PGC Worldwide Lab Call Details

Friday, November 8, 2013

PRESENTERS:

Nancy J. Cox, Ph.D. and Abe Palmer, Ph.D.

Depts. of Medicine and Human Genetics

The University of Chicago

TITLE: REVERSING GENETICS: (AGAIN)

- 10:00 EST - US East Coast
- 09:00am CST
- 03:00pm GMT
- 04:00pm CET
- 02:00am AED Saturday, November 9

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- Operators will be on standby to assist with technical issues. “*0” will get you assistance.
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LINES ARE **MUTED** NOW

- Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

- Operators announce callers one at a time during question and answer sessions.

- Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

- Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC WORLDWIDE LAB

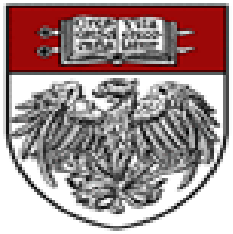
Friday, December 13, 2013

PRESENTER:
Professor John McGrath, AM, MBBS, MD, PhD, FRANZCP
Queensland Brain Institute
The University of Queensland
Queensland, Australia

TITLE:
Where GWAS and epidemiology meet: opportunities for the simultaneous study of genetic and environmental risk factors in schizophrenia.

Reversing Genetics

(Again)



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It all comes back …

In the Olden Days …

- **Geneticists reasoned from biochemistry and observations on metabolites to deduce the cause of Mendelian diseases**
- **Worked for a discrete set of diseases**
- **Systematic and agnostic process-based investigations were first called “reverse” genetics**

Linkage, Positional Cloning, GWAS (by typing or sequencing)

- **Have brought us near-complete identification of Mendelian disease genes (and promise the rest)**
- **Have enabled unprecedented discovery for common, complex disease**
- **No one is satisfied with what we have actually learned from these discoveries**

What We Have Learned

- **Common variants associated with common disease and complex traits are largely regulatory**
  - **May collectively account for substantial heritability**
  - **Give us little biological insight until we discover driving genes**
- **Rare variant discoveries give us major biological insight**
  - **Perhaps disproportionate to magnitude of contribution to common disease**

Improving Understanding

- **Can we use more about *what we already know* about genome function, biochemical (and other) pathways, Mendelian diseases, and potentially related phenotypes to learn more about what we still need to learn of complex traits?**
- **Starting with what we know is reversing genetics (again)**

We Propose to Use …

- **Potentially related phenotypes**
- **Genome function**
- **Biochemical (and other) pathways**
- **Mendelian diseases**

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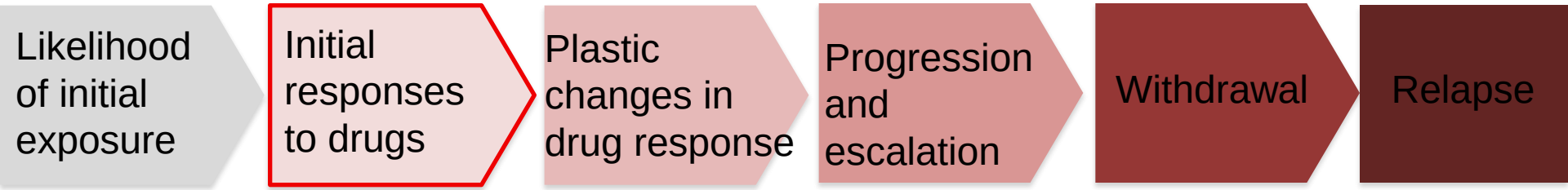
Acute amphetamine response is an intermediate phenotype



Adapted from Palmer and de Wit, 2011

- Individuals vary in acute responses to *d*-amphetamine
- Acute *d*-amphetamine response is heritable
- Probes dopaminergic system
- Originally examined for its possible role in drug abuse suseptabiltiy

Study design

Recruitment

- Healthy volunteers, 18-35
- Primarily Caucasian

Screening

- BMI 19-26 kg/m^2
- Limited past and current drug use
- High school education
- No history of psychiatric disorder

Final sample

398 participants

Phenotyping

- Placebo, 10 mg AMPH, 20 mg AMPH
- Randomized order
- Double-blind
- 6 time points

Genotyping

381 participants
(325 Caucasian)

Harriet de Wit

Sample self-report scale questions

Profile of Mood States (POMS)
72 adjectives

Friendliness: "Agreeable", "Helpful", "Forgiving"

Drug Effects Questionnaire (DEQ)
Five questions; visual analog scale

Want More: "Would you like more of what you consumed, right now?"

Addiction Research Center Inventory (ARCI)
53 true/false questions

MBG: "I would be happy all the time if I felt as I feel now"

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53 true/false questions

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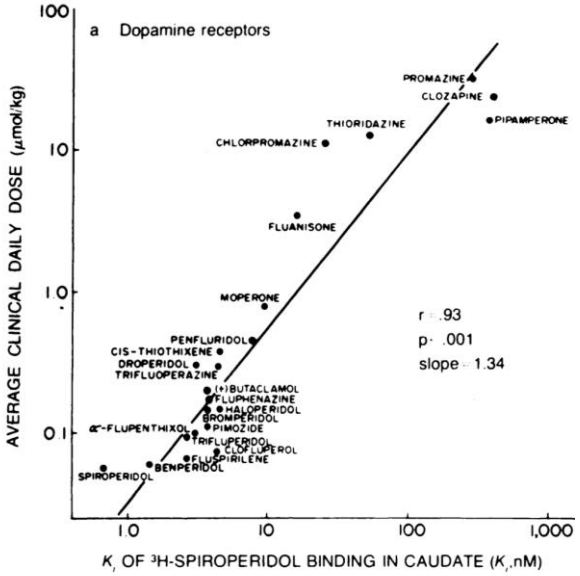
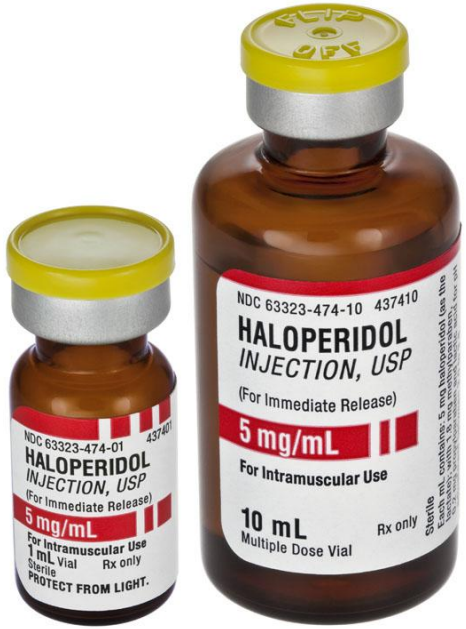
Hypothesis

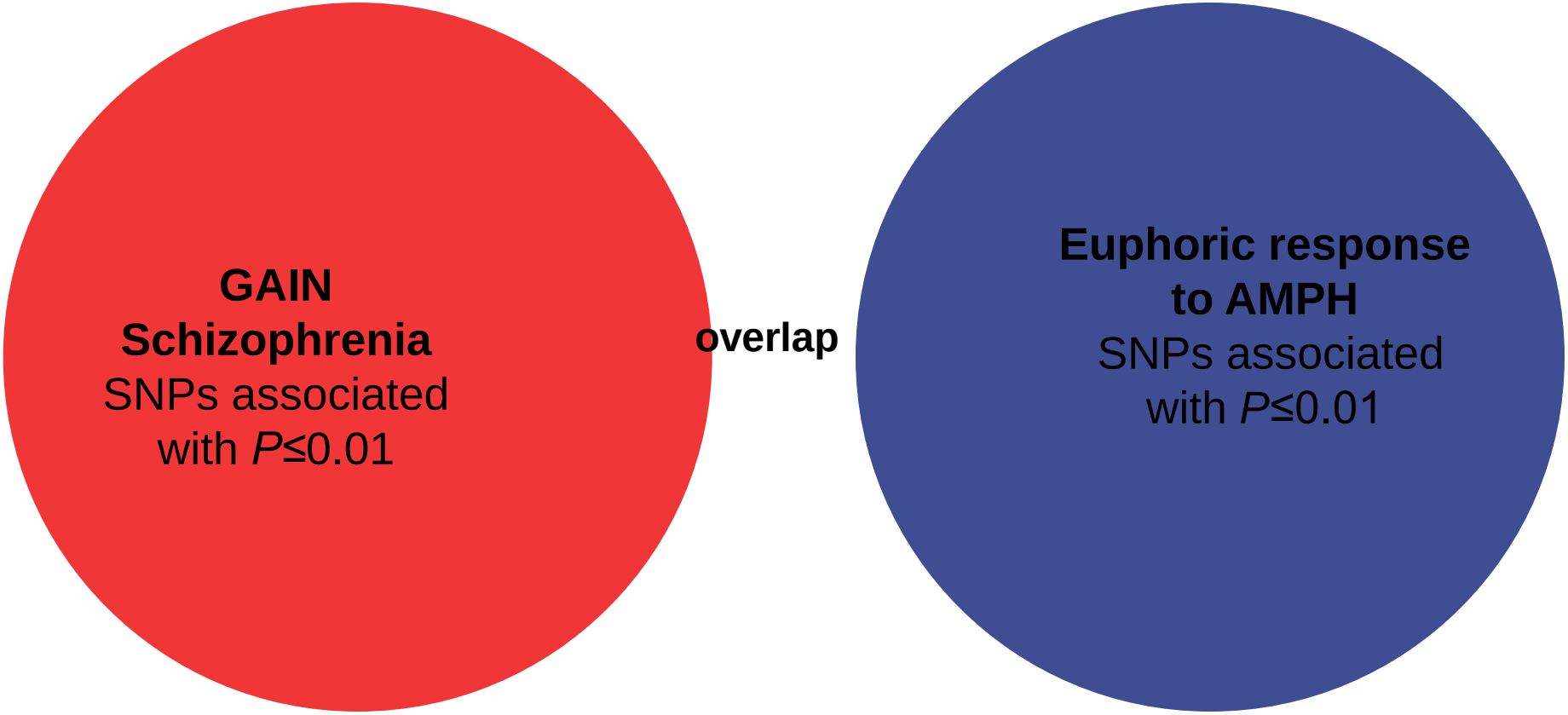
SNPs nominally associated with the euphoric response to *d*-amphetamine will be enriched among SNPs associated with dopaminergic psychiatric disorders



