Washington University in St. Louis
School of Medicine

PGC
Psychiatric Genomics Consortium

Shared genetic influences underlie alcohol use disorder and schizophrenia

University of Pennsylvania Seminar - 04/27/2020

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American Foundation for Suicide Prevention

- Funding from NIAAA (F32AA027435) and AFSP (YIG-0-064-18)
- No other disclosures

- The research presented here has not undergone peer-review. Please email emma.c.johnson@wustl.edu for further distribution or cites.

Three observations

1. Schizophrenia (SCZ) is relatively rare, with approx. 1% population prevalence, but the prevalence of AUD within this group is as high as 40%

2. Dual diagnosis is associated with longer hospital stays, higher incarceration, lower treatment success/medication compliance

3. Up to 60% of early deaths in individuals with SCZ are at least partially attributable to the use of alcohol and other drugs

Drake et al., 1990; Fowler et al., 1998;
Margolese et al., 2004; Hartz et al., 2014

What produces this comorbidity?

- Self-medication (relieve SCZ symptoms, or side-effects of certain antipsychotics)
- Shared environmental risk factors
- Impairments in cognitive processes associated with SCZ
- Shared genetic pathways

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- Impairments in cognitive processes associated with SCZ
- **Shared genetic pathways**

Evidence of genetic overlap

- Both disorders are heritable
  - SCZ twin-h^2 = 81%
  - AUD twin-h^2 = 49%
- Significant genetic correlation in genome-wide association studies (**GWAS**)
  - r_g=0.32, p = 1.4e-29
- Polygenic risk scores (**PRS**) of AUD are associated with SCZ liability and vice versa
- BUT: r_g between SCZ and typical alcohol *consumption* is weak
  - e.g., drinks/week: r_g = 0.01, p = 0.670

Sullivan et al., 2003; Verhulst et al., 2015; Zhou et al., 2020; Liu et al., 2019; Carey et al., 2016; Hartz et al., 2017

The genetic overlap of AUD and SCZ

1. Examine evidence for **causal relationships**
    - Latent causal variable analysis (**LCV**)

2. Identify variants with **pleiotropic** and **disorder-specific** effects
    - Conduct cross-disorder *as*sociation analysis based on sub*set*s (**ASSET**)
    - Incorporate expression data

3. **Partition the genetic correlation** into salient functional categories and to specific genomic regions.
    - Genetic covariance analyzer (**GNOVA**) and bivariate heritability estimator from summary statistics (**rho-HESS**)

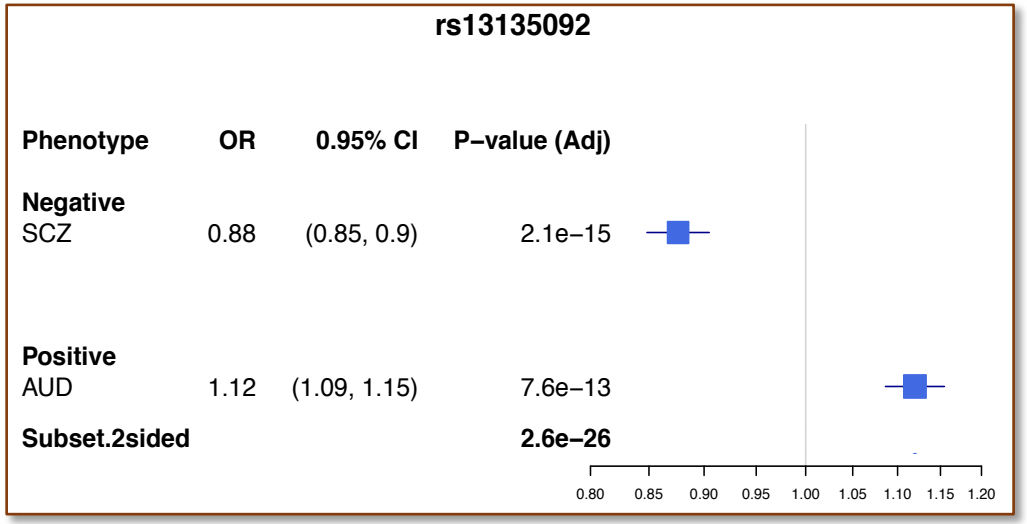
4. Contrast the genetic relationship between SCZ and **AUD** with that for SCZ and **typical alcohol intake**.
    - Linkage disequilibrium score regression (**LDSC**)
    - Associations between polygenic scores for SCZ and a range of alcohol-related phenotypes

ASSET vs. traditional meta-analysis

"Association analysis based on SubSETs"

- In traditional cross-disorder meta-analyses, the effects of genetic variants with significant influences on both disorders but in *opposite* directions of effect get washed out
- ASSET pools the effects of variants with opposite directions of effect into a combined meta-analysis p-value

This SNP would not show up as significant in a traditional meta-analysis – thanks to ASSET, we can identify these variants!



Bhattacharjee et al., 2012 (https://doi.org/10.1016/j.ajhg.2012.03.015)

Talk outline

- Aim 1 – examine evidence for causal relationships
- Aim 2 – cross-disorder analysis using ASSET, integrate with expression data
- Aim 3 – partition genetic covariance
- Aim 4 – contrast genetic correlation between SCZ and AUD vs. alcohol consumption & examine whether polygenic liability for SCZ predicts alcohol-related phenotypes in an independent sample
- Summary
- Next steps

Aim 1

Examine evidence for **causal relationships**

- Latent causal variable analysis (**LCV**)

No evidence of causal relationships

- **Latent causal variable** (LCV) analysis
  - Whole-genome alternative to Mendelian Randomization
  - Fewer false positives for correlated traits and high polygenicity
  - Genetic causality proportion (GCP) ranges between 0 (no partial genetic causality) to 1 (full genetic causality)

- p-value for H_0(GCP = 0) = 0.320;
- p-values for H_0(GCP = -1 or 1) = 3.41e-35 and 3.56e-50, respectively.

LCV; O'Connor & Price, 2018; https://doi.org/10.1038/s41588-018-0255-0

Aim 2

Identify variants with **pleiotropic** and **disorder-specific** effects

- Conduct cross-disorder *as*sociation analysis based on sub*set*s (**ASSET**)
- Incorporate expression data

European ancestry results

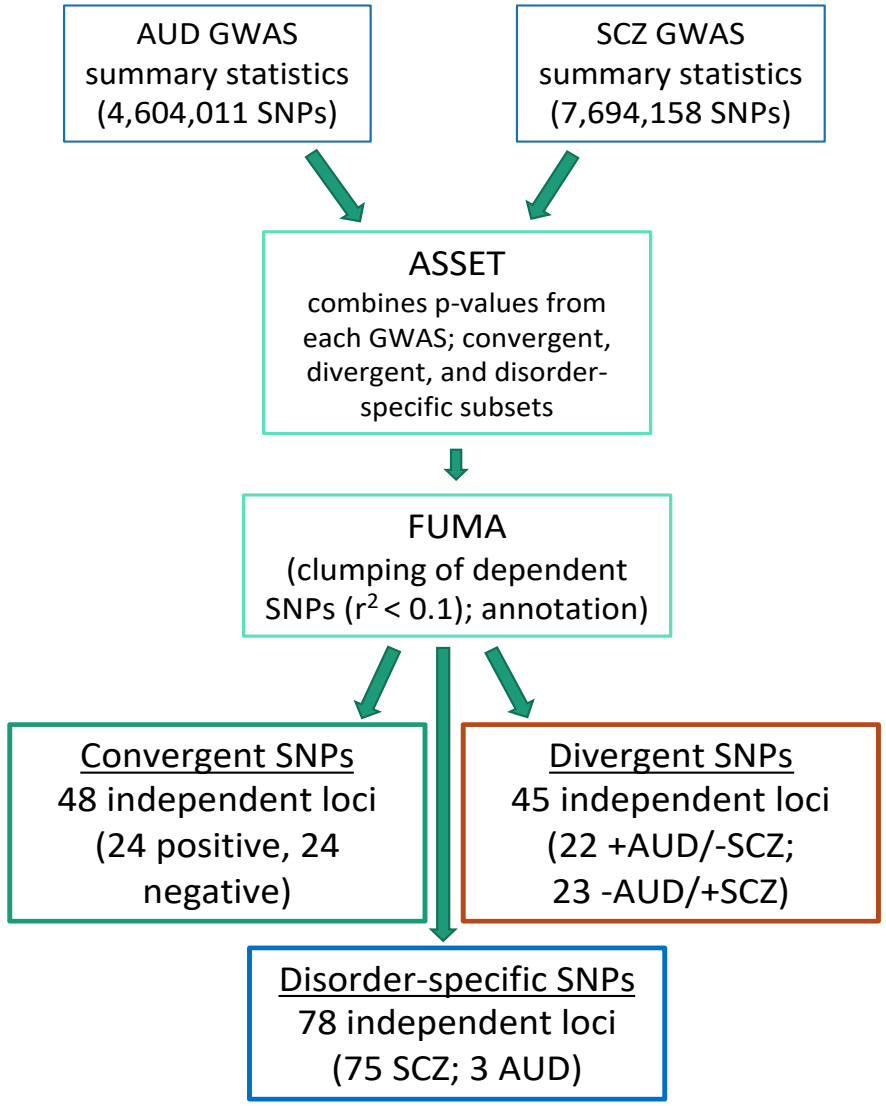
Summary statistic samples: European ancestry

