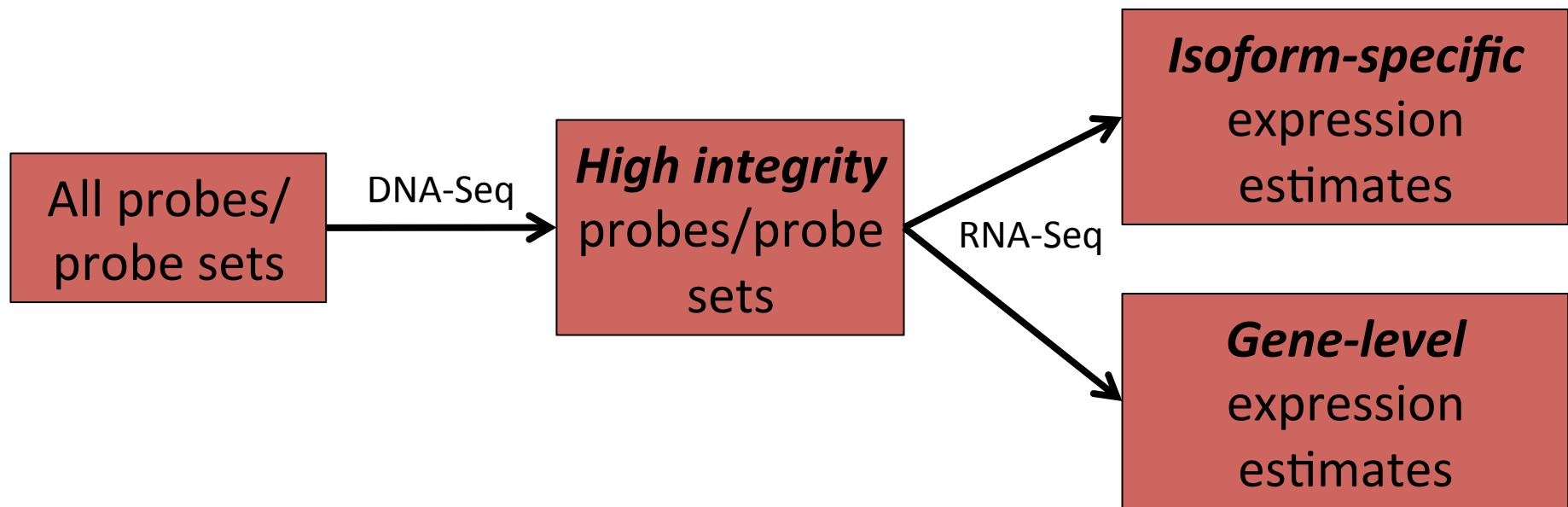


2. Identify co-expression modules that are correlated/associated with the complex trait

Image copied from Saba et al, The Marriage of Phenomics and Genetical Genomics: A Systems Approach to Complex Trait Analysis. In Systems Biology in Psychiatric Research: From High-Throughput Data to Mathematical Modeling, edited by Tetter F, Winterer G, Gebicke-Haerter PG, and Mendoza E. Wiley-VCH 2010.

RNA Expression Estimates – HXB/BXH Panel

Using RNA-Seq Data to “Clean” Hybridization Arrays

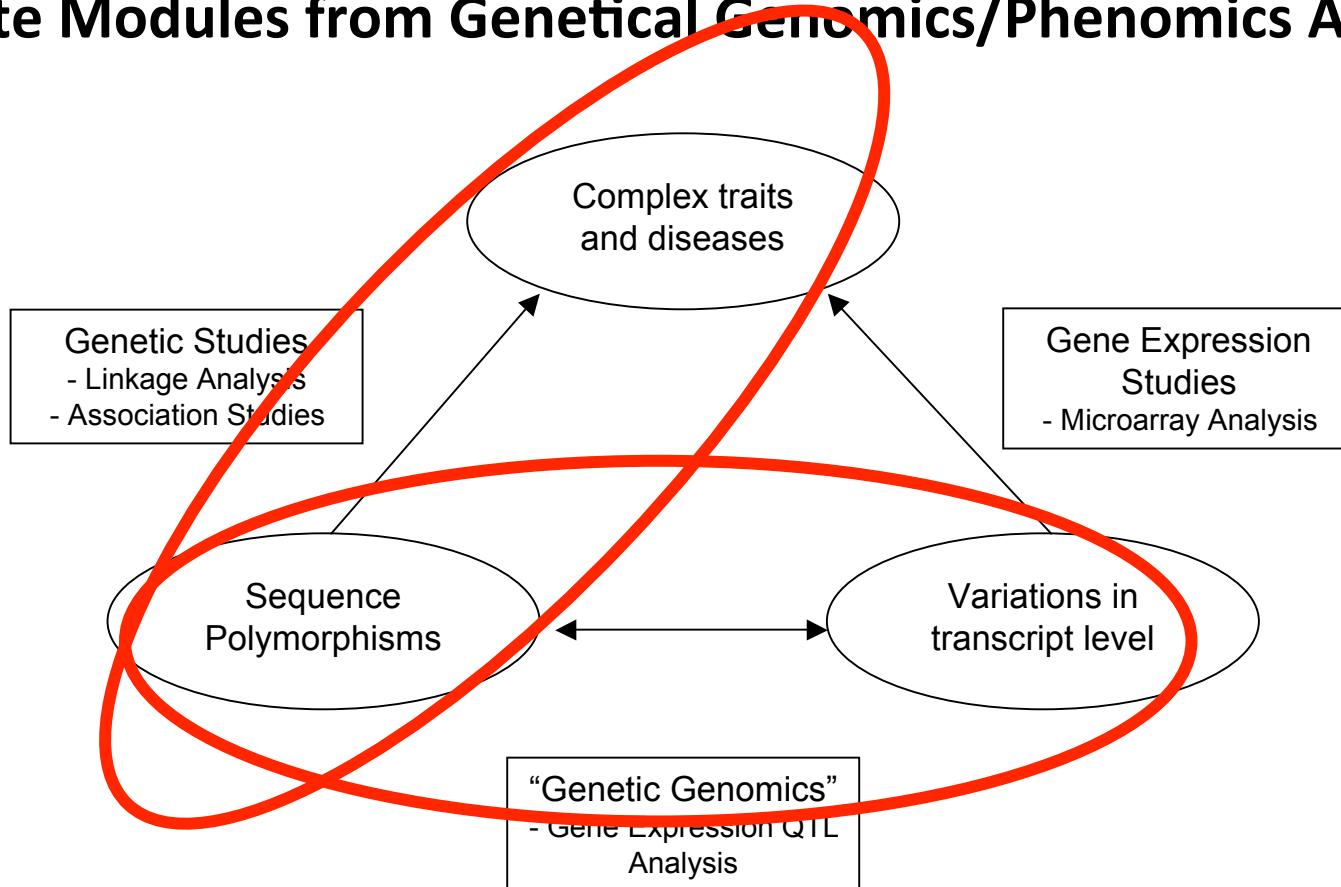


Modules Associated With Alcohol Consumption

5 out of 364 modules in gene-level analysis

5 out of 582 modules in isoform-specific analysis

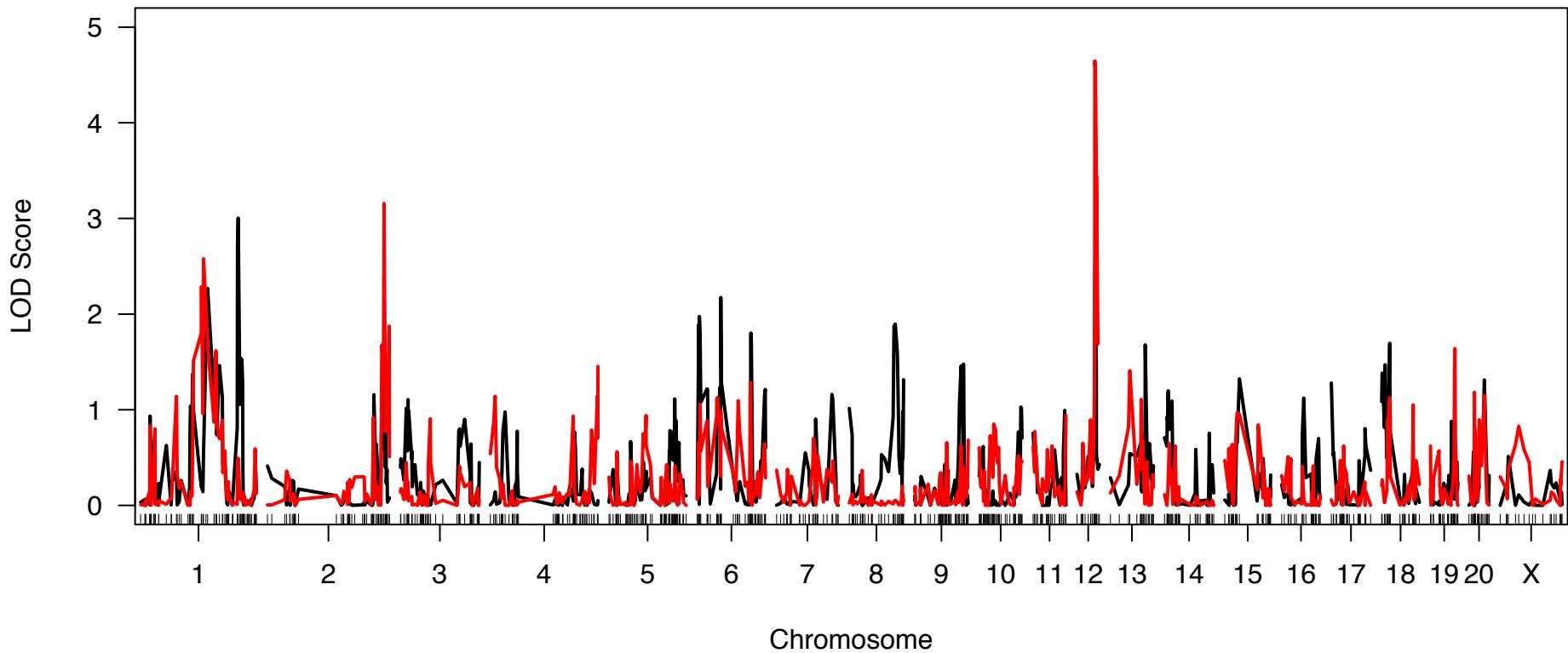
Candidate Modules from Genetical Genomics/Phenomics Approach