Peroutka *et al* 1980 *Am J Psychiatry*

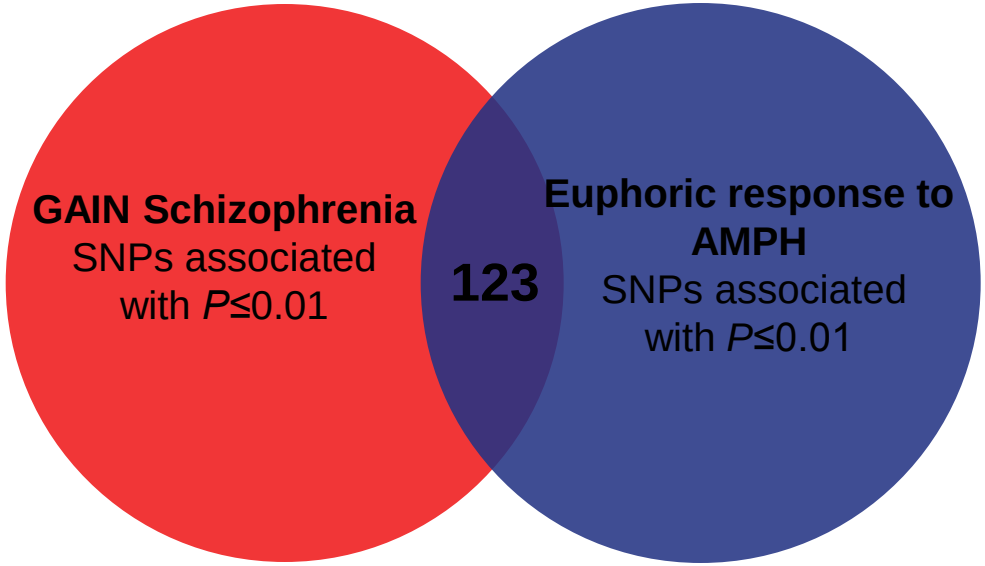


Enrichment methods

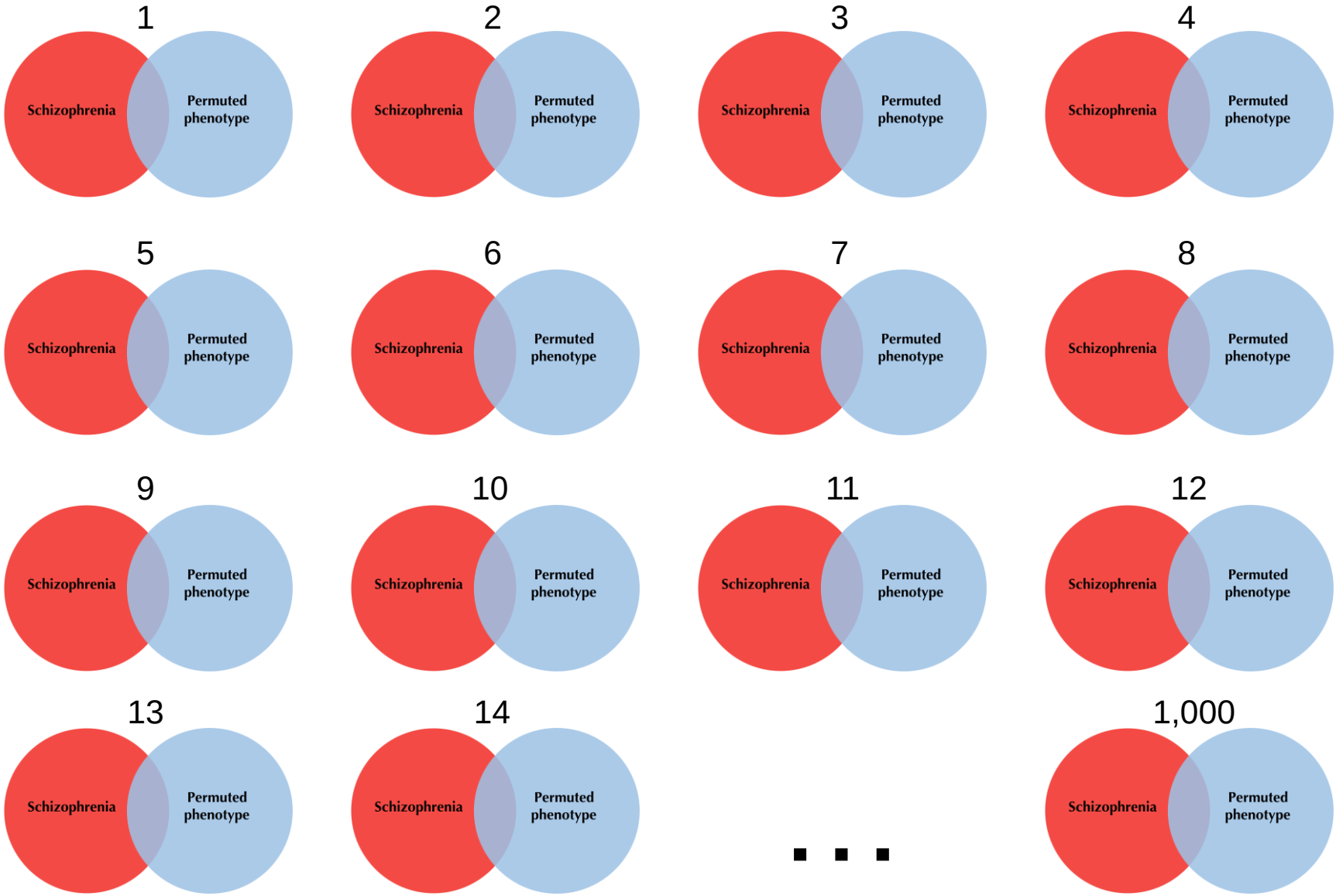


Is the overlap between the two datasets larger than you would expect by chance?

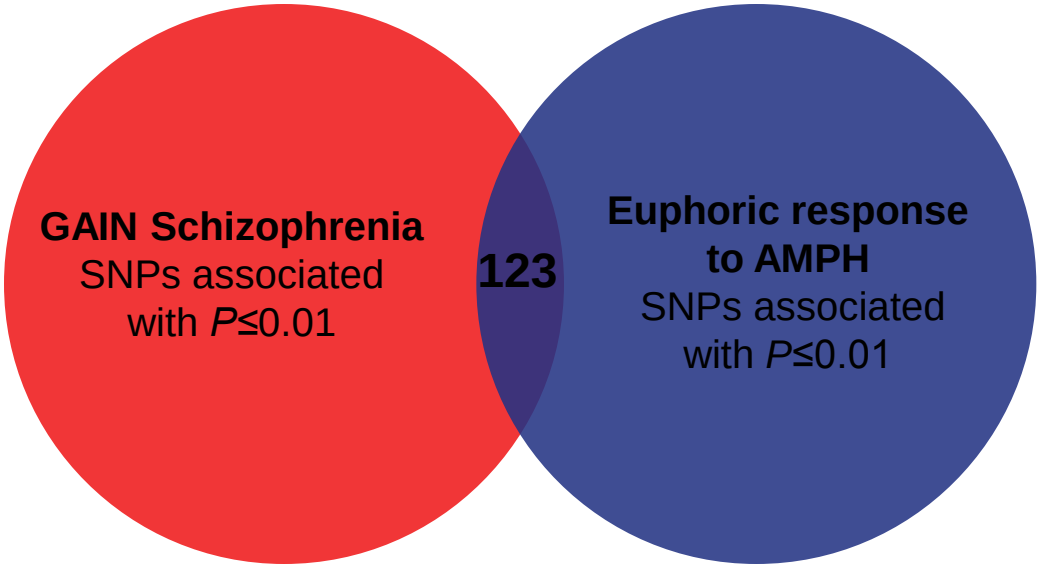
What is the magnitude of overlap?