- **Schizophrenia:**
  - **PGC SCZ3** GWAS (N_{case} = 49,407; $N_{control}$ = 71,785)
  - **151** independent genome-wide significant loci
- **Alcohol use disorder:**
  - **AUD** GWAS (total N_{case} = 43,143; $N_{control}$ = 187,618)
  - PGC Alcdep (Walters et al., 2018) & MVP AUD (Kranzler et al., 2019)
  - **11** independent genome-wide significant loci
- **Drinks per week:**
  - GSCAN **DPW** GWAS (total N = 537,349; Liu et al. 2019)
  - **99** reported genome-wide significant variants

Pleiotropic and disorder-specific variants

- Used ASSET to identify SNPs with convergent and divergent effects

	Risk effect on AUD	Protective effect on AUD	No effect on AUD
Risk effect on SCZ	24	23	37
Protective effect on SCZ	22	24	38
No effect on SCZ	1	2	--



Bhattacharjee et al., 2012 (https://doi.org/10.1016/j.ajhg.2012.03.015)
Watanabe et al, 2017 (https://www.nature.com/articles/s41467-017-01261-5)

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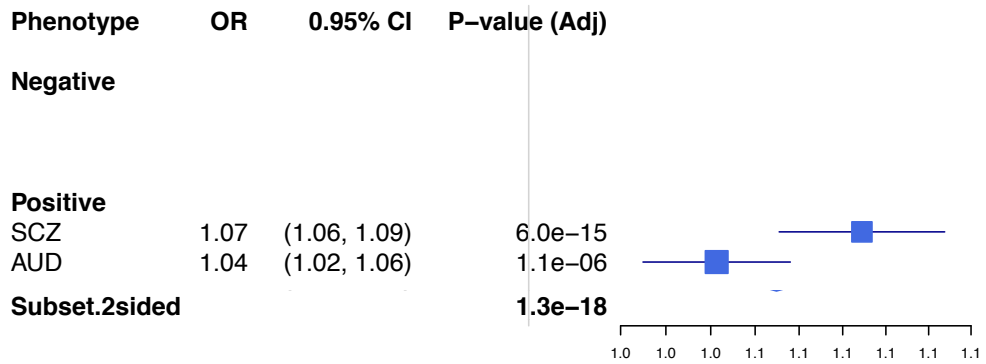
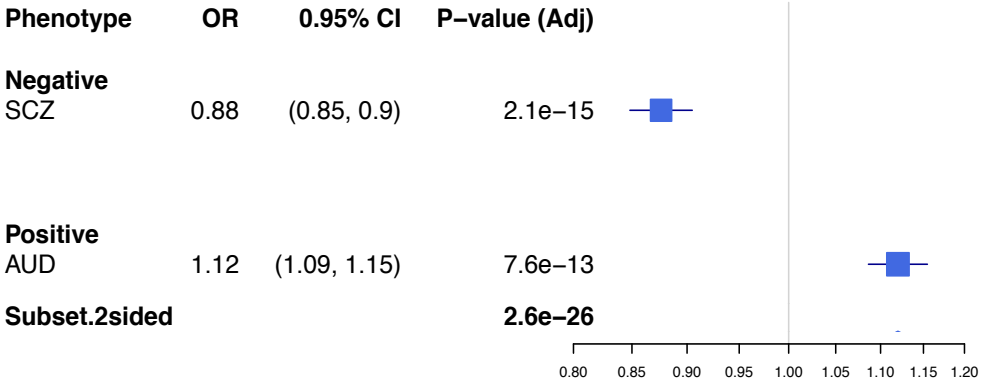
Top convergent SNP -> rs11805871



Top divergent SNP -> rs13135092



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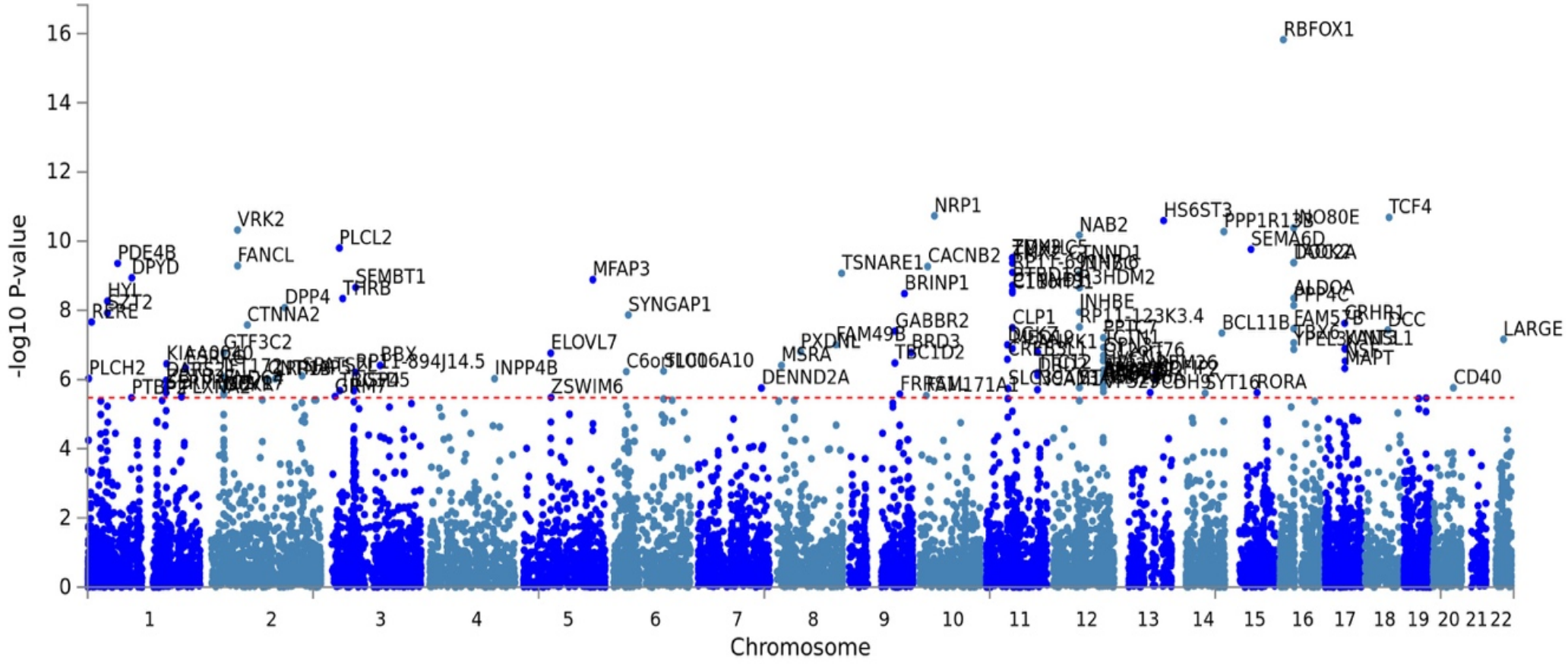
MAGMA gene-based test