3. Limit to co-expression modules that are whose expression is influenced from the same region that influences the complex trait

Image copied from Saba et al, The Marriage of Phenomics and Genetical Genomics: A Systems Approach to Complex Trait Analysis. In Systems Biology in Psychiatric Research: From High-Throughput Data to Mathematical Modeling, edited by Tetter F, Winterer G, Gebicke-Haerter PG, and Mendoza E. Wiley-VCH 2010.

Overlap of module eQTL and alcohol consumption QTL

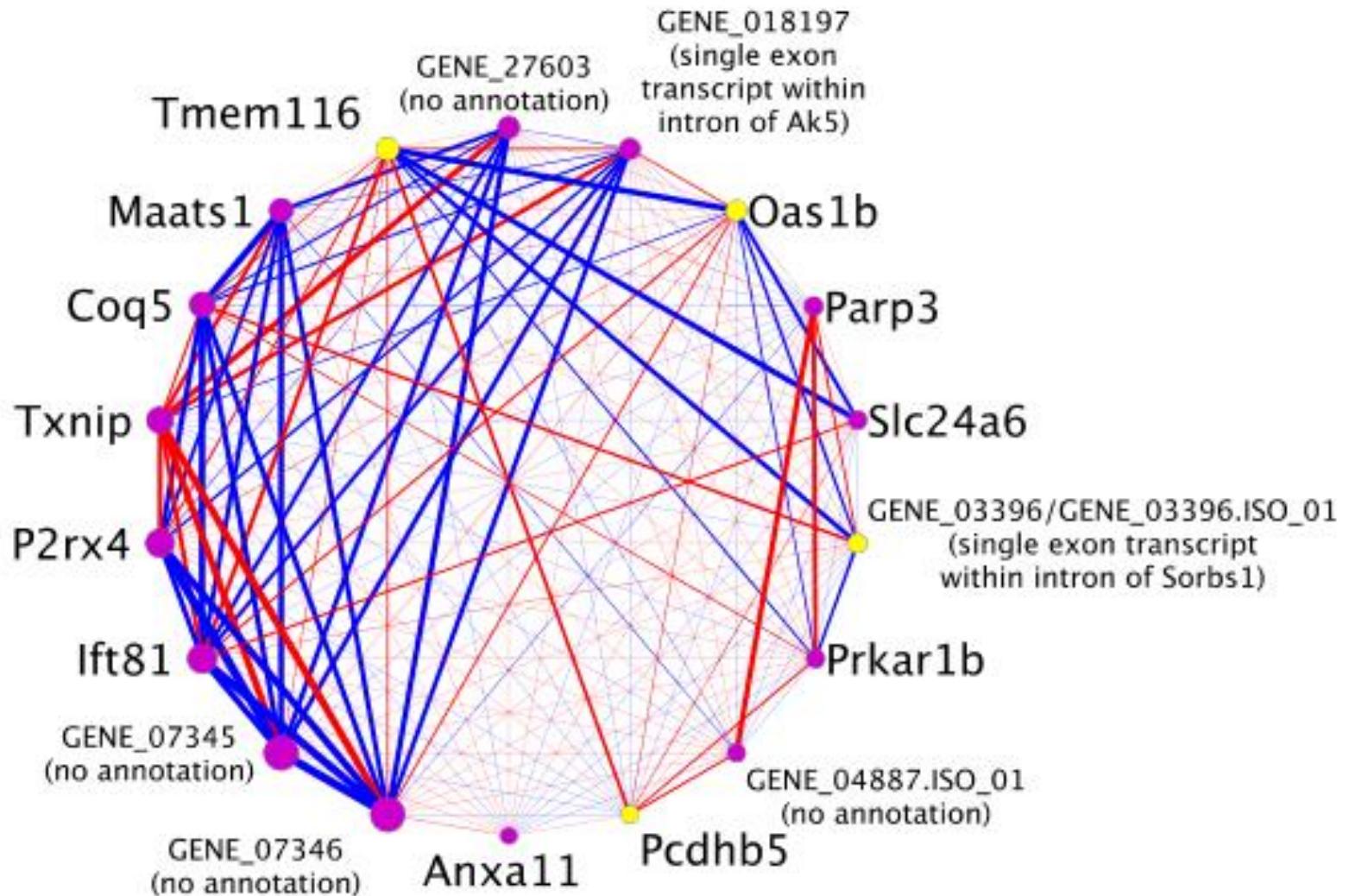


QTL → quantitative trait locus

Alcohol consumption QTL (black) → genetic locus associated with the alcohol consumption

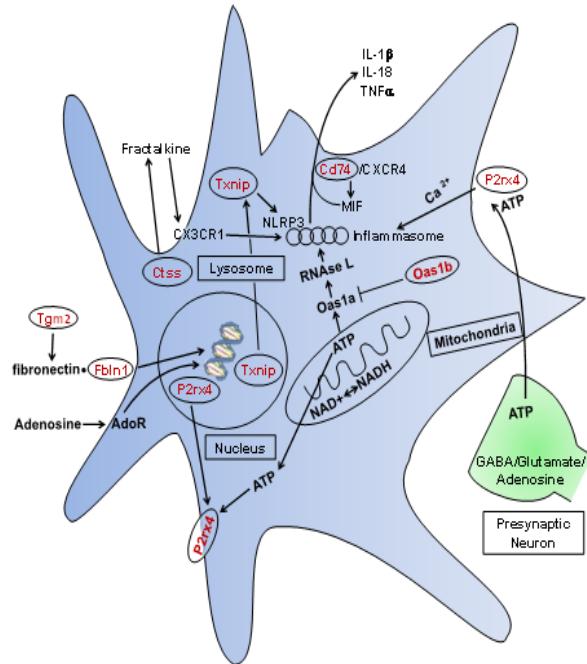
Module eQTL (red) → genetic locus associated with RNA expression levels within the module (module eigengene)

Combined Candidate Module

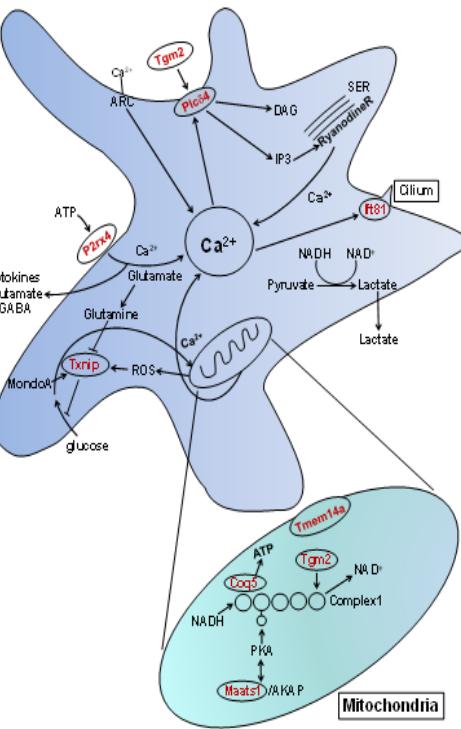


Saba et al (2015). The sequenced rat brain transcriptome, its use in identifying networks predisposing alcohol consumption. Under review at FEBS.

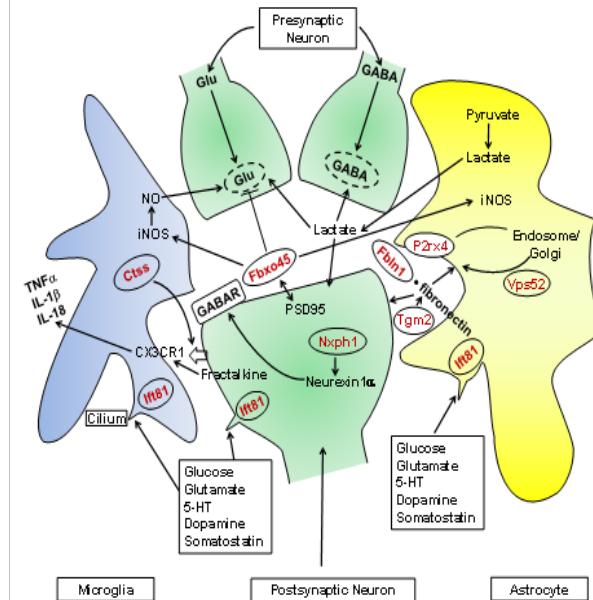
Biological Context from Pathway



Inflammation/Immune Response



Energy/Ca²⁺ Homeostasis/Redox



Glial/Neuronal Communication

Saba et al (2015). The sequenced rat brain transcriptome, its use in identifying networks predisposing alcohol consumption. Under review at FEBS.