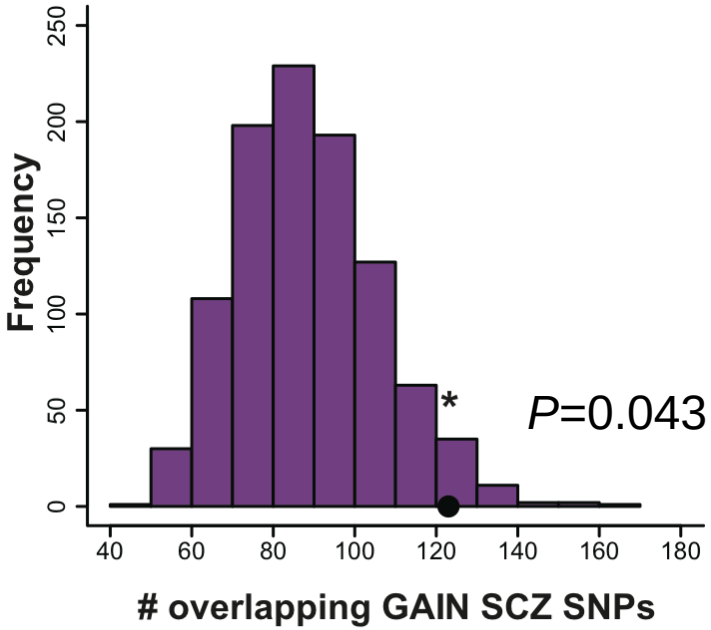


Permutation generates a null distribution of overlapping SNPs

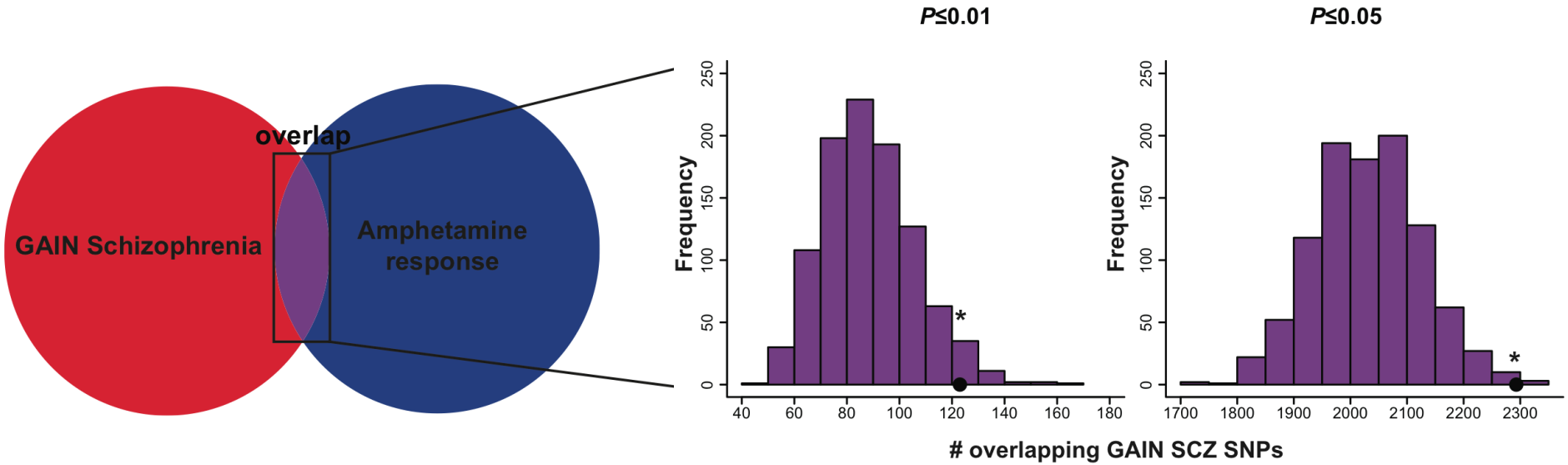


Evaluation of enrichment of schizophrenia-associated SNPs



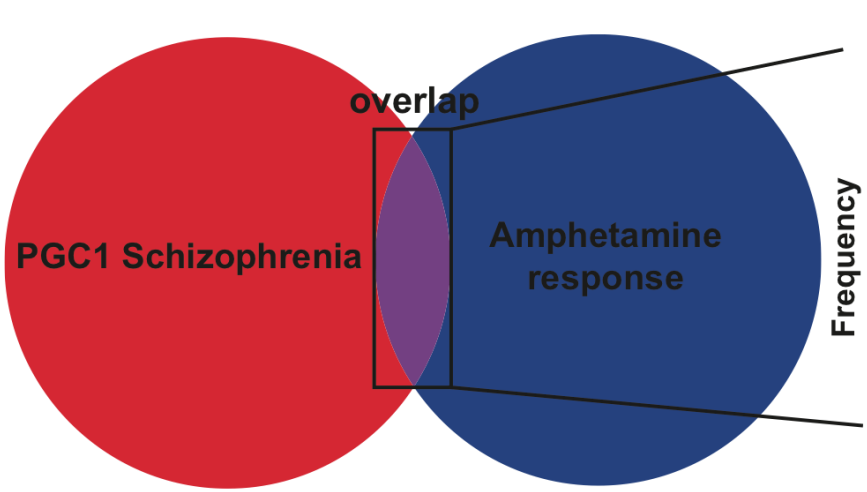


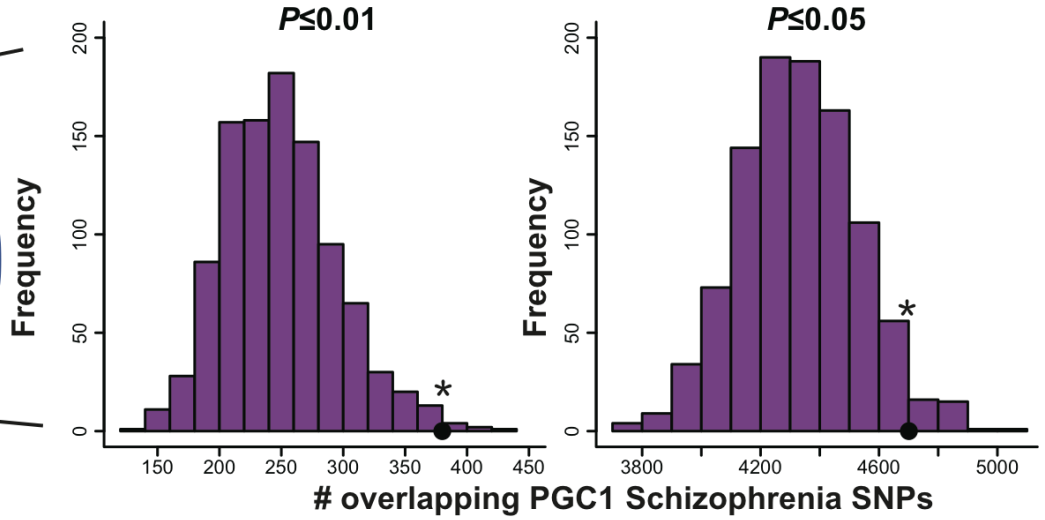
SNPs associated with the euphoric response to *d*-amphetamine are enriched among SNPs associated with schizophrenia



1,351 cases
1,378 controls

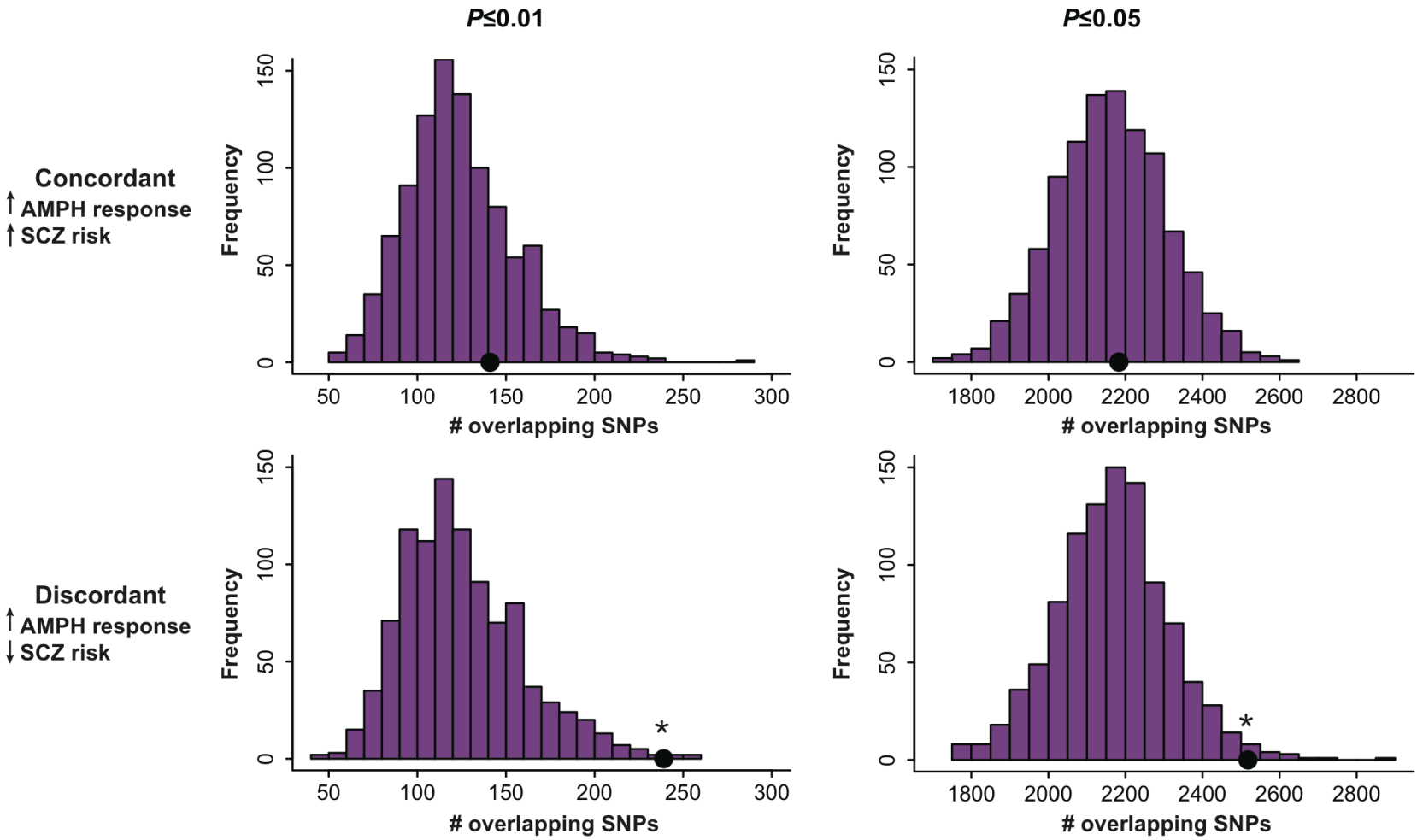
Results from the GAIN Schizophrenia enrichment analysis are replicated in a more powerful sample