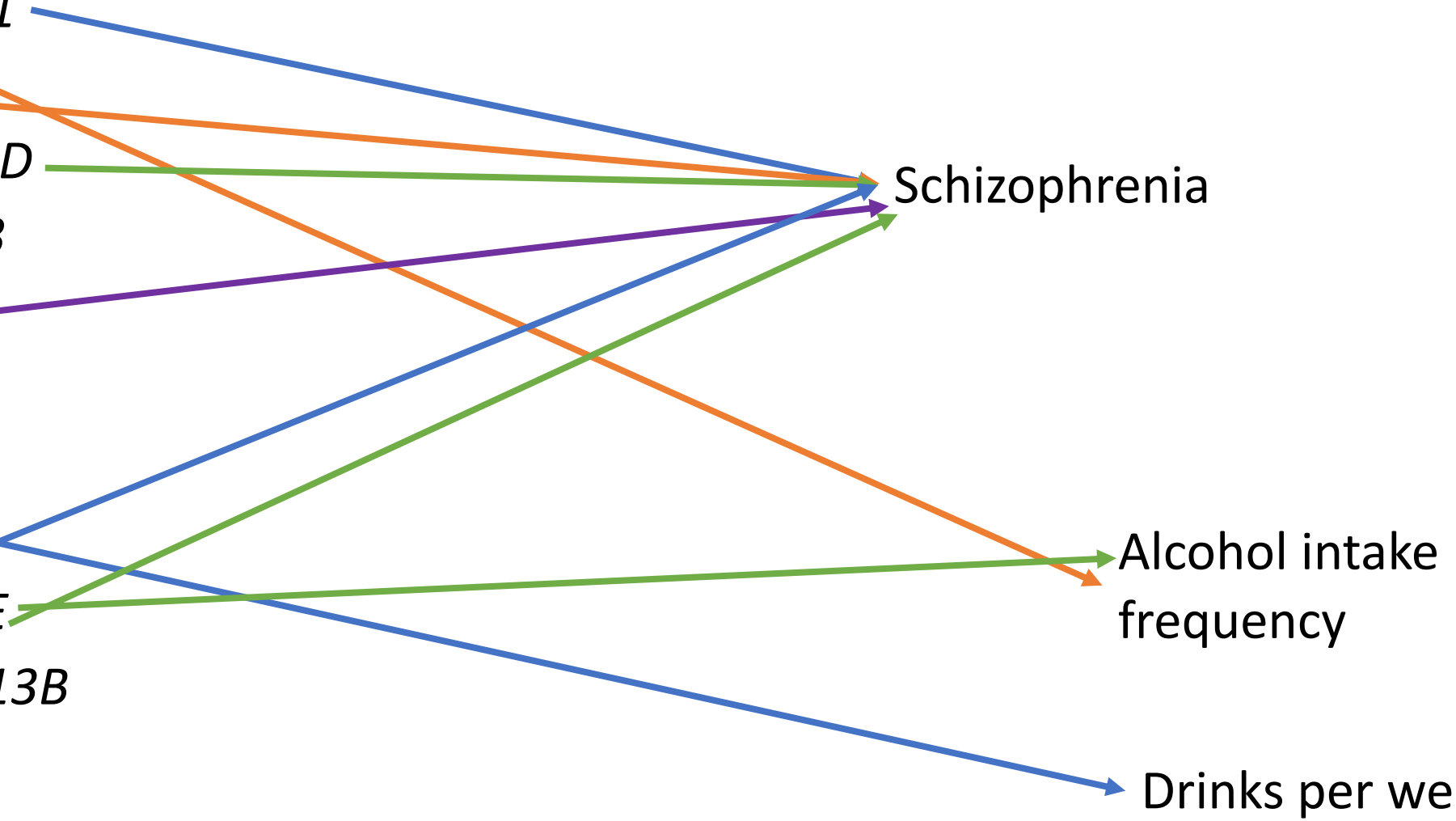
- Convergent subset of SNPs



Top 10 genes

PheWAS

- *RBFOX1*
- *TCF4*
- *SEMA6D*
- *HS6ST3*
- *NAB2*
- *NRP1*
- *PLCL2*
- *VRK2*
- *INO80E*
- *PPP1R13B*



(atlas.ctglab.nl)

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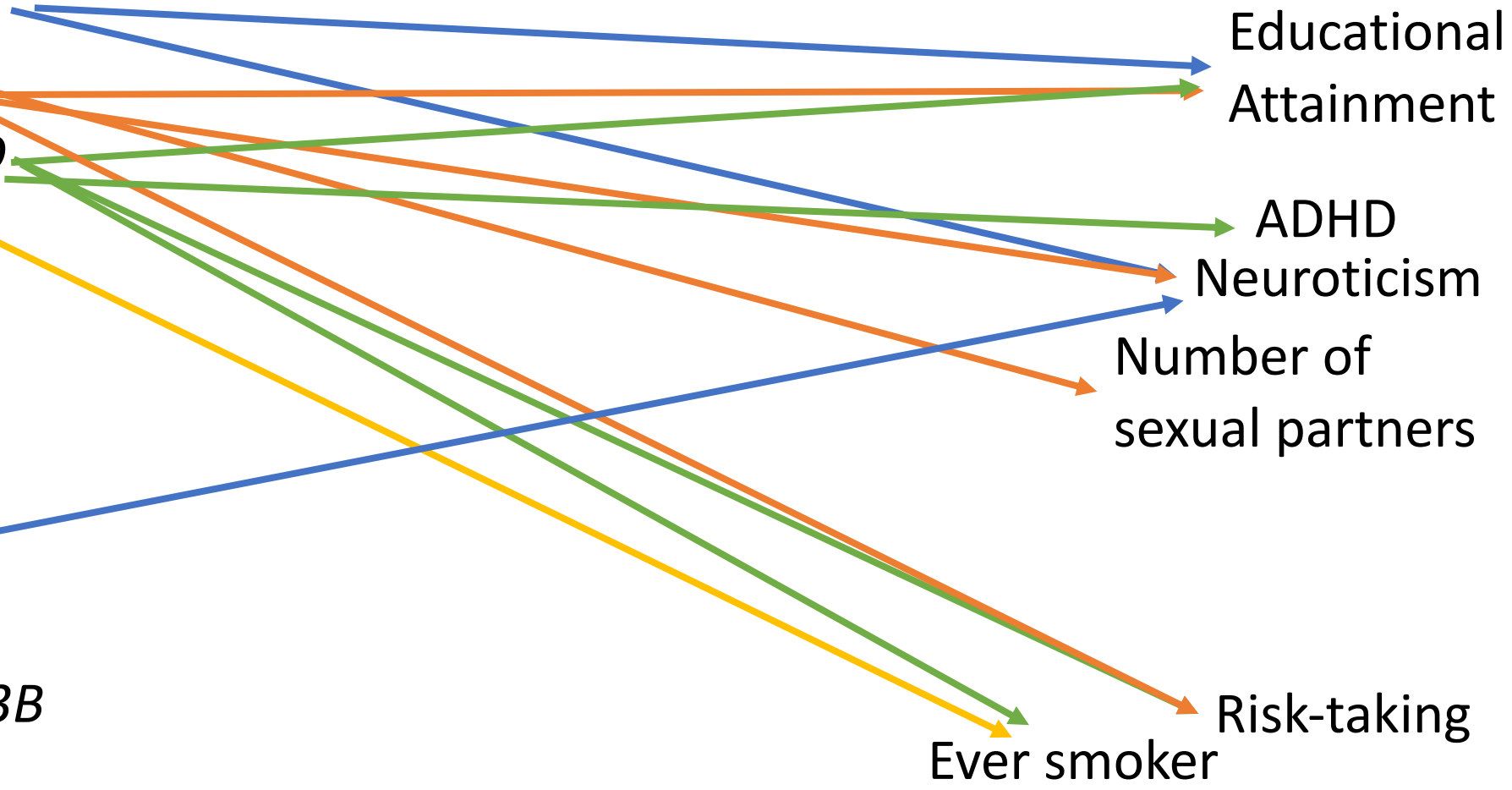