Conclusions

Phenotype-Driven Analysis

- Using systems genetics, we were able to ...
 - identify a common pathway, rather than focusing on a common gene
 - identify a unannotated non-coding transcript and unannotated isoforms of known genes involved in the common pathway

Grant Applications

- **Pending Grant Applications Using Rat Diversity Panel**
 - Effects of ethanol from gut to liver to brain in human and rat
 - Pending Center Grant application (lead statistician for biostatistics component)
- **Pending Grant Applications Using Similar Techniques**
 - Role of genetics in mast cell responses to ENM exposure using a hybrid mouse diversity panel
 - Pending RO1 led by Jared Brown (SOP)
 - Differential susceptibility to toxic insults of Down Syndrome patients
 - Pending RO1 led by James Roede (SOP)
 - Transcriptional sources of neuronal excitability in epileptic tissue
 - Pending ADR pilot grant with Molly Huntsman (SOP) and Brent O'Neill (SOM)

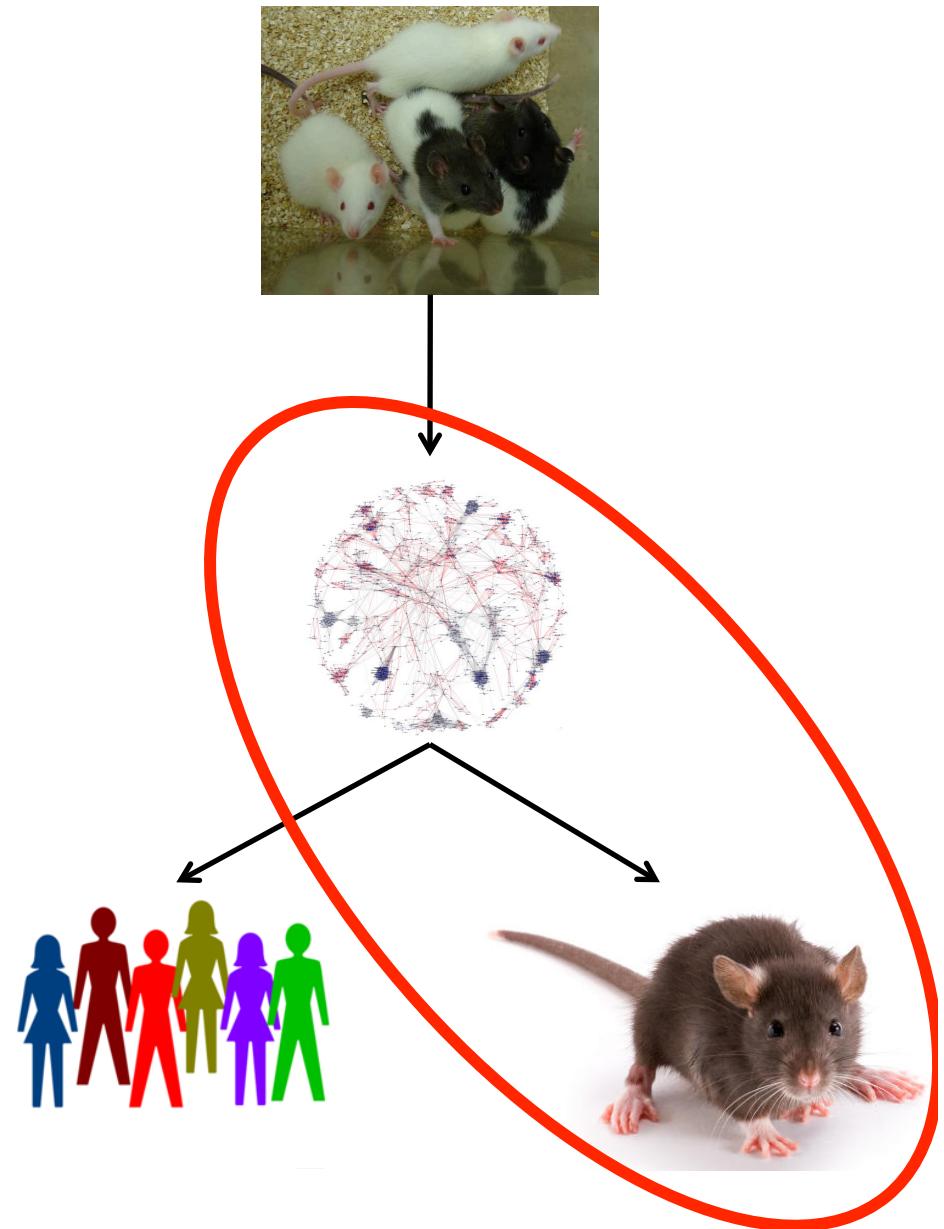
PREDICTION FROM NETWORKS

Validating/improving statistical methods
for inferring causality among the INIA-
West RNA transcripts of emphasis (INIA-
West Pilot Grant)

Laura Saba – PI

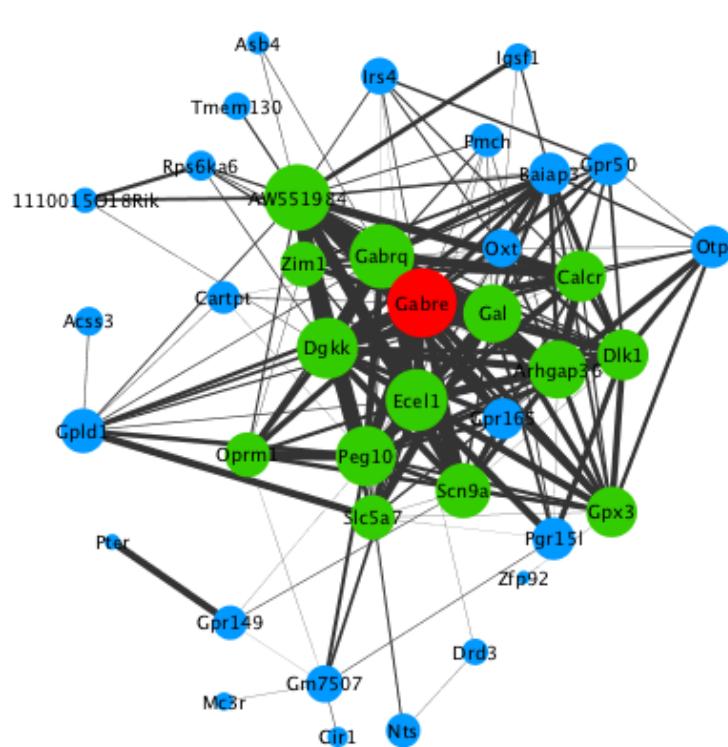
Genome-wide identification of miRNAs
associated with alcoholism
endophenotypes (NIH/NIAAA R01
AA021131)

Katerina Kechris – PI (Laura Saba, Co-I)