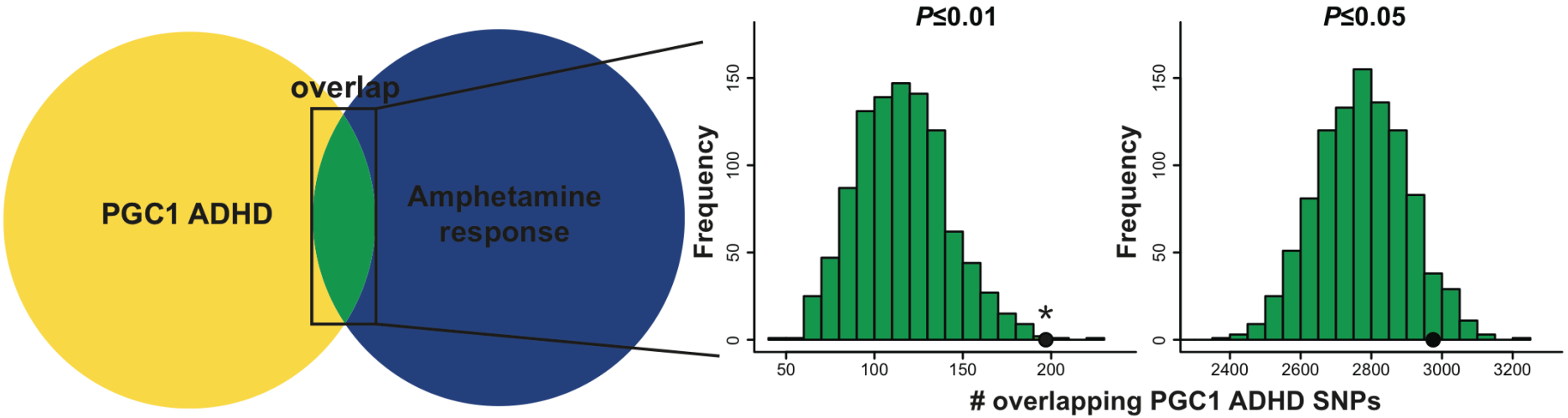


9,394 cases
12,462 controls

Enrichment is driven by alleles associated with increased euphoria and decreased schizophrenia risk

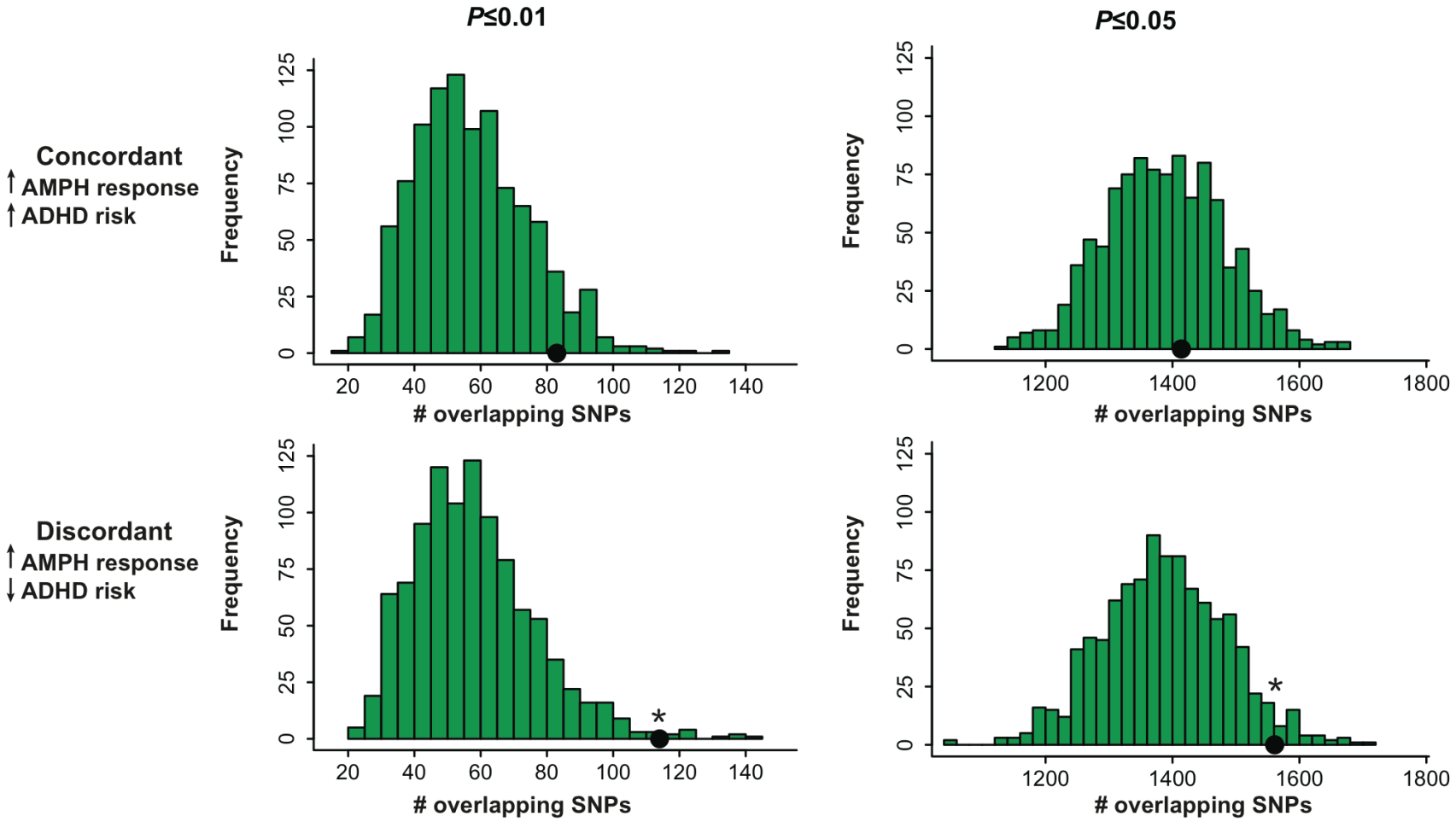


SNPs associated with the euphoric response to *d*-amphetamine are enriched among SNPs associated with ADHD



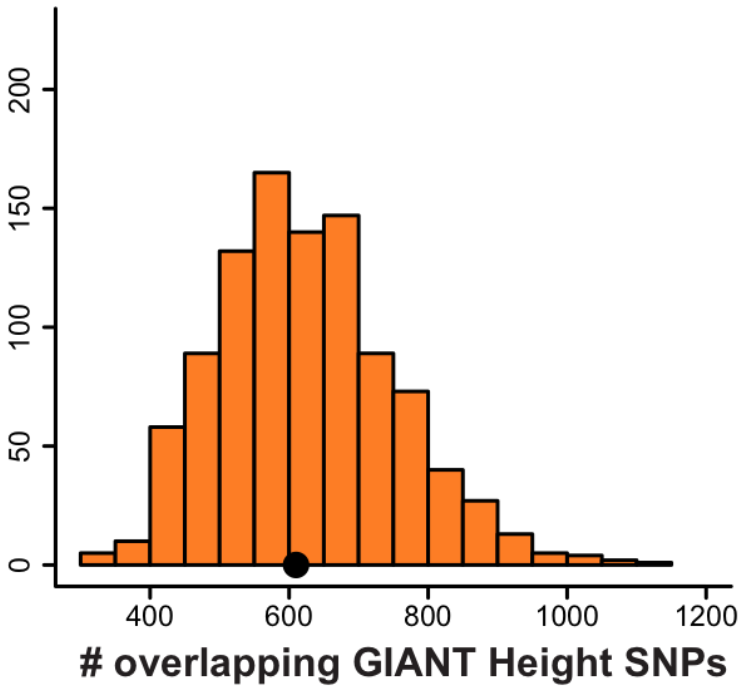
2,064 trios
896 cases
2,455 controls

Enrichment is driven by alleles associated with increased euphoria and decreased ADHD risk



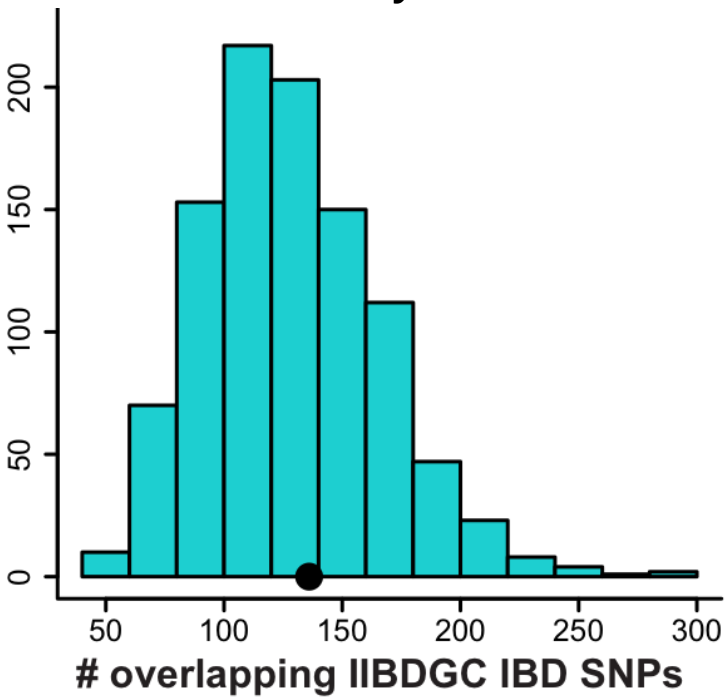
No enrichment is observed for negative control phenotypes