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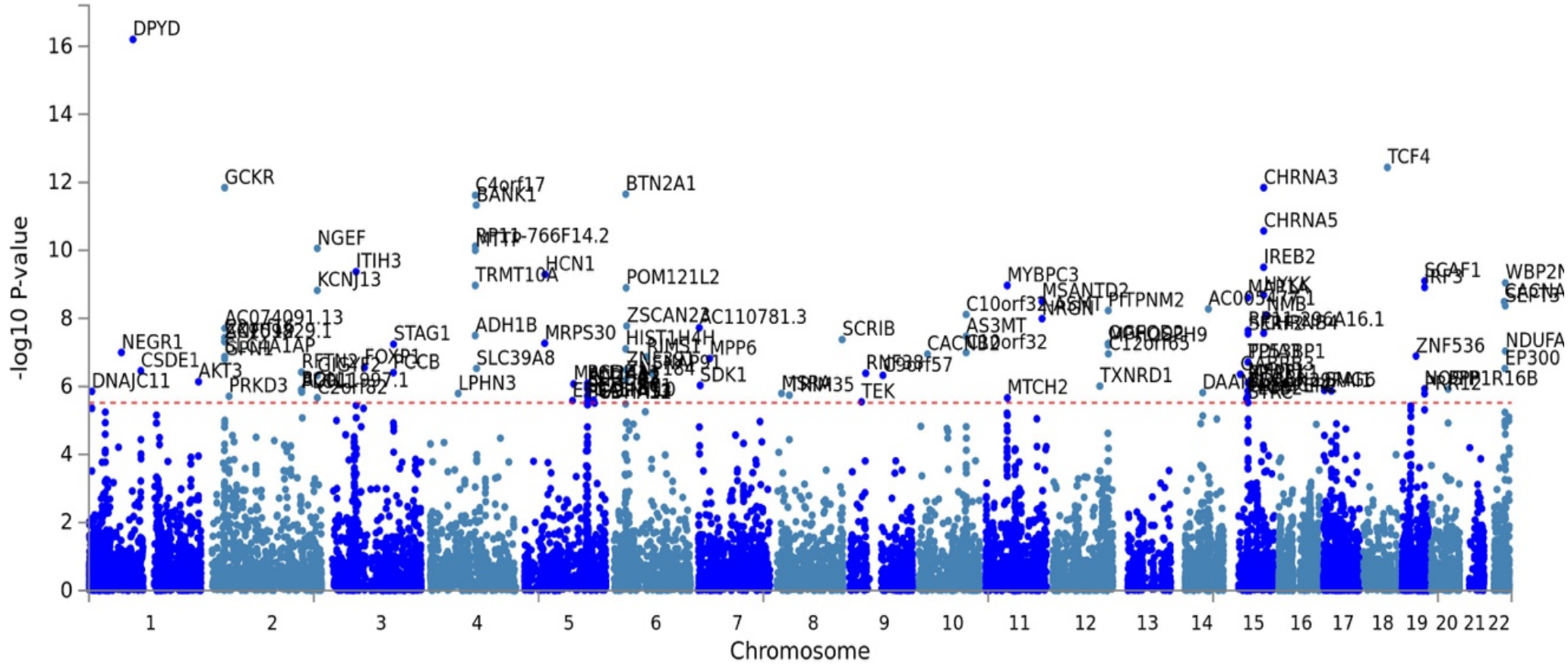
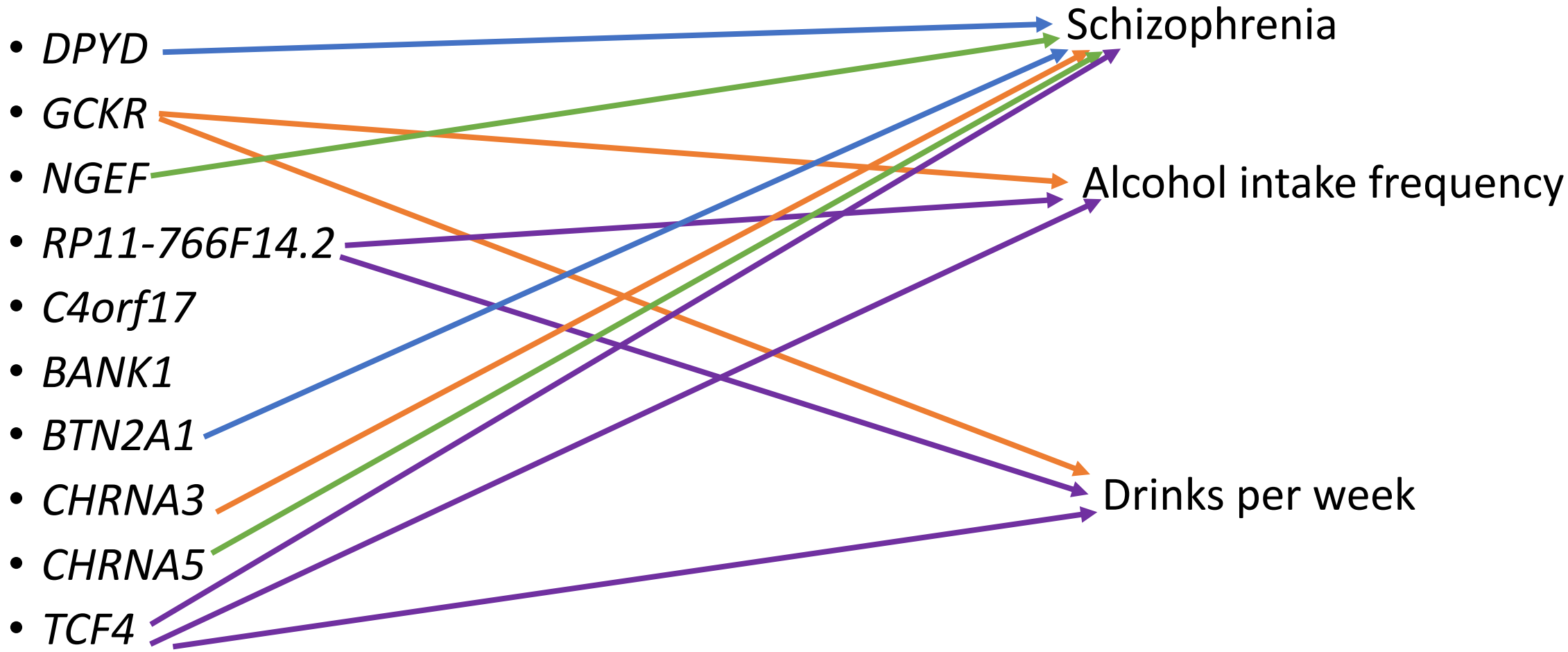
MAGMA gene-based test