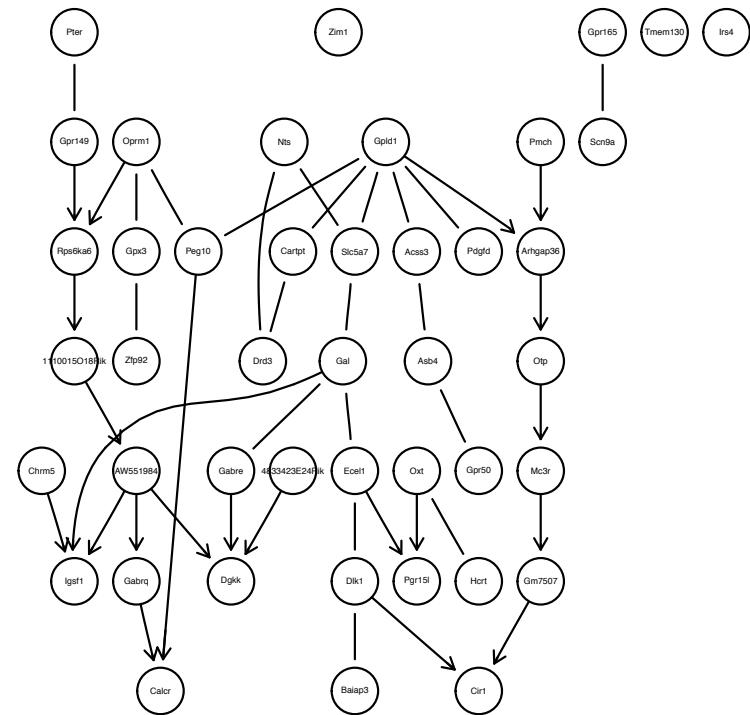


Types of Networks

WGCNA

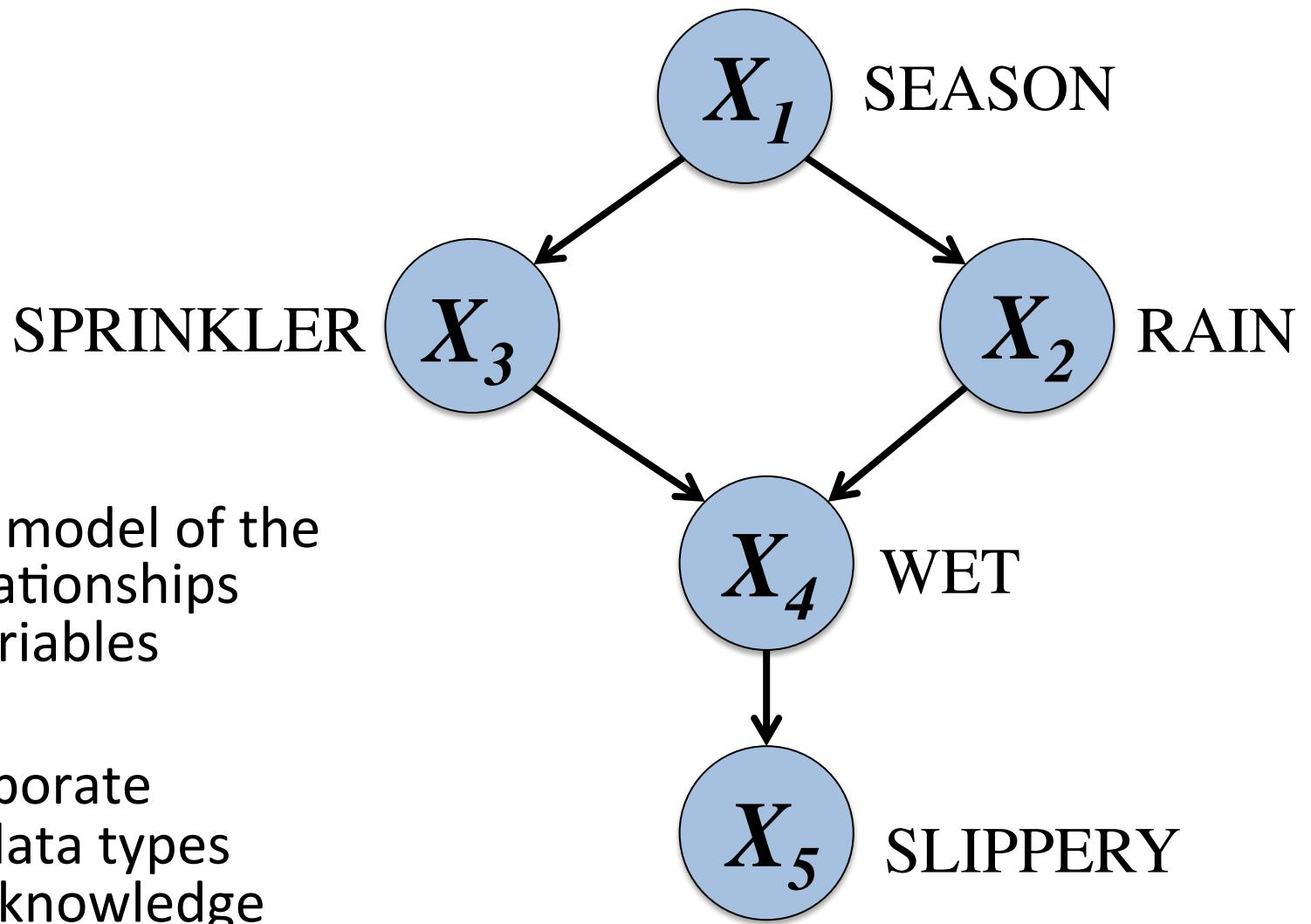


Bayesian Networks



Moving from Description to Prediction

Bayesian Network Models

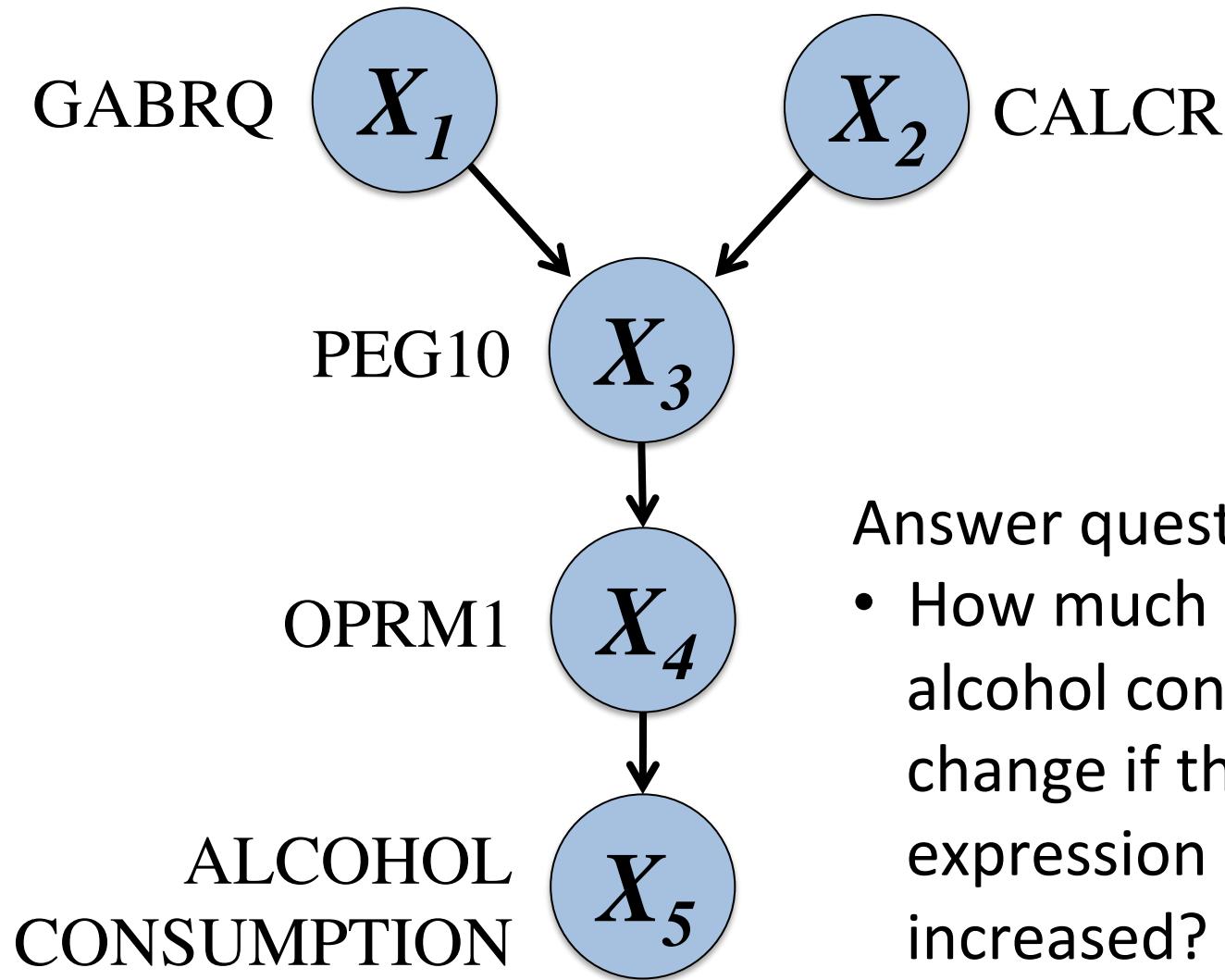


- Graphical model of the causal relationships among variables
- Can incorporate multiple data types and prior knowledge

Reasoning with Bayesian Networks

- With new information (e.g., new observation or proposed pharmacological manipulation) these models can be used for **probability propagation**.
 - Diagnostic reasoning – what is the probability that it rained if the ground is slippery?
 - Predictive reasoning – what is the probability of the sidewalk being slippery if it rained last night?