Height



133,653 individuals

Inflammatory Bowel Disease



12,882 cases
21,770 controls

We Propose to Use …

- Potentially related phenotypes
- **Genome function**
- Biochemical (and other) pathways
- Mendelian diseases

Classes of Functional Variants Enriched in SNPs Associated with Common Disease and Complex Human Traits

- **eQTLs – SNPs associated with mRNA transcript levels**
- **mQTLs – SNPs associated with methylation status at sites that are variably methylated**
- **pQTLs – SNPs that are associated with protein levels**
- **miRNA QTLs – SNPs associated with levels of miRNAs**
- **ENCODE annotations**
- **…**

WE ACCELERATE DISCOVERY

HOME PROGRAMS RESEARCH FUNDING NEWS & EVENTS MULTIMEDIA HIGHLIGHTS ABOUT CONTACTS

Genotype-Tissue Expression (GTEx)

Publications Search GO

OVERVIEW WORKING GROUP MEMBERS FUNDING PROGRAM RESOURCES PUBLICATIONS/NEWS MEETING/ACTIVITIES

Common Fund Home > Programs > Genotype-Tissue Expression (GTEx)

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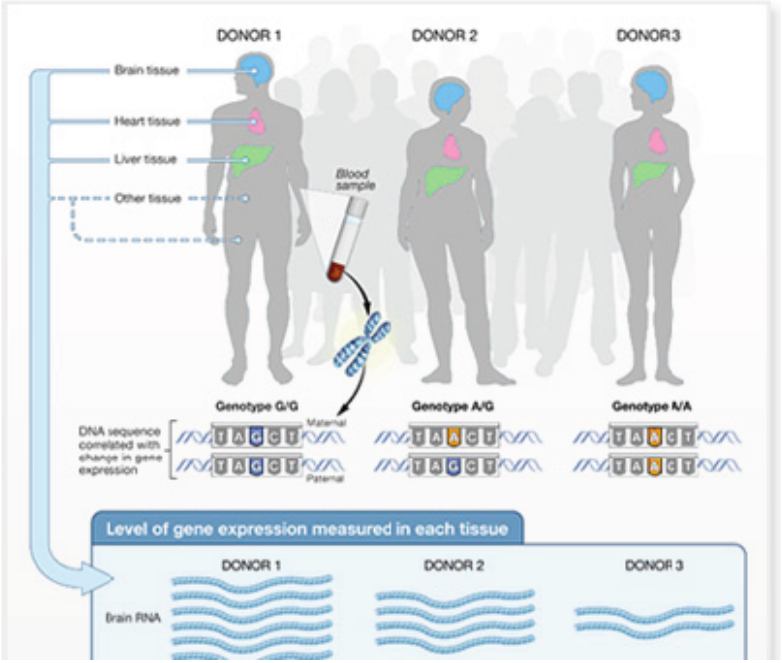
GO

Program Snapshot

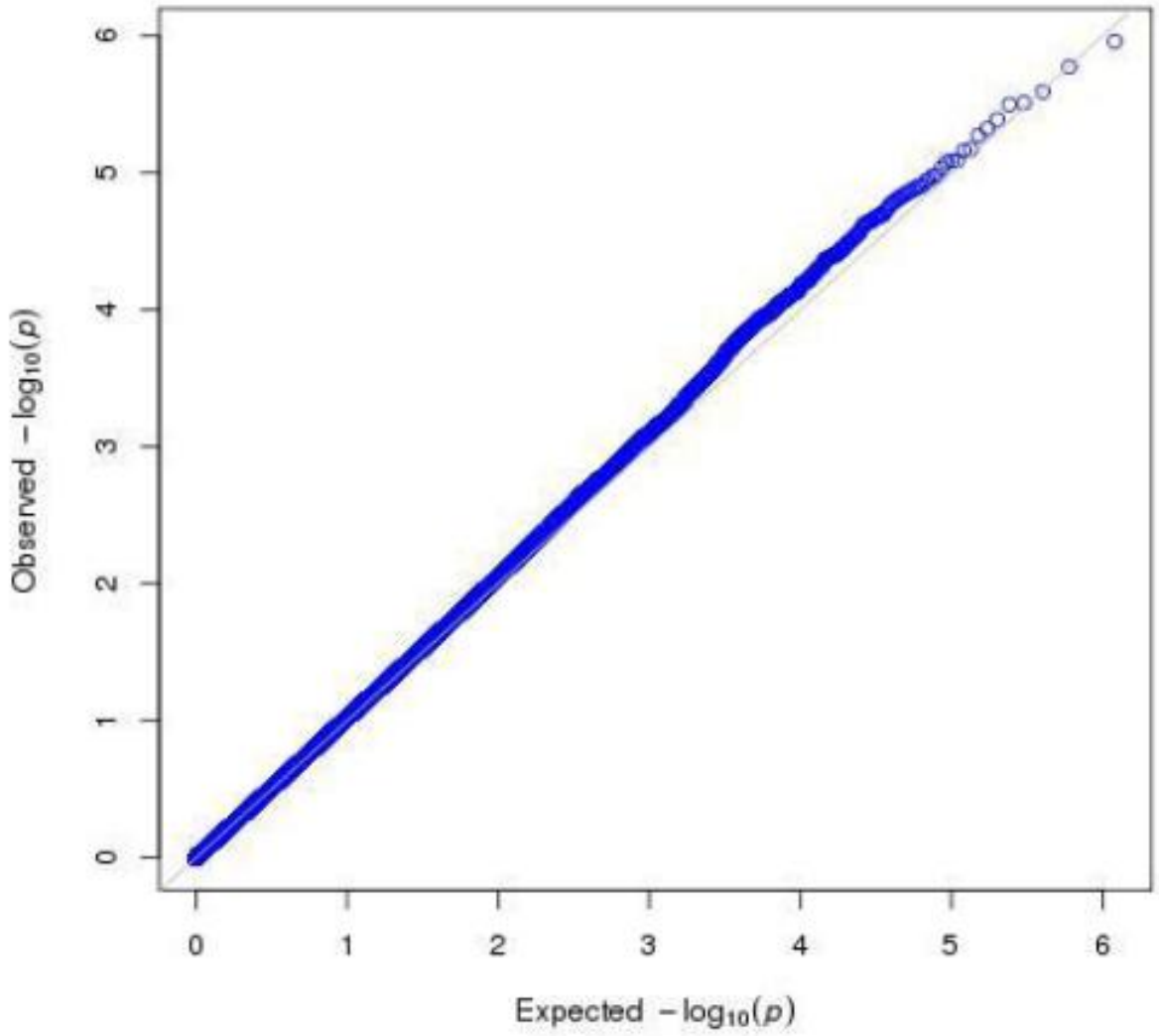
The Common Fund's **Genotype-Tissue Expression (GTEx)** program aims to study human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations. Genetic variation between individuals will be examined for correlation with differences in gene expression level to identify regions of the genome that influence whether and how much a gene is expressed. The GTEx project includes the following initiatives:

- Novel Statistical Methods for Human Gene Expression Quantitative Trait Loci (eQTL) Analysis
- Laboratory, Data Analysis, and Coordinating Center (LDACC)
- caHUB Acquisition of Normal Tissues in Support of the GTEx Project