- Divergent subset of SNPs



Top 10 genes

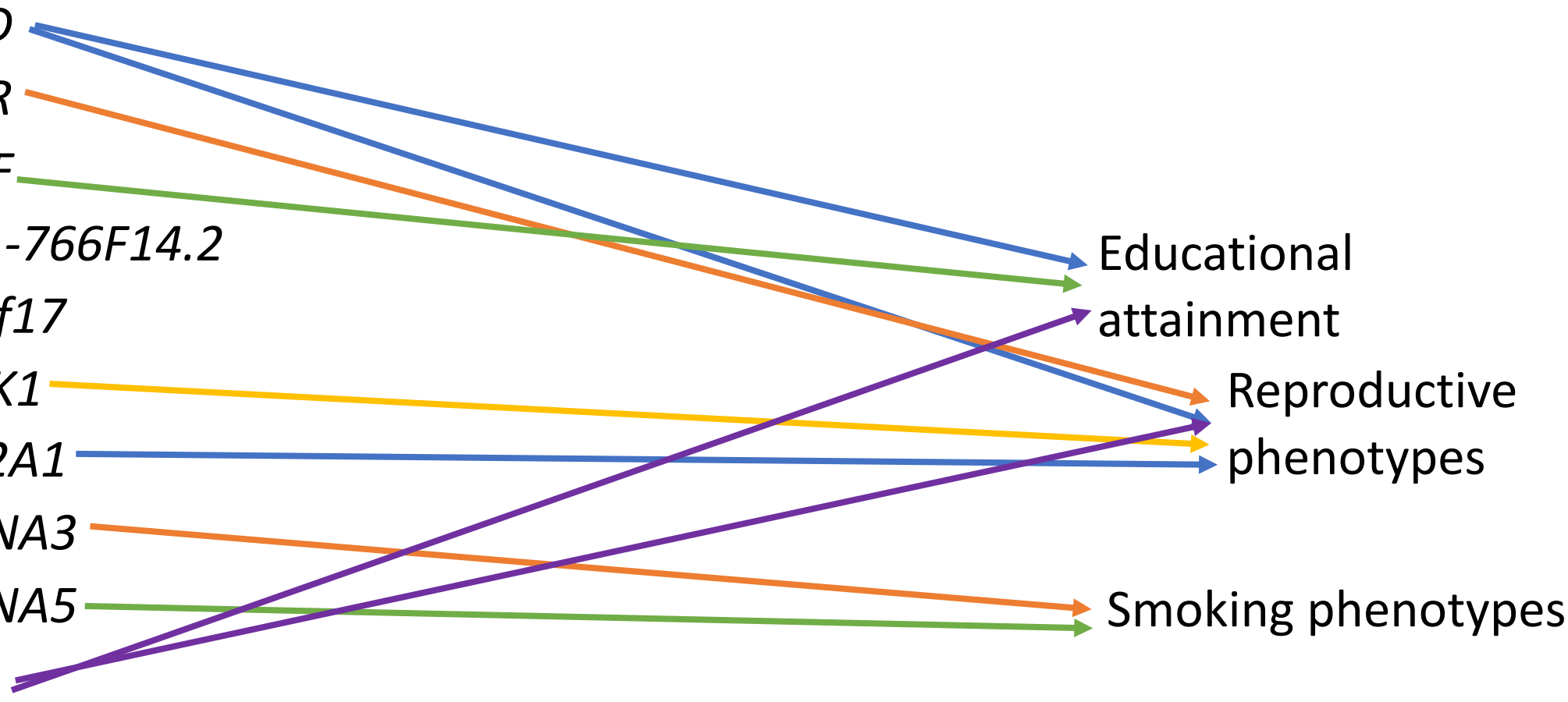
PheWAS



Top 10 genes

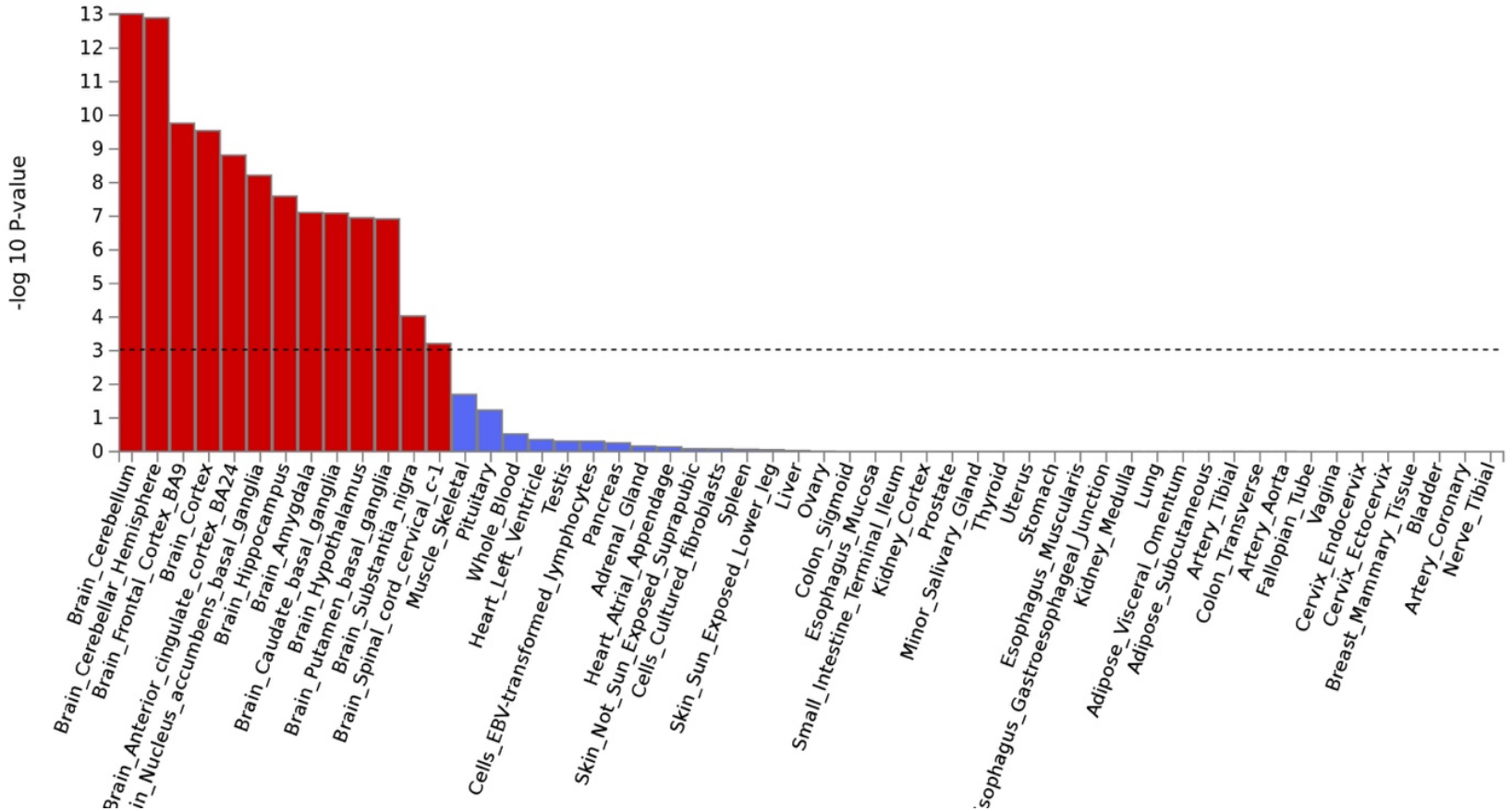
PheWAS

- *DPYD*
- *GCKR*
- *NGEF*
- *RP11-766F14.2*
- *C4orf17*
- *BANK1*
- *BTN2A1*
- *CHRNA3*
- *CHRNA5*
- *TCF4*



Gene property analysis implicates brain tissues

Results of MAGMA gene-property analysis of tissue-specific gene expression (using GTEx v8 data, 53 tissue types).