Bayesian Networks in Drug Target Identification

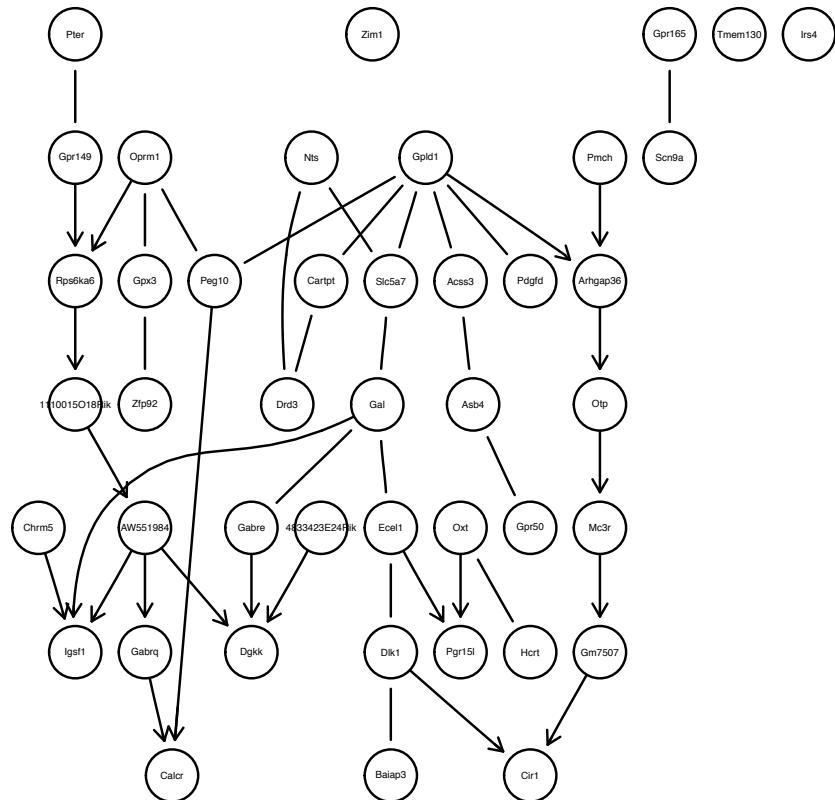


Answer questions like...

- How much will the alcohol consumption change if the expression of Calcr is increased?

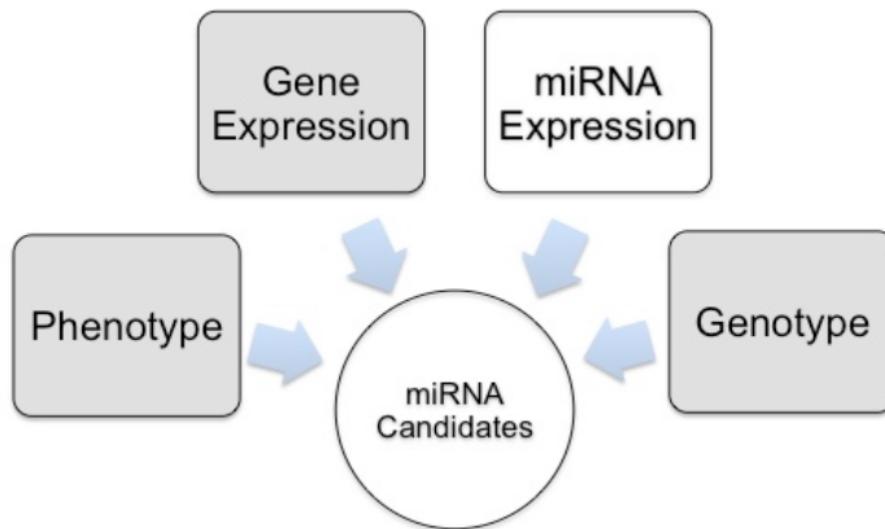
Validating/improving statistical methods for inferring causality among the INIA-West RNA transcripts of emphasis

Integrative Neuroscience Initiative on Alcoholism (INIA) West Pilot Grant



- **Main Goal:** Identify transcripts whose expression level is altered by manipulation of *Oprm1* expression in mouse brain
- **Secondary Goal:** Use this information to evaluate and improve statistical methods for inferring causality about RNA expression levels among genes.

Genome-wide identification of miRNAs associated with alcoholism endophenotypes



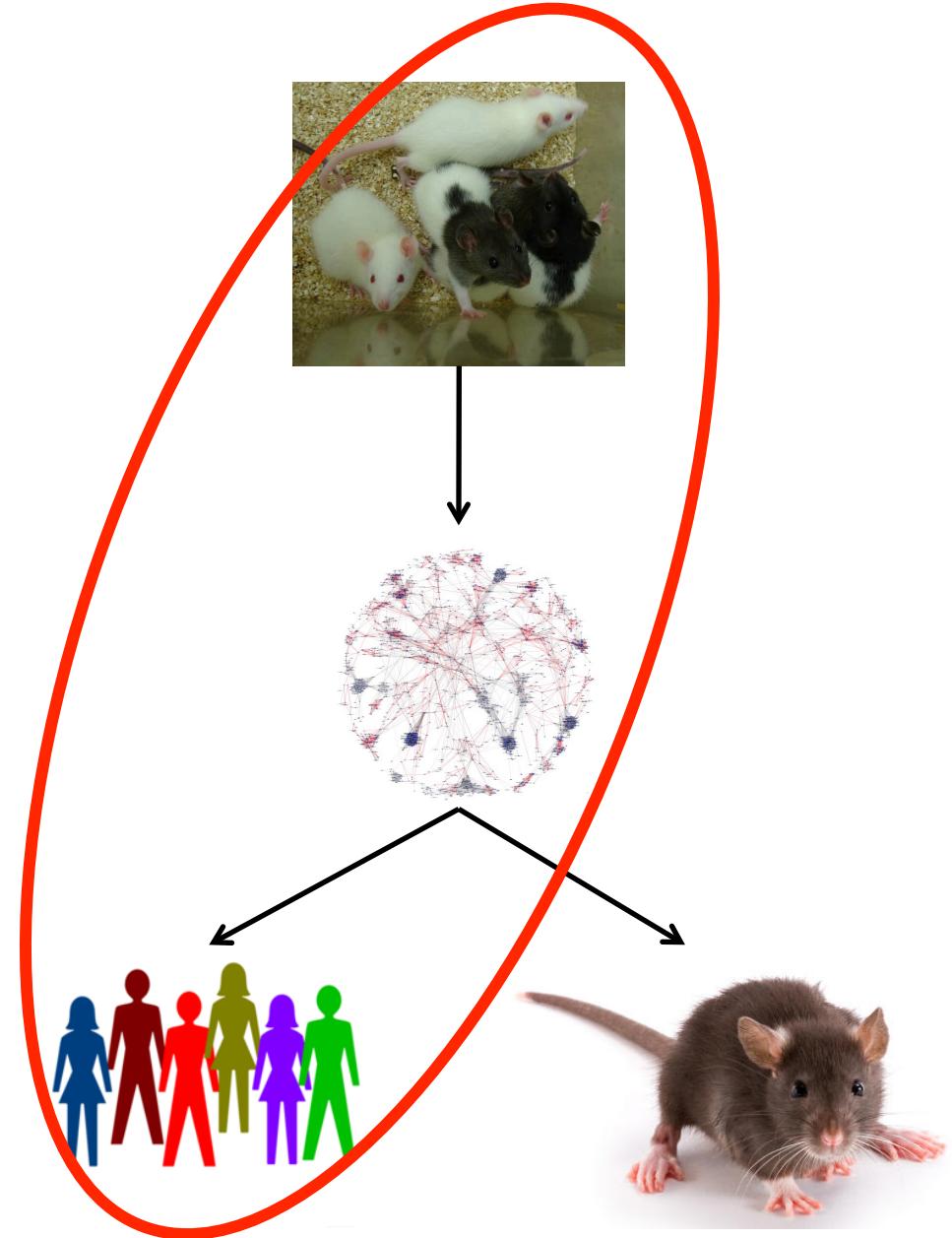
Goals:

1. to perform high-throughput miRNA brain expression profiling in a large panel of RI mice (DONE)
2. to identify miRNAs and respective target mRNA expressed in the brain that are associated with the predisposition to alcoholism endophenotypes (IN PROGRESS)

Potential Grant Applications

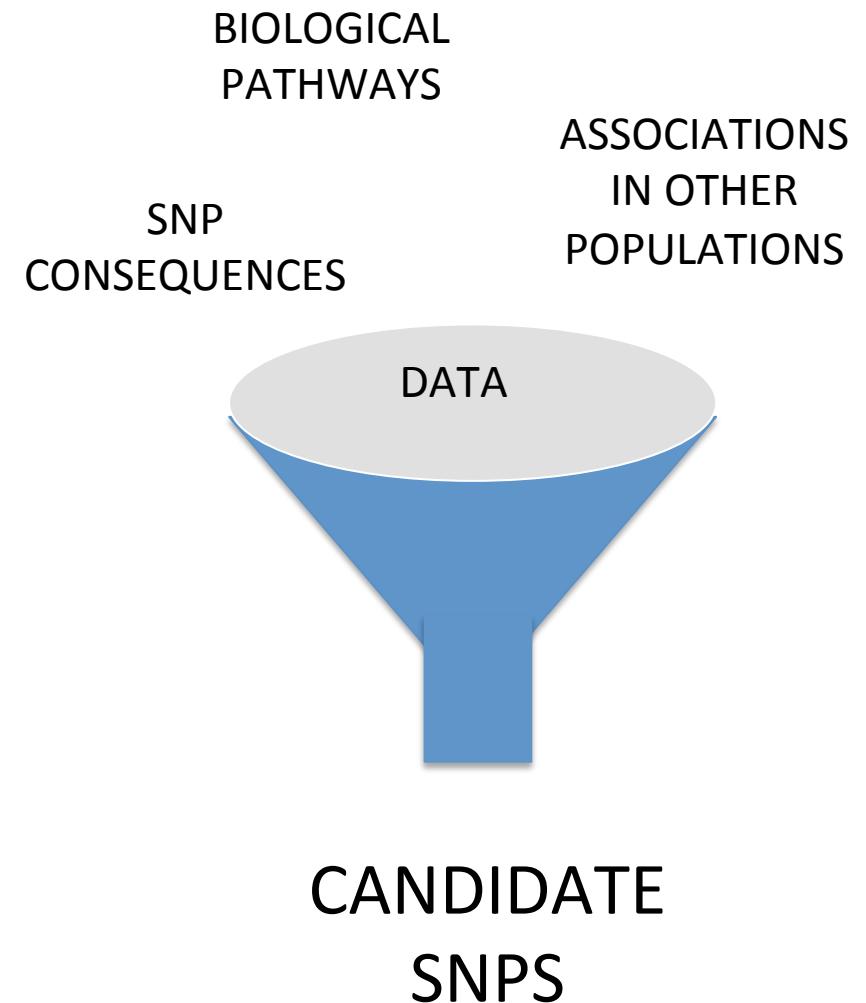
- Neuroinflammation and alcohol preference in the Rat Diversity Panel: Genetic differences in LPS effects
 - In response to PA-14-139 (Neuroimmune Mechanisms of Alcohol Related Disorders)
- Effects of chronic intermittent alcohol exposure on brain networks
 - In response to PA-14-268 (International Research Collaboration on Alcohol and Alcoholism – U01)