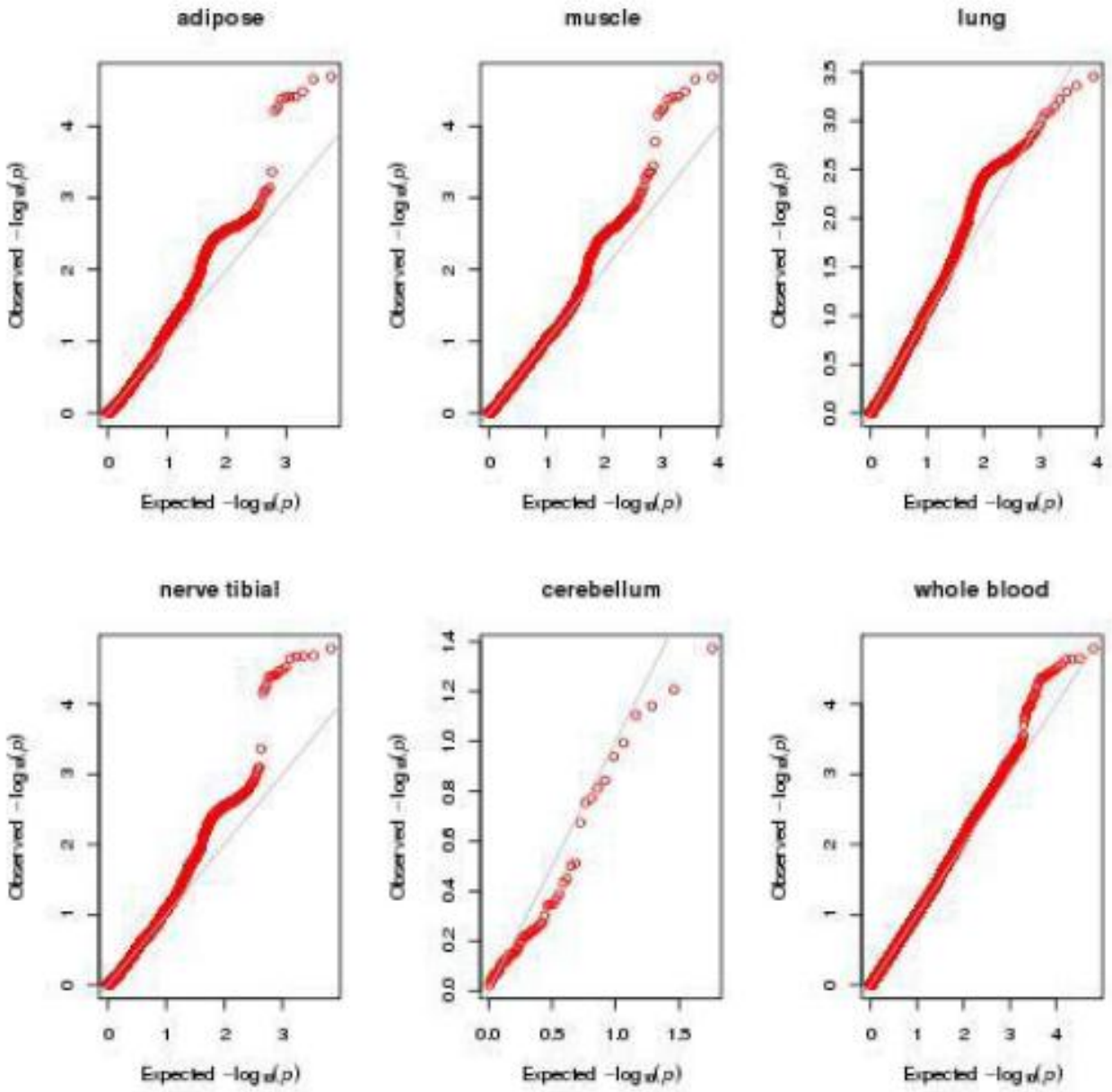
Read more...



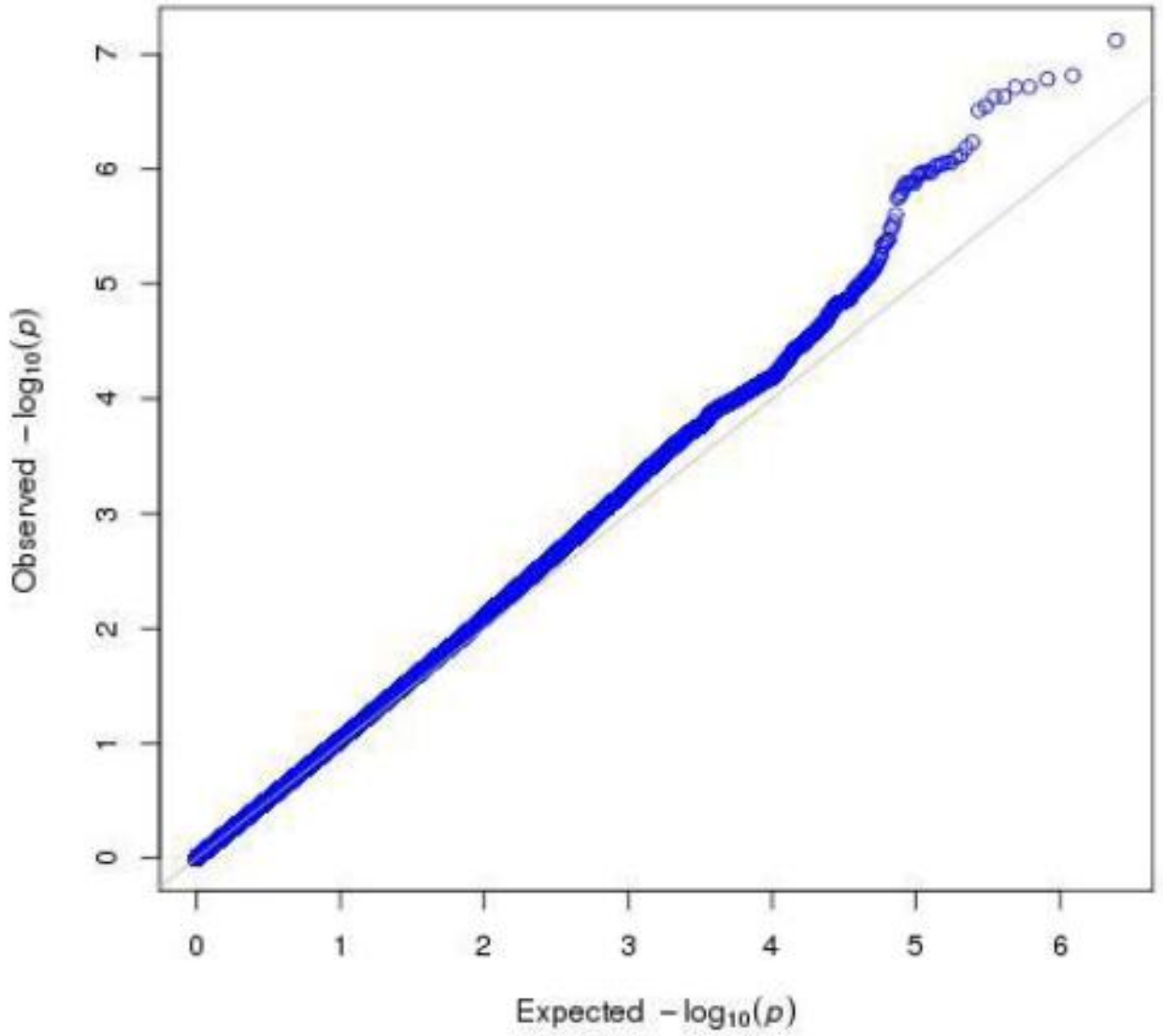
PGC: ADHD (all SNPs)



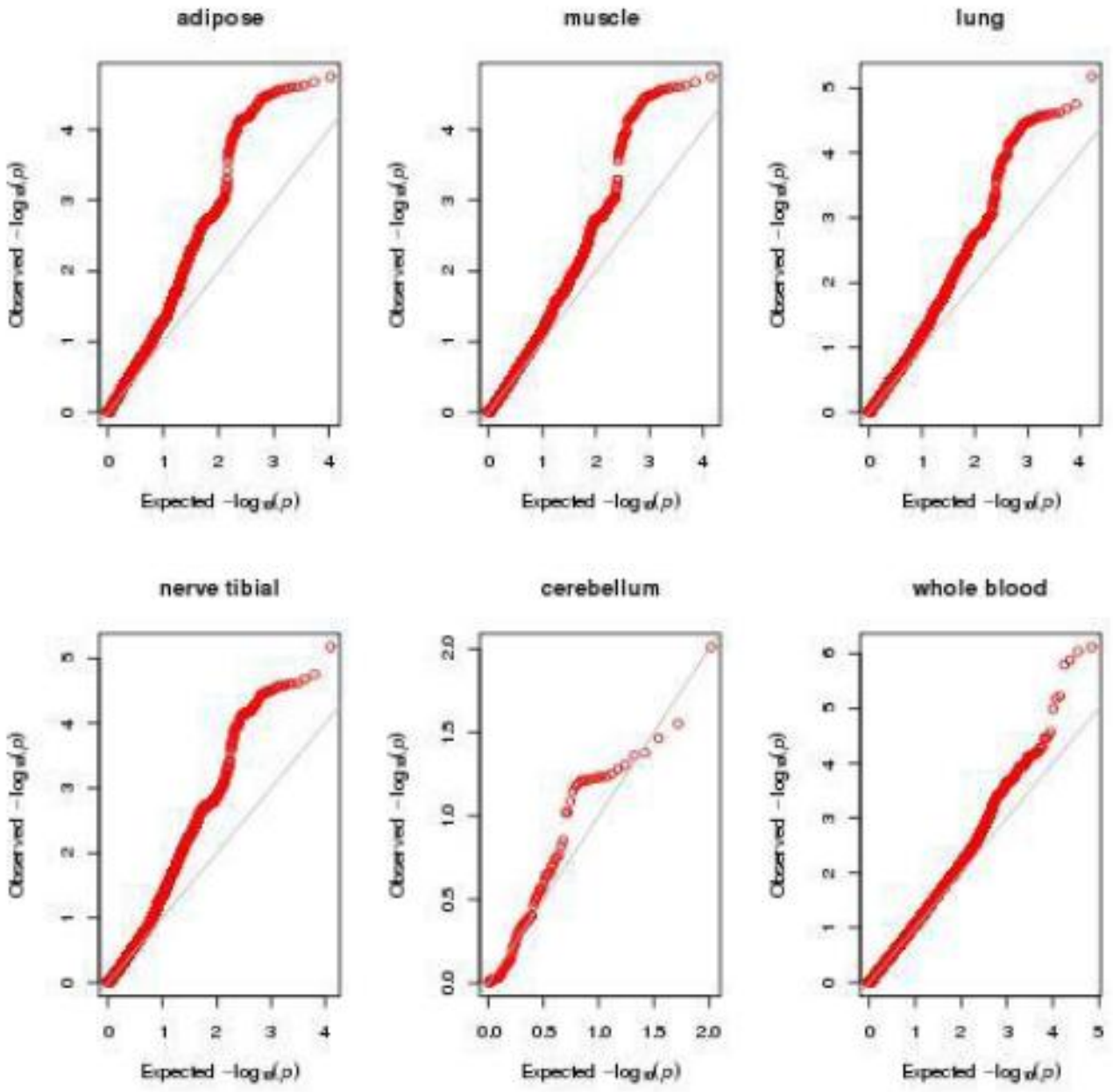
PGC: ADHD


adipose
muscle
lung
nerve tibial
cerebellum
whole blood
Observed −log10(p)
Expected −log10(p)