FUMA: Watanabe et al, 2017 (https://www.nature.com/articles/s41467-017-01261-5); MAGMA: de Leeuw et al., 2015 https://doi.org/10.1371/journal.pcbi.1004219

Pathway analysis

- Convergent SNPs:
  - “REACTOME_DEVELOPMENTAL_BIOLOGY”
    - Involved in developmental processes, including transcriptional regulation of pluripotent stem cells and the activation of HOX genes during differentiation
  - “KEGG_AXON_GUIDANCE”
    - Involves genes influential in axon guidance, a pivotal aspect of the development of neuronal connections
- SCZ-specific SNPs:
  - “KEGG_MAPK_SIGNALING_PATHWAY”
    - Highly conserved pathway that is involved in various cellular functions, including cell proliferation, differentiation and migration
- No significantly enriched pathways for divergent SNPs or AUD-specific variants

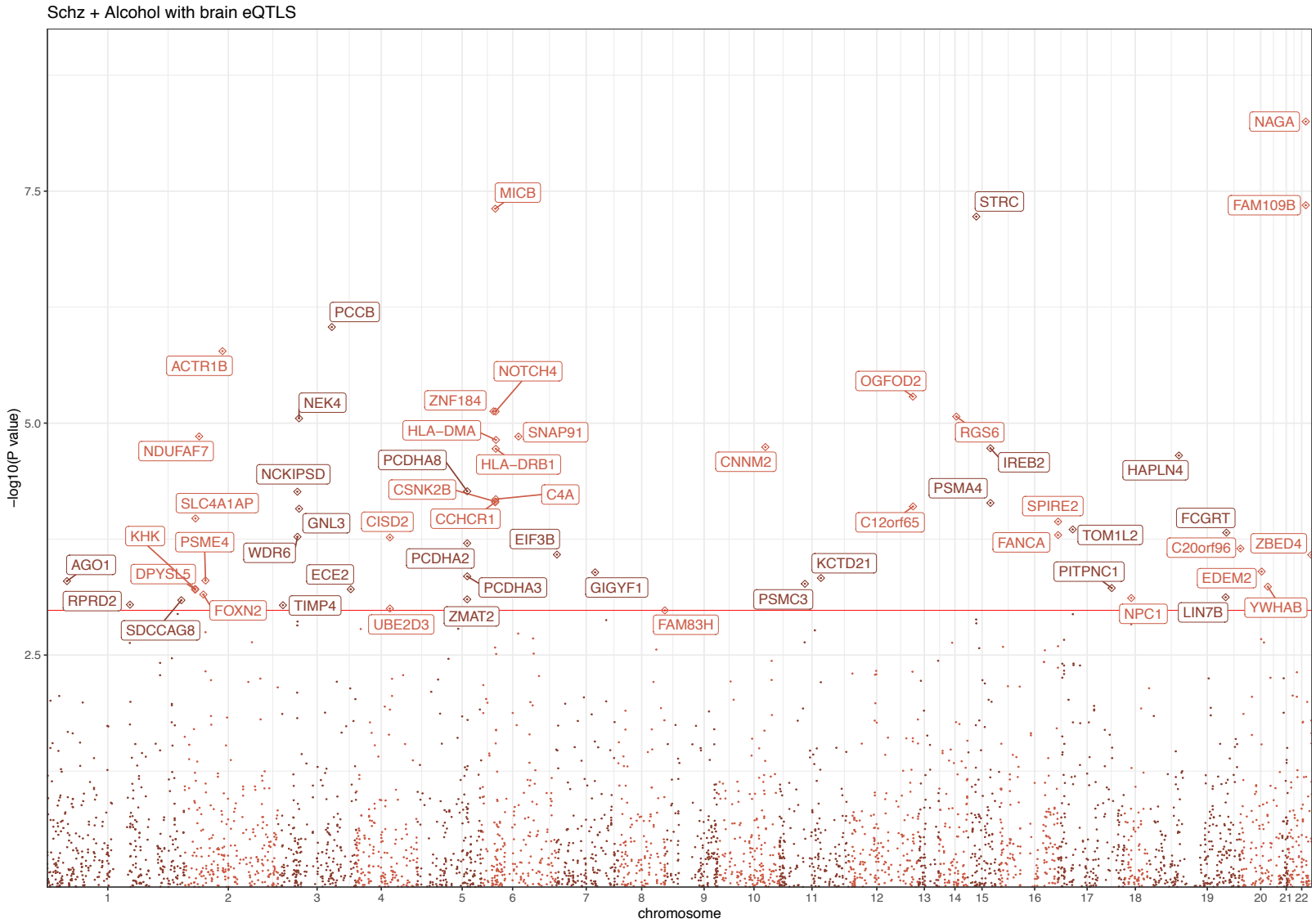
PASCAL; Lamparter et al., 2016; https://doi.org/10.1371/journal.pcbi.1004714

Linking cross-disorder genes to expression

(eQTL summary data)

- Used summary data-based Mendelian randomization (SMR) to test whether the effects of pleiotropic genes are mediated by gene expression in PFC
- Top genes implicated previously in SCZ, immunological, cognitive, and metabolic traits

Dr. Manav Kapoor



Linking cross-disorder genes to expression
(Differential gene expression)

- Differential gene expression data from SCZ (N = 258) vs. controls (N = 259), and AUD (N = 65) vs. controls (N = 73)

- Genes with convergent effects enriched in differentially expressed genes in prefrontal cortex tissue of SCZ vs. controls (435 genes significant for cross-disorder AND differentially expressed, p = 0.008)

African ancestry results

SCZ N = 10,070; AUD N = 62,447

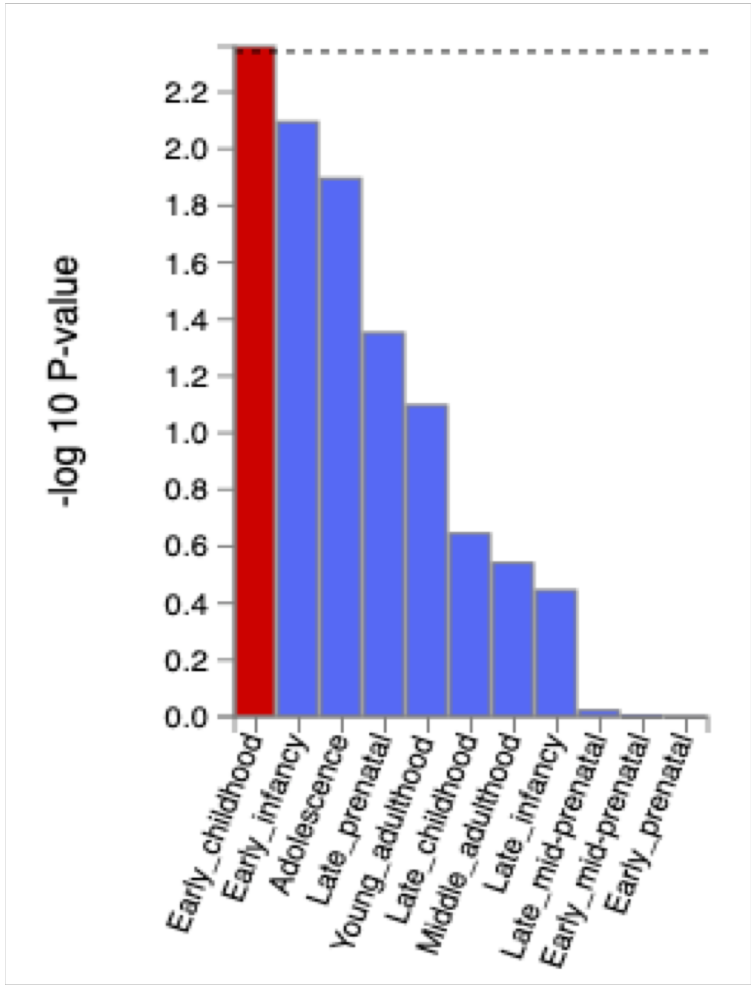
Summary statistic samples: African ancestry (AFR)

- **Schizophrenia:**
  - Genomic Psychiatry Cohort **(GPC)** GWAS (N_{case} = 6,152; $N_{control}$ = 3,918)
  - **0** independent genome-wide significant loci (Bigdeli et al., 2019)
- **Alcohol use disorder:**
  - **AUD** GWAS (total N_{case} = 20,258; $N_{control}$ = 42,189)
  - PGC Alcdep & MVP AUD
  - **1** independent genome-wide significant locus