ENHANCING HUMAN GENETIC STUDIES WITH THE RODENT TRANSCRIPTIONAL CONNECTOME



Hierarchical Bayesian Modeling and GWAS

- Instead of assuming that prior to analysis each SNP is equally likely to be ‘causal’ for the trait...
 - Prior knowledge
 - Boost power
 - “meta-analysis”



Link Between eQTL and GWAS

OPEN  ACCESS Freely available online

PLOS GENETICS

Trait-Associated SNPs Are More Likely to Be eQTLs: Annotation to Enhance Discovery from GWAS

Dan L. Nicolae^{1,2,3}, Eric Gamazon¹, Wei Zhang¹, Shiwei Duan^{1*}, M. Eileen Dolan^{1,2}, Nancy J. Cox^{1,2*}

1 Department of Medicine, University of Chicago, Chicago, Illinois, United States of America, **2** Department of Human Genetics, University of Chicago, Chicago, Illinois, United States of America, **3** Department of Statistics, University of Chicago, Chicago, Illinois, United States of America

frontiers in
GENETICS

ORIGINAL RESEARCH ARTICLE
published: 31 May 2013
doi: 10.3389/fgene.2013.00103



Using eQTL weights to improve power for genome-wide association studies: a genetic study of childhood asthma

Lin Li^{1†}, Michael Kabesch², Emmanuelle Bouzigon^{3,4}, Florence Demenais^{3,4}, Martin Farnell⁵,
Miriam E. Moffatt⁶, Xihong Lin¹ and Liming Liang^{1,7*}



Theory

Integrative eQTL-Based Analyses Reveal the Biology of Breast Cancer Risk Loci

Ouyuan Li^{1,2,4}, Ji-Heui Seo^{1,2}, Barbara Stranger^{6,11}, Aaron McKenna^{5,7}, Itsik Pe'er⁸, Thomas LaFramboise⁹, Myles Brown¹, Svitlana Tyekucheva^{3,10} and Matthew L. Freedman^{1,2,4,*}

¹Department of Medical Oncology, The Center for Functional Cancer Epigenetics

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³Department of Biostatistics and Computational Biology

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¹¹Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, OH 44106, USA

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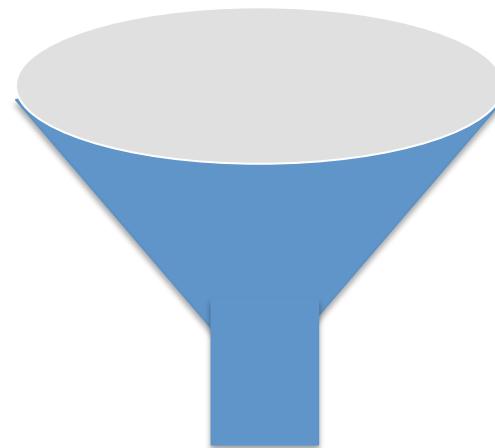
*Correspondence: freedman@broadinstitute.org

<http://dx.doi.org/10.1016/j.cell.2012.12.034>

- eQTL are more likely to be true associations
- Lend mechanistic evidence for SNP with obvious consequences

Improving Identification of Human eQTL

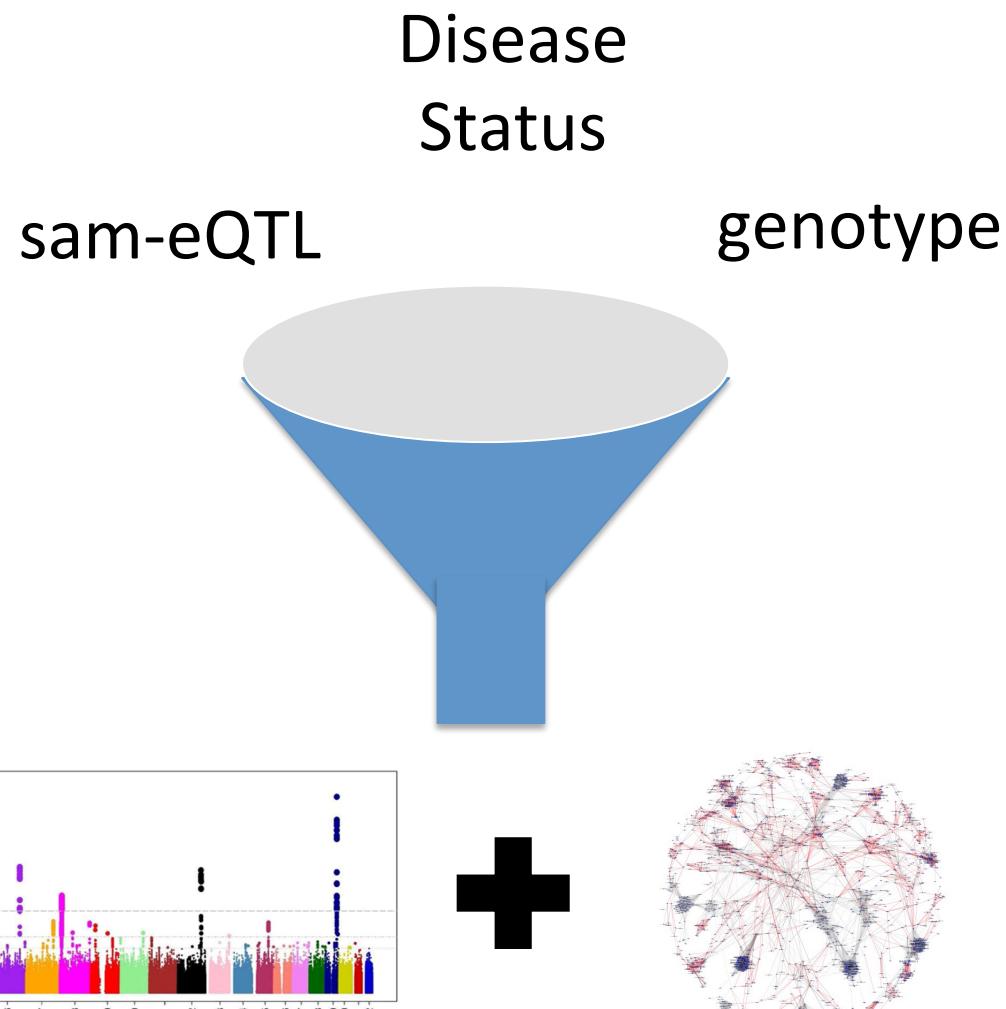
Current topic of research for Yonghua Zhuang
(Biostatistics MS student; expected graduation May 2016)



Species augmented modeling of
eQTL (sam-eQTL)

Integrating eQTL information in Human GWAS

One topic of research for incoming post doctoral fellow, Pratyaydipta Rudra in collaboration with Katerina Kechris (CSPH)