MAGIC: HOMA-IR (all SNPs)

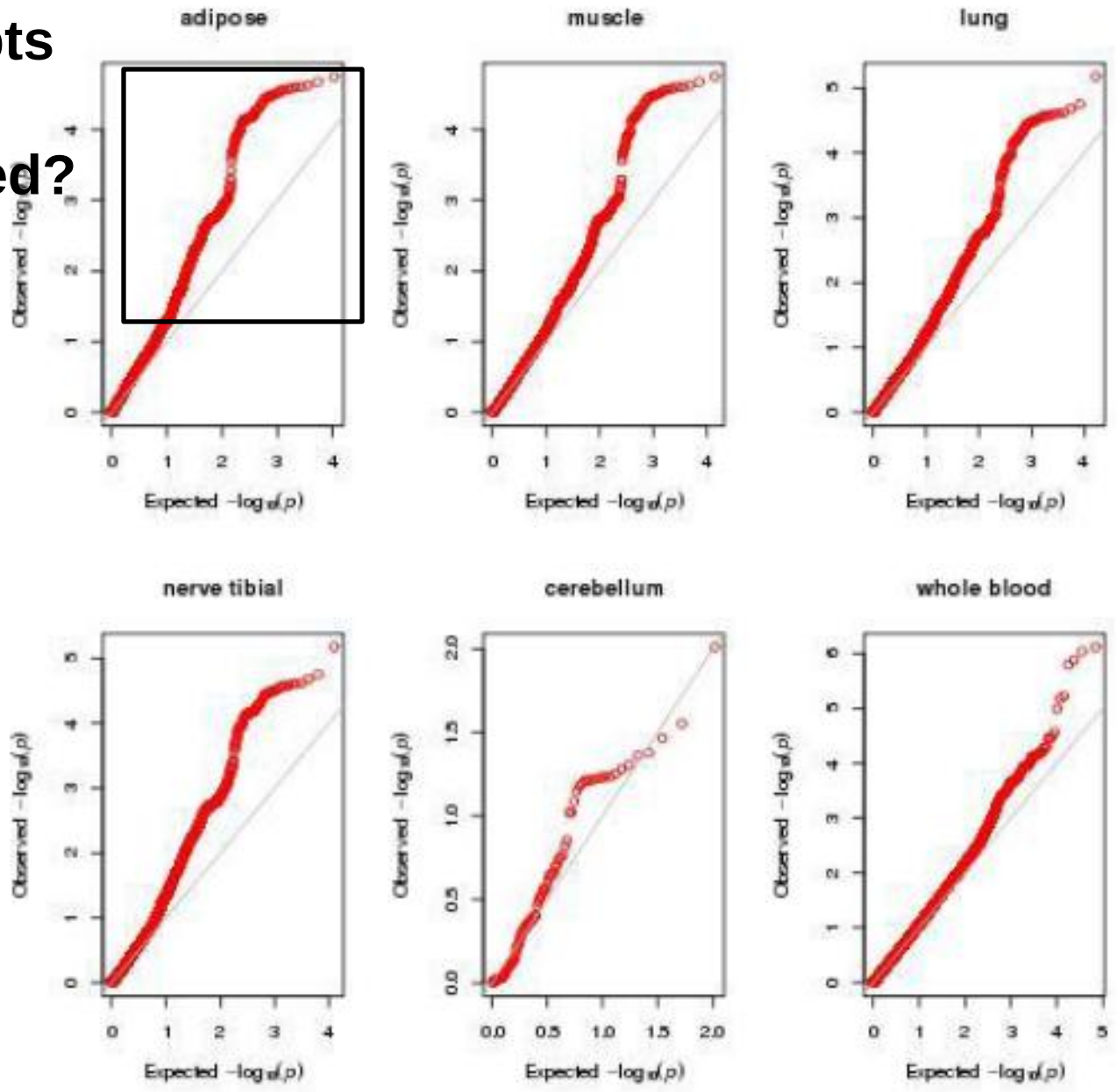


MAGIC: HOMA-IR

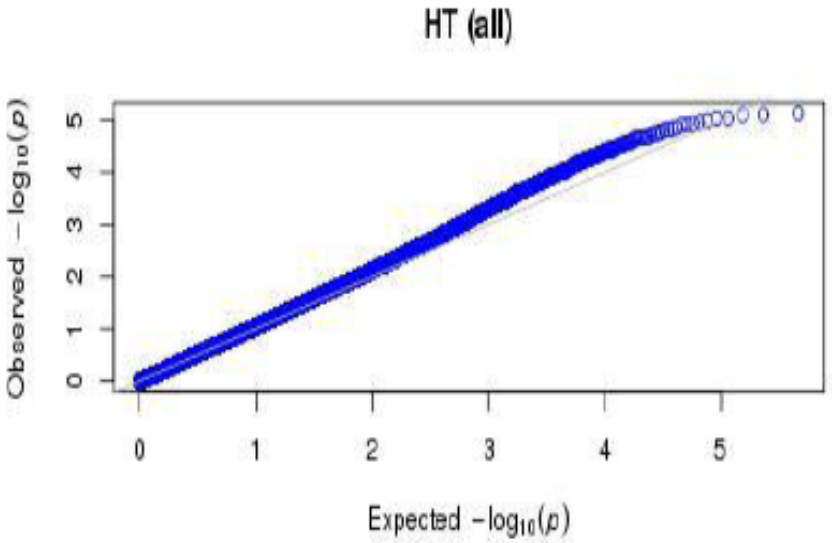


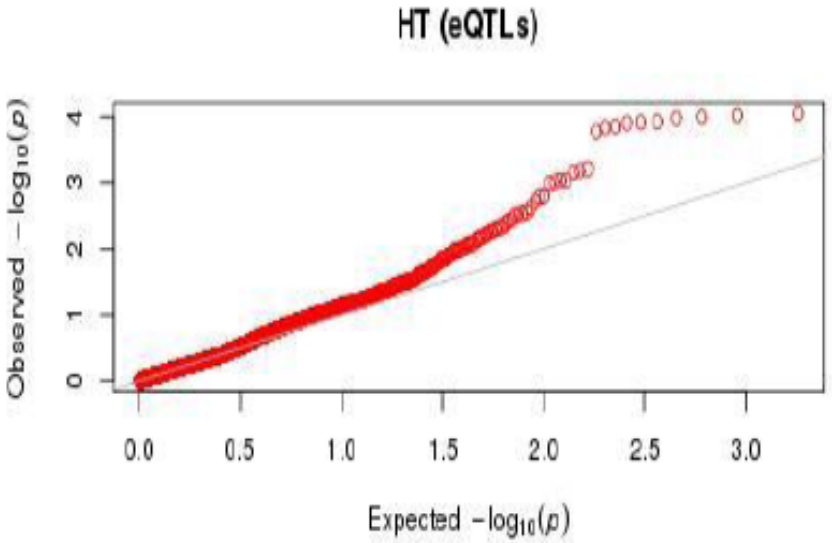
MAGIC: HOMA-IR

What transcripts are implicated?



Hypertension and Adipose eQTLs





Concentrating Heritability

REPORT

GCTA: A Tool for Genome-wide Complex Trait Analysis

Jian Yang,[1,*] S. Hong Lee,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

ARTICLE

Estimating Missing Heritability for Disease from Genome-wide Association Studies

Sang Hong Lee,[1] Naomi R. Wray,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1,*]

Table 2 Comparison of results of different polygenic methods across diseases

			Caused by common GWAS SNPs		
			LMM-based heritability (s.e.)	Polygenic modeling and Bayesian inference	
Disease	Prevalence (%)	Family based heritability[a]		Total variance explained (50% CI)	*N* SNPs (50% CI)
Rheumatoid arthritis	1	0.53–0.68 (–0.13 MHC)[b]	0.32 (0.037)	0.18 (0.15–0.20) (+0.04 known non-MHC)[b]	2,231 (1,588–2,740)
Celiac disease	1	0.5–0.87 (–0.35 MHC)[b]	0.33 (0.042)	0.44 (0.40–0.47)	2,550 (1,907–3,061)
MI/CAD	6	0.3–0.63	0.41 (0.067)	0.48 (0.43–0.54)	1,766 (1,215–2,125)
T2D mellitus	8	0.26–0.69	0.51 (0.065)	0.49 (0.46–0.53)	2,919 (2,335–3,442)

[a]Family based heritability estimates were taken from previous data for rheumatoid arthritis[27,28], celiac disease[18,30], MI/CAD[31,32] and T2D[33,34]. [b]We excluded some loci in certain analyses: although the family based heritability estimates are based on the whole genome, the extended MHC region was removed from the common GWAS SNP analyses for rheumatoid arthritis and celiac disease, and validated non-MHC loci were further removed from the polygenic modeling analysis of the rheumatoid arthritis GWAS data. 50% CI, 50% credible interval; s.e., standard error.