- Due to lower power in the AFR samples, we focused on the overall set of pleiotropic cross-disorder variants (no separation into convergent/divergent)

African ancestry results

- One genome-wide significant locus for pleiotropic SNPs
- One significant gene, *ADH4*, in the gene-based analysis
- Significant enrichment for early childhood brain development (BrainSpan data)



African ancestry results

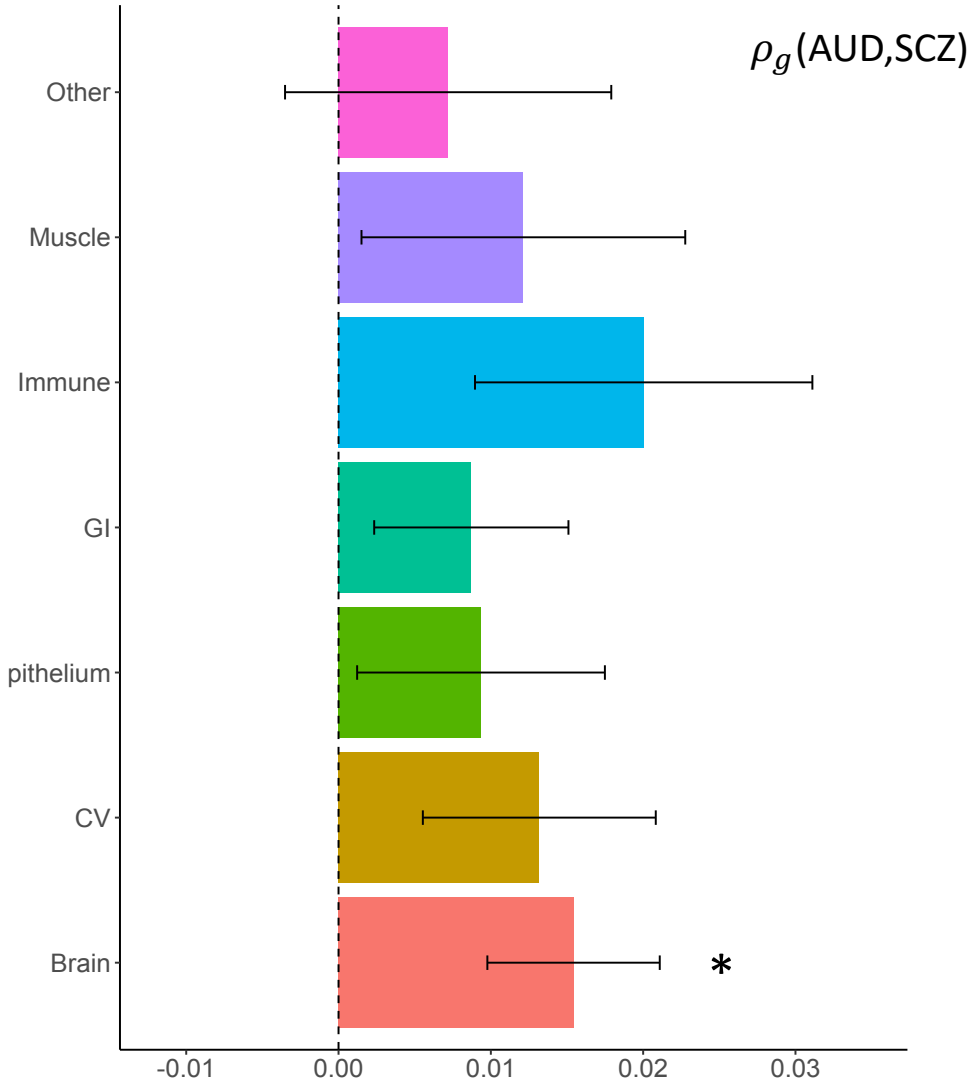
- Underpowered – seem to be driven by AUD sample
- Next steps:
  - Conduct trans-ancestral analysis?

Aim 3

Partition the genetic correlation into salient functional categories and to specific genomic regions.

- Genetic covariance analyzer (**GNOVA**) and bivariate heritability estimator from summary statistics (**rho-HESS**)

Genetic covariance stratified by broad tissue type



Genetic covariance stratified by functional vs. non-functional regions of the genome

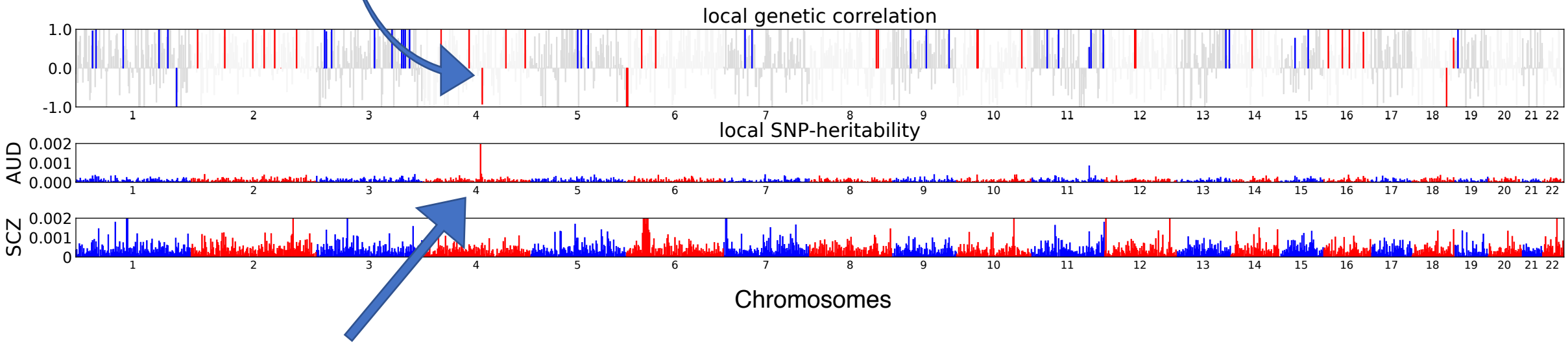
Genomic Annotations	rho (corrected for sample overlap)	SE	p-value (corrected)
Functional	0.028	0.005	7.67E-08
Non-functional	0.049	0.006	3.15E-16

Both categories are significant, but the concentration in non-functional regions is nearly twice that of functional regions

* Significant after multiple testing corrections (p = 0.004)

Lu et al., 2017 https://doi.org/10.1016/j.ajhg.2017.09.022

Significant negative correlation/covariance at regions adjacent to *ADH1B* (also identified in the ASSET analyses!)



Large proportion of h^2 for AUD at *ADH1B* locus

Shi et al., 2017 https://doi.org/10.1016/j.ajhg.2017.09.022

Aim 4

Contrast the genetic relationship between SCZ and **AUD** with that for SCZ and **typical alcohol intake**.

- Linkage disequilibrium score regression (**LDSC**)
- Associations between polygenic scores for SCZ and a range of alcohol-related phenotypes

Contrast with DPW

- Little prior evidence of genetic correlation between SCZ and drinks per week: $r_g = 0.01$, $p = 0.670$ (Liu et al. 2019)
- Plan:
  1. Calculate LDSC r_g of DPW and the newest SCZ3 sum stats
  2. Test whether r_g(DPW,SCZ) and r_g(AUD,SCZ) are significantly different

r_g(DPW, SCZ) = 0.097, SE = 0.023, p = 2.34e-5

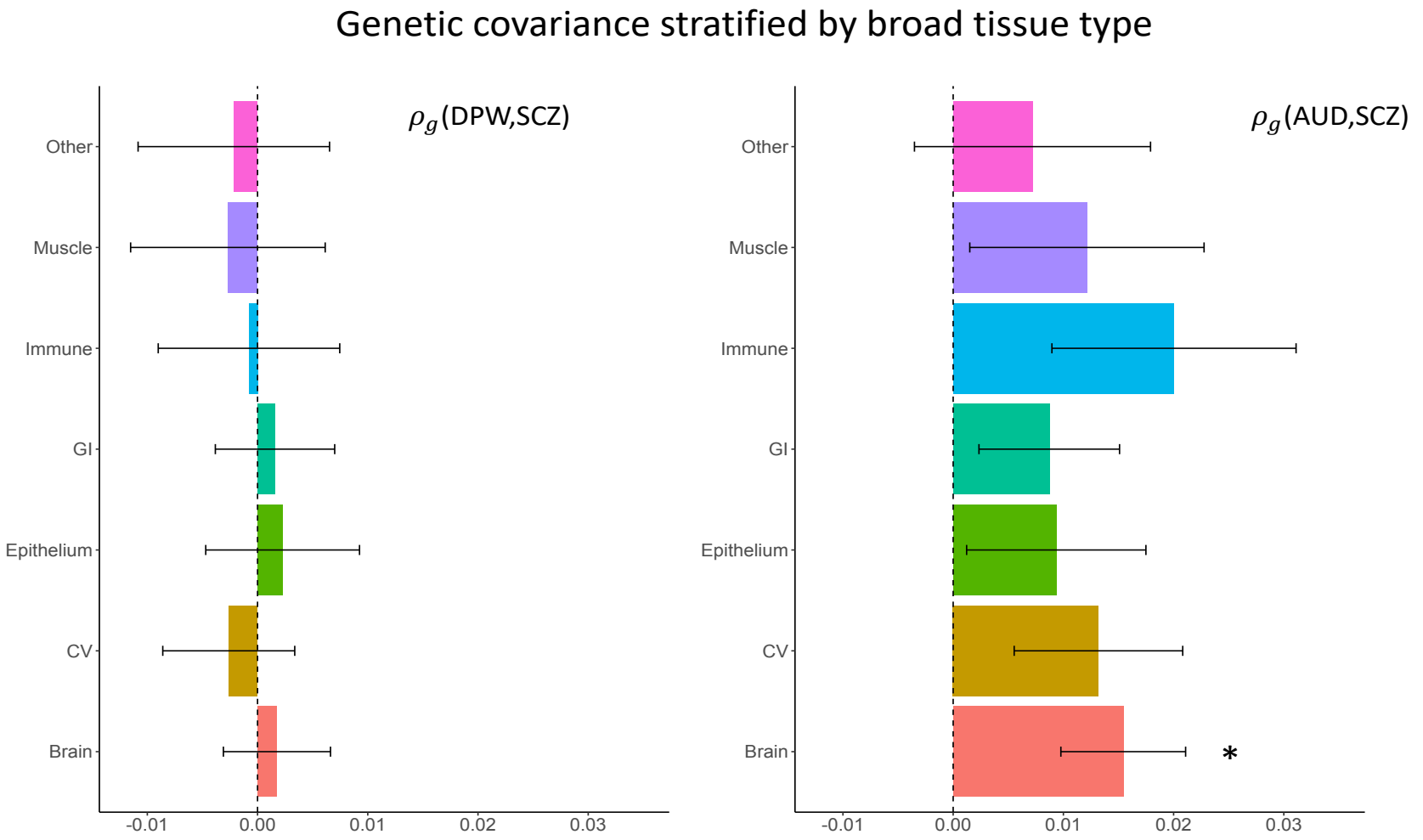
r_g(AUD, SCZ) = 0.375, SE = 0.035, p = 4.15e-27;

Z-score of the difference = 7.114, p = 1.13e-12

Genetic correlation between SCZ and AUD is *significantly larger* than the correlation between SCZ and DPW.

Bulik-Sullivan et al., 2015 https://doi.org/10.1038/ng.3211 & https://doi.org/10.1038/ng.3406

Genetic covariance between DPW and SCZ (left panel) and AUD and SCZ (right panel), stratified by broad tissue type.



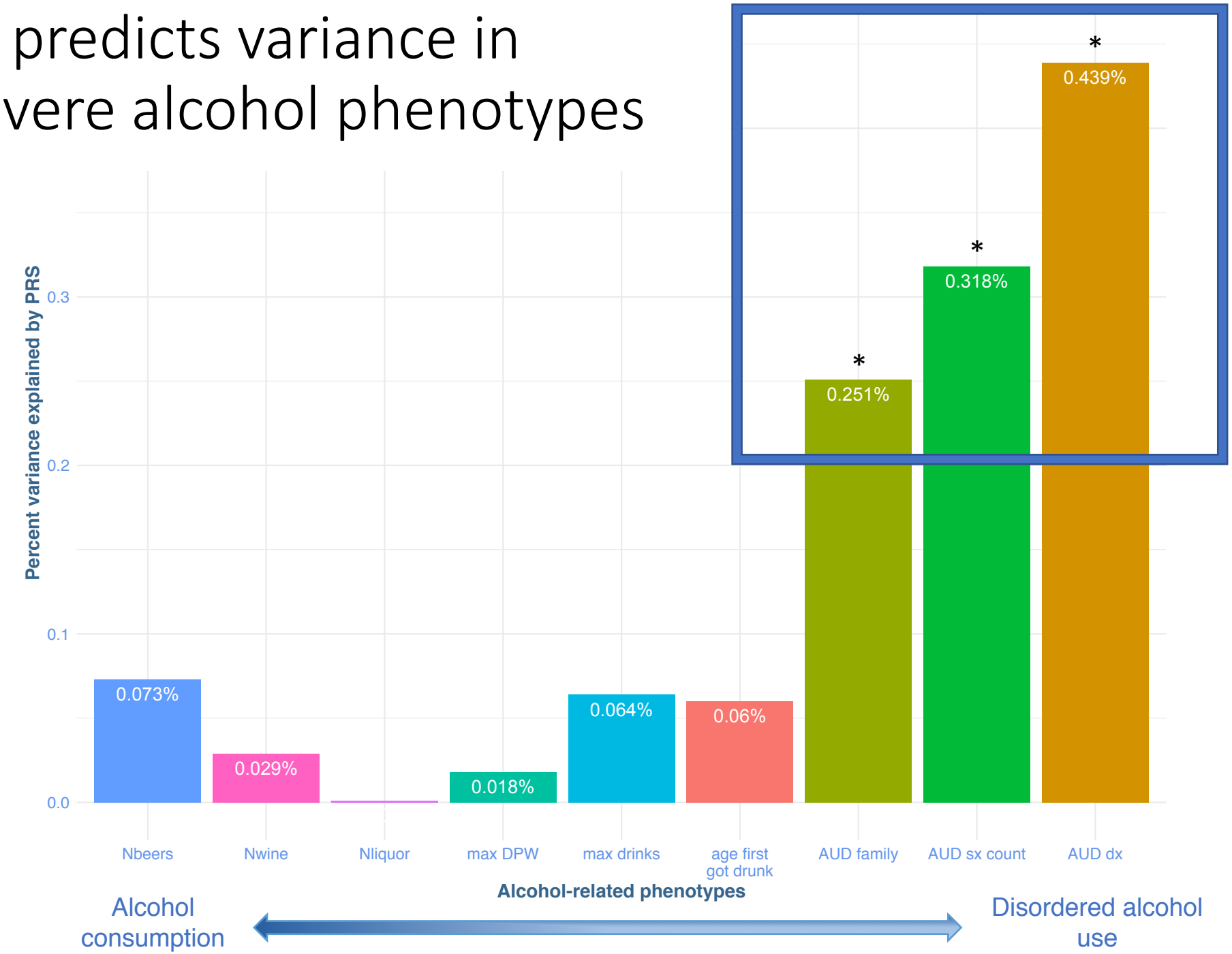
Polygenic associations across a range of alcohol phenotypes

- Wanted to test the association between polygenic scores for SCZ and a range of alcohol outcomes in an independent sample

- Created polygenic scores for SCZ using PRS-CS (https://github.com/getian107/PRScs)
  - Bayesian method that infers posterior SNP effect sizes under continuous shrinkage (CS) priors using GWAS summary statistics and an external LD reference panel