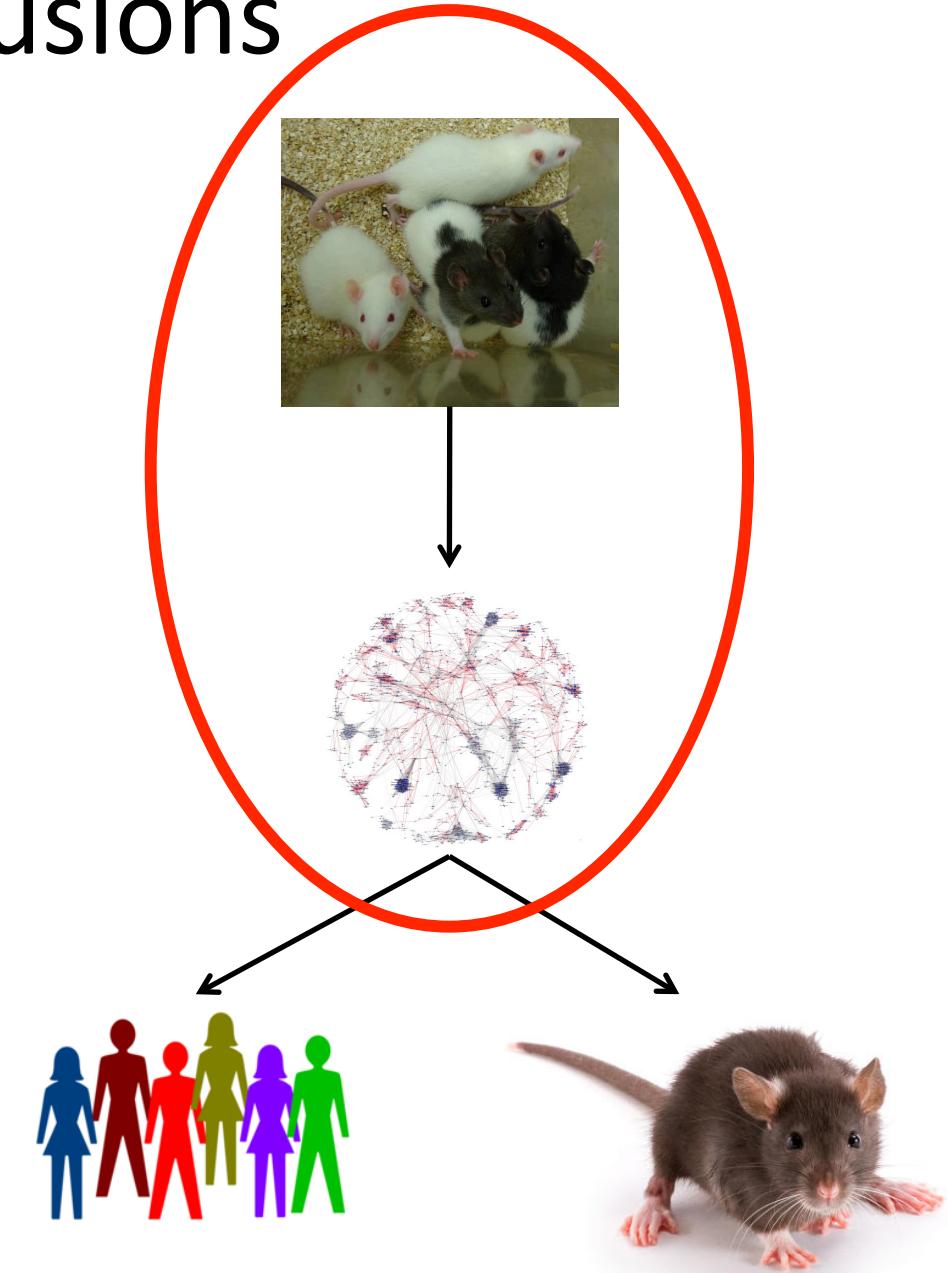


Funding

- Recently Funded ADR Grant
 - Genetic predictors of cardiac allograft vasculopathy following cardiac transplantation
 - ADR Pilot Grant lead by Christina Aquilante (SOP) and Robert Page (SOP)
- Potential Grant Applications
 - Prioritizing and interpreting genetic pathways associated with a predisposition to stimulant sensitivity in humans by incorporating data from animal models
 - In response to PA-14-025 (Discovering Novel Targets: The Molecular Genetics of Drug Addiction and Related Co-Morbidities)

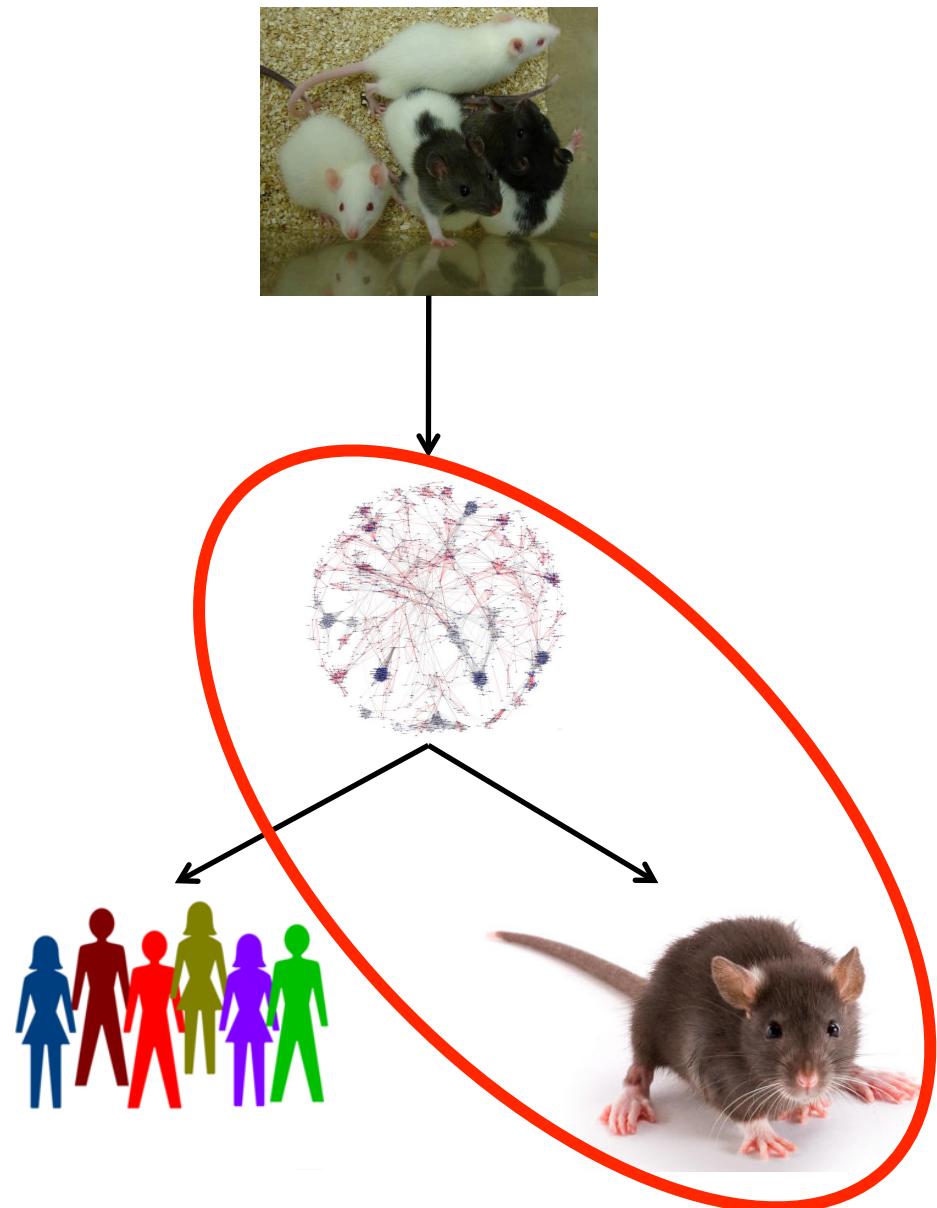
Conclusions

- **Generating and Sharing Baseline Transcriptional Connectomes**
 - Developed PhenoGen database and website
 - Developed statistical pipeline for RNA-Seq analysis
 - Identifying the transcription landscape of rat brain, liver, and heart
 - Defining baseline transcriptional connectomes



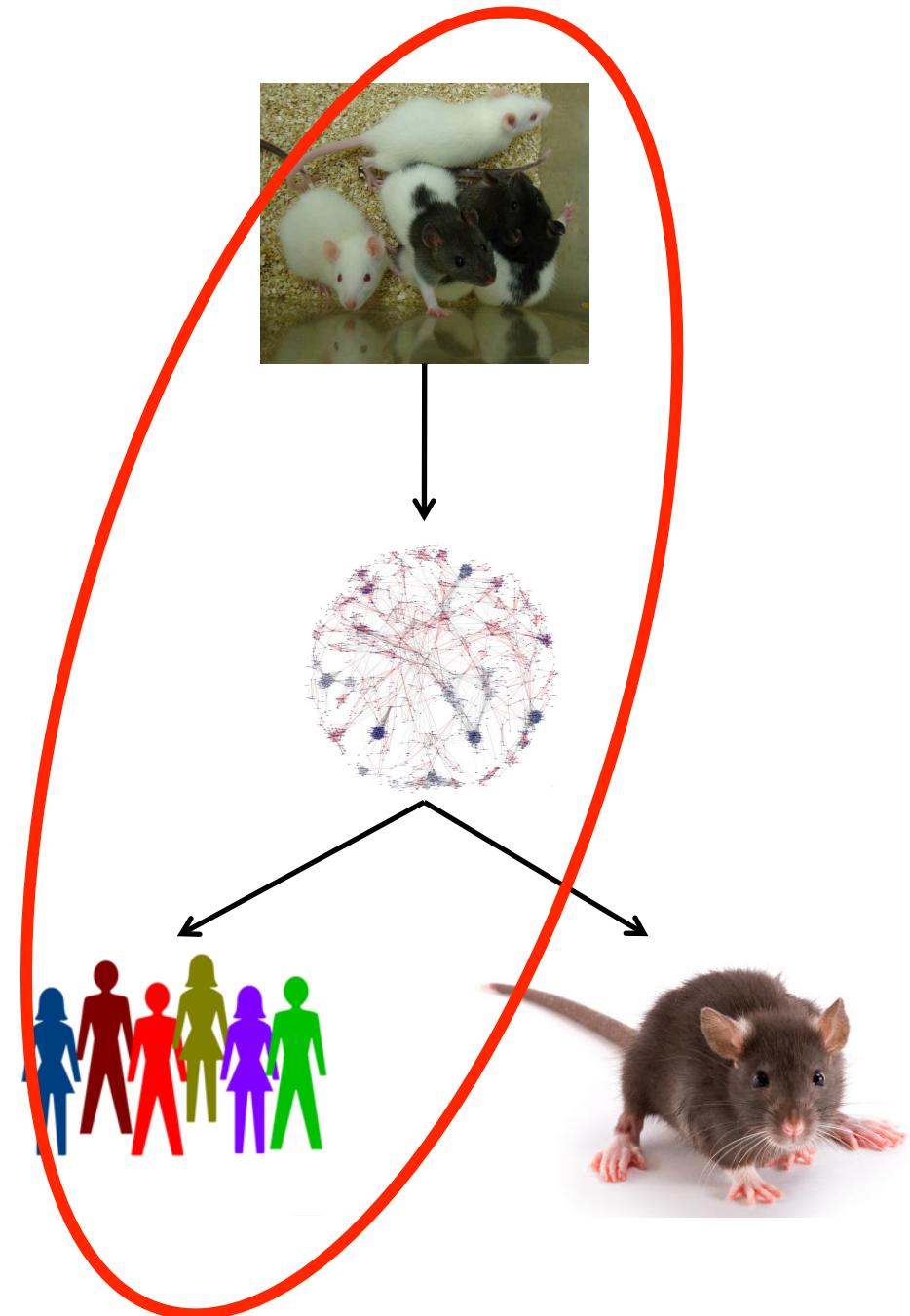
Conclusions

- **Prediction from baseline connectome**
 - Causal inference within connectomes
 - Modeling a disruption to a network.



Conclusions

- **Enhancing Human Genetic Studies with the Rodent Transcriptional Connectome**
 - Incorporating prior information on expression QTL and results from rodent model into GWAS and candidate gene association studies



My Contributions to PhenoGen

Database
Development

Web Site
Development

Lead
Biostatistician

Student/
Fellow
Mentoring

Consulting

3 Main Types of Data PhenoGen

- SNP data sets
- Microarray data sets
- RNA-Seq data sets



My Contributions to PhenoGen

Database
Development

Web Site
Development

Lead
Biostatistician

Student/
Fellow
Mentoring

Consulting

Main Roles:

- Develop analysis pipeline
- Conceptualize statistical graphics
- Documentation of analysis methods

BMC Genetics



Database

The PhenoGen Informatics website: tools for analyzing quantitative trait loci and complex traits

Sanjiv V Bhave¹, Cheryl Hornbaker¹, Tzu L Phang¹, Laura Razvan Lapadat¹, Katherina Kechris^{1,2}, Jeanette Gaydos¹, Daniel McGoldrick¹, Andrew Dolbey¹, Sonia Leach¹, Bri Allison Ellington¹, Eric Ellington¹, Kendra Jones¹, Jonathan John K Belknap⁴, Robert W Williams⁵, Lawrence E Hunt Paula L Hoffman¹ and Boris Tabakoff^{*1}

EXPRESSION QUANTITATIVE TRAIT LOCI AND THE PHENOGEN DATABASE

Laura Saba, Ph.D.; Paula L. Hoffman, Ph.D.; Cheryl Hornbaker; Sanjiv V. Bhave, Ph.D.; and Boris Tabakoff, Ph.D.

KEY WORDS: Genetic theory of alcohol and other drug use; microarray technologies; microarray analysis; phenotype; candidate gene; qualitative trait locus (QTL); expression quantitative trait loci (eQTL); gene expression; gene transcription; genetics; transcriptomics; high-throughput analysis; messenger RNA; brain; laboratory mice; laboratory rats; PhenoGen

Addiction Biology

PRECLINICAL STUDY



doi:10.1111/j.1369-1600.2010.00254.x

Using the Phenogen website for 'in silico' analysis of morphine-induced analgesia: identifying candidate genes

Behav Genet (2011) 41:625–628
DOI 10.1007/s10519-010-9427-0

BRIEF COMMUNICATION

Genetical Genomic Analysis of Complex Phenotypes Using the PhenoGen Website

Beth Bennett · Laura M. Saba ·
Cheryl K. Hornbaker · Katerina J. Kechris ·
Paula Hoffman · Boris Tabakoff

My Contributions to PhenoGen

Database
Development

Web Site
Development

Lead
Biostatistician

Student/
Fellow
Mentoring

Consulting



Candidate genes and their regulatory elements: alcohol preference and tolerance

Laura Saba,¹ Sanjiv V. Bhave,¹ Nicholas Grahame,³ Paula Bice,⁴ Razvan Lapadat,¹ John Belknap,² Paul Hoffman,¹ Boris Tabakoff¹

Mamm Genome (2008) 19:352–365

DOI 10.1007/s00335-008-9115-z

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³Department of Psychology, UIC
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Received: 23 December 2005

The genomic determinants of alcohol preference in mice

BMC Biology



Research article

Genetical genomic determinants of alcohol preference in mice in humans

Boris Tabakoff^{*1}, Laura Saba¹, Michael J. Cullinan², Colin Hodgkinson⁴, David Goldstein³, Heather N Richardson^{5,16}, Katerin

Open Access

Neuropharmacology 60 (2011) 1269–1280



Contents lists available at ScienceDirect

Neuropharmacology



The sequenced rat brain transcriptome, its use in identifying networks predisposing alcohol consumption

Saba, Laura M.¹, Flink, Stephen C.¹, Vanderlinde, Lauren A.¹, Israel, Yedy², Tampier, Lutske², Colombo, Giancarlo³, Kianmaa, Kalervo⁴, Bell, Richard L.⁵, Printz, Morton P.⁶, Flodman, Pamela⁷, Koob, George^{8,11}, Richardson, Heather N.^{8,12}, Lombardo, Joseph¹⁰, Hoffman, Paula L.^{1,9}, and Tabakoff, Boris^{1,9}

My Contributions to PhenoGen

Database
Development

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Lead
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0028-3565(20080229)7:2;1-100\$15.00/0
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JPET 329:792-800, 2008

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Journal of Pharmacology and Experimental Therapeutics

Genomic Insights into Acute Alcohol Tolerance[§]

Wei Hu, Laura Saba, Katherina Kechris, Sanjiv V. Bhave, Paula L. Hoffman, and Boris Tabakoff

Departments of Pharmacology (W.H., L.S., S.V.B., P.L.H., B.T.) and Preventive Medicine and Biometrics (K.K.), University of Colorado School of Medicine, Aurora, Colorado

Received February 4, 2008; accepted June 9, 2008

OPEN  ACCESS Freely available online



Whole Brain and Brain Regional Coexpression Network Interactions Associated with Predisposition to Alcohol Consumption

Laure E. Hwang,¹ Laura Saba,¹ Katherina Kechris,¹ Sanjiv V. Bhave,¹ Paula L. Hoffman,¹ Boris Tabakoff,¹ and Katerina Kechris²

Boris

¹ Depart
Universit
Biologica

Liver Metabolism Networks in Recombinant Inbred HXB/BXH Rats

Kylie Harrell (Biostatistics MS Candidate)

My Contributions to PhenoGen

Database
Development

Web Site
Development

Lead
Biostatistician

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Exome-Wide Association Study of Replicable Nonsynonymous Variants Conferring Risk for Alcohol Dependence

LINGJUN ZUO, M.D.,^{a,*} LAURA SABA, PH.D.,^b KESHENG WANG, PH.D.,^c XIANGYANG ZHANG, M.D., PH.D.,^d JOHN H. KRYSAL, M.D.,^a BORIS TABAKOFF, PH.D.,^b AND XINGGUANG LUO, M.D., PH.D.^{a,*}

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 39, No. 4
April 2015

Quantitative Trait Locus Mapping of Acute Functional Tolerance in the LXS Recombinant Inbred Strains

Beth Bennett, Colin Larson, Phillip A. Richmond, Aaron T. Odell, Laura M. Saba,
Boris Tabakoff, Robin Dowell, and Richard A. Radcliffe

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- National Foundation for Prevention of Chemical Dependency Disease (PI - NFPCDD Career Development Award)
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CU Skaggs School of Pharmacy and Pharmaceutical Sciences Collaborators:

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- Richard Radcliffe
- Jared Brown
- James Roede
- Christina Aquilante
- Robert Page
- Molly Huntsman
- Kris Fritz

CU School of Medicine Collaborators:

- Paula Hoffman
- Steve Britt
- Mark Dell'Acqua

Colorado School of Public Health Collaborators:

- Katerina Kechris
- Alison Bauer

The PhenoGen Group:

- Steve Flink
- Lauren Vanderlinden
- Spencer Mahaffey
- Yinni Yu

Other Collaborators:

- Michal Pravanec, Academy of Sciences of the Czech Republic
- Morton Printz, UCSD
- Rob Williams, UTHSC

Current/Former Students:

- Wendy Dye (MS '10)
- Lauren Vanderlinden (MS '11)
- Kylie Harrell (MS expected '16)
- Yonghua Zhuang (MS expected '16)

THANK YOU