Stahl et al, Nat Gen

	Type 1 Diabetes			Crohns Disease	
	V(G)/V(P)	SE		V(G)/V(P)	SE
adipose	0.21	0.019		0.03	0.008
heart	0.199	0.02		0.017	0.006
lung	0.192	0.018		0.02	0.007
muscle	0.188	0.018		0.028	0.008
nerve	0.191	0.018		0.025	0.008
whole blood	0.187	0.023		0.17	0.024
Overall	0.48	0.06		0.50	0.07

Concentration of Heritability

- **Smaller numbers of eQTLs (3-30K) account for 30-60% of heritability estimated for all variants after QC (150-600K)**
- **Observed across autoimmune and inflammatory diseases, neuropsychiatric, metabolic, etc.**
- **Partitioning by cross vs. single tissues, cis- and trans-, common and rare**

Davis et al, PLoS Genetics

	Tourette Syndrome		Obsessive-Compulsive Disorder	
MAF	Number of SNPs	h2 (s.e.)	Number of SNPs	h2 (s.e.)
> 0.001 – 0.05	20,316	0.13 (0.04)	19,605	0 (0.03)
> 0.05 – 0.1	49,445	0.02 (0.05)	47,976	0.04 (0.05)
> 0.1 -0.2	96,398	0.11 (0.07)	91,661	0.08 (0.08)
> 0.2-0.3	81,924	0.12 (0.07)	77,641	0.01 (0.01)
> 0.3-0.4	74,393	0.16 (0.07)	70,193	0.11 (0.05)
> 0.4 -0.5	70,911	0.07 (0.06)	66,770	0.11 (0.05)

We Propose to Use …

- Potentially related phenotypes
- Genome function
- Biochemical (and other) pathways
- **Mendelian diseases**

Cell
Volume 155
Number 1
September 26, 2013
www.cell.com

A Nondegenerate Code of Deleterious Variants in Mendelian Loci Contributes to Complex Disease Risk

Blair DR, Lyttle CS, Mortensen JM, Bearden CF, Jensen AB, Khiabanian H, Melamed R, Rabadan R, Bernstam EV, Brunak S, Jensen LJ, Nicolae D, Shah NH, Grossman RL, Cox NJ, White KP, Rzhetsky A

Systems Approaches

- **Use GTEx and other resources to build directional, tissue-specific, and cross-tissue SNP regulators (cis and trans, a-zQTLs) for each gene**
- **Assemble gene-sets using knowledge from rare variant associations (Mendelian, animal models, QTs) to "probe" common diseases and complex traits**

Examples

- **What proportion of the overall heritability to neuropsychiatric phenotypes is attributable to the regulation of Mendelian disease genes?**
- **What proportion of the overall heritability to autism is attributable to regulation of genes leading to Mendelian phenotypes including autism as part of the spectrum?**

Examples – other BioProbes

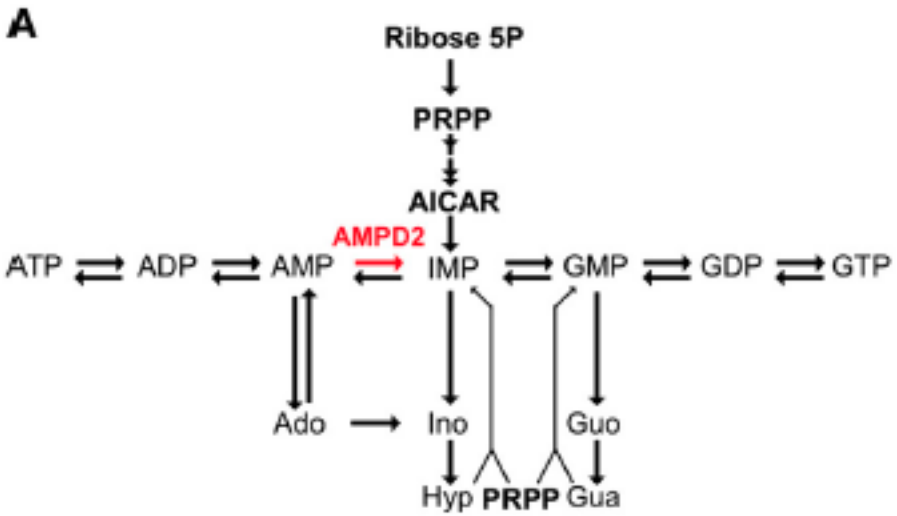
- **For diseases with large-scale meta-analyses completed and publicly available, and for biomarkers with large-scale meta-analyses, can build direction –specific bioprobes to test neuropsychiatric disorders**
- **What is the "opposite" of diabetes? What phenotypes might chronic, genetically determined low blood glucose increase risk for? Does inflammation increase risk of autism?**

We Propose to Use …

- Potentially related phenotypes
- Genome function
- **Biochemical (and other) pathways**
- Mendelian diseases

Examples

- **Can we translate biochemical pathways where Mendelian traits give us clear directionality to test how regulatory variation that would push the pathway in the same direction will affect risk of human disease?**



Akizu et al.
Cell *154*, 505–517

Pathways and More …

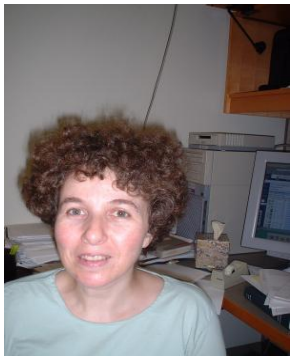
- **Build regulatory SNP set to assay concentration of heritability (where possible) and direction-specific probes to test association with neuropsychiatric phenotypes**
- **Can we build up "regulatory code" for each disease – the list of contributory genes prioritized by how much regulation of that gene contributes to heritability to disease?**

What We Offer

- **Boundless enthusiasm!**
- **Long-time experience working within large consortium efforts**
  - **We want to see the work done, but if others have committed to doing any of these things – great!**
- **Manpower and computing resources through neuropsychiatric genetics training grant, Conte Center, and ability to use and offer University of Chicago cloud computing environment**

We Have Been Picking the Cherries

Cox Lab



Anna Pluzhnikov

Steven Zhang

Pat Evans

Jason Torres

Anna Tikhomirov

Lea Davis (Bridget)

Anuar Konkashbaev

Keston Aquino-Michaels

Carolyn Jumper

Vasily Trubetskoy

Eric Gamazon

The “nitty gritty” analysis group!

Colleagues & Collaborators

Dan Nicolae

M. Eileen Dolan

Haky Im

Bob Grossman

Chun-yu Liu

Andrey Rzhetsky

Amy Hart

Abraham Palmer

The GTEx Consortium Investigators (GTEx Pilot phase)

cancer Human Biobank (caHUB)

Biospecimen Source Sites (BSS)

John Lonsdale, Jeffrey Thomas, Mike Salvatore, Rebecca Phillips, Edmund Lo, Saboor Shad, *National Disease Research Interchange, Philadelphia, PA*
Richard Hasz, *Gift of Life Donor Program, Philadelphia, PA*
Gary Walters, *LifeNet Health, Virginia Beach, VA*
Nancy Young, *Albert Einstein Medical Center, Philadelphia, PA*

Laura Siminoff (ELSI Study), Heather Traino, Maghboeba Mosavel, Laura Barker, *Virginia Commonwealth University, Richmond, VA*

Barbara Foster, Mike Moser, Ellen Karasik, Bryan Gillard, Kimberley Ramsey, *Roswell Park Cancer Institute, Buffalo, NY*
Susan Sullivan, Jason Bridge, *Upstate New York Transplant Service, Buffalo, NY*

Comprehensive Biospecimen Resource (CBR)

Scott Jewell, Dan Rohr, Dan Maxim, Dana Filkins, Philip Harbach, Eddie Cortadillo, Bree Berghuis, Lisa Turner, Melissa Hanson, Anthony Watkins, Brian Smith, *Van Andel Institute, Grand Rapids, MI*

Pathology Resource Center (PRC)

Leslie Sobin, James Robb, *SAIC-Frederick, Inc., Frederick, MD*
Phillip Branton, *National Cancer Institute, Bethesda, MD*
John Madden, *Duke University, Durham, NC*
Jim Robb, Mary Kennedy, *College of American Pathologists, Northfield, IL*

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US National Institutes of Health

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Training in Emerging Multidisciplinary Approaches to Mental Health and Disease (T32MH020065)

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- Russ Altman at TEDxStanford: Personalized Prescriptions
- Visit us at the World Congress of Psychiatric Genetics & American Society of Human Genetics meetings in Boston

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GROSSMAN INSTITUTE FOR NEUROSCIENCE, QUANTITATIVE BIOLOGY AND HUMAN BEHAVIOR

Psychiatric Genetics Training Grant

Our training grant supports both graduate and postdoctoral students that work in labs of our training faculty.

Overview

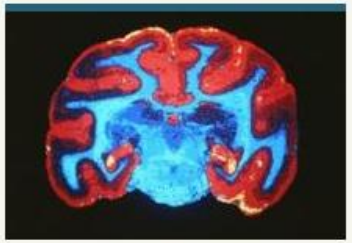
The Training in Emerging Multidisciplinary Approaches to Mental Health and Disease Training Grant (T32MH020065) is funded by the NIMH and provides specialized training to both graduate and postdoctoral students. The training grant organizes a series of on-campus retreats as well as a journal club and seminar series. We have a broad view of psychiatric genetics which emphasizes the following areas:

- Integration of computational and statistical approaches to complex datasets
- Hypothesis driven laboratory-based experimental approaches
- Multidisciplinary science

Program Directors: Abraham A Palmer and Nancy Cox

Executive Committee: Abraham A Palmer, Nancy Cox, Elliot Gerson, Harriet de Wit and Andrey Rzhetsky

Training Grant Administrator: Erin Brady



CONTE CENTER FOR COMPUTATIONAL NEUROPSYCHIATRIC GENOMICS

The Psychiatric Training grant is coordinating activities such as seminars and symposia speakers with the Conte Center for Computational Neuropsychiatric Genomics.

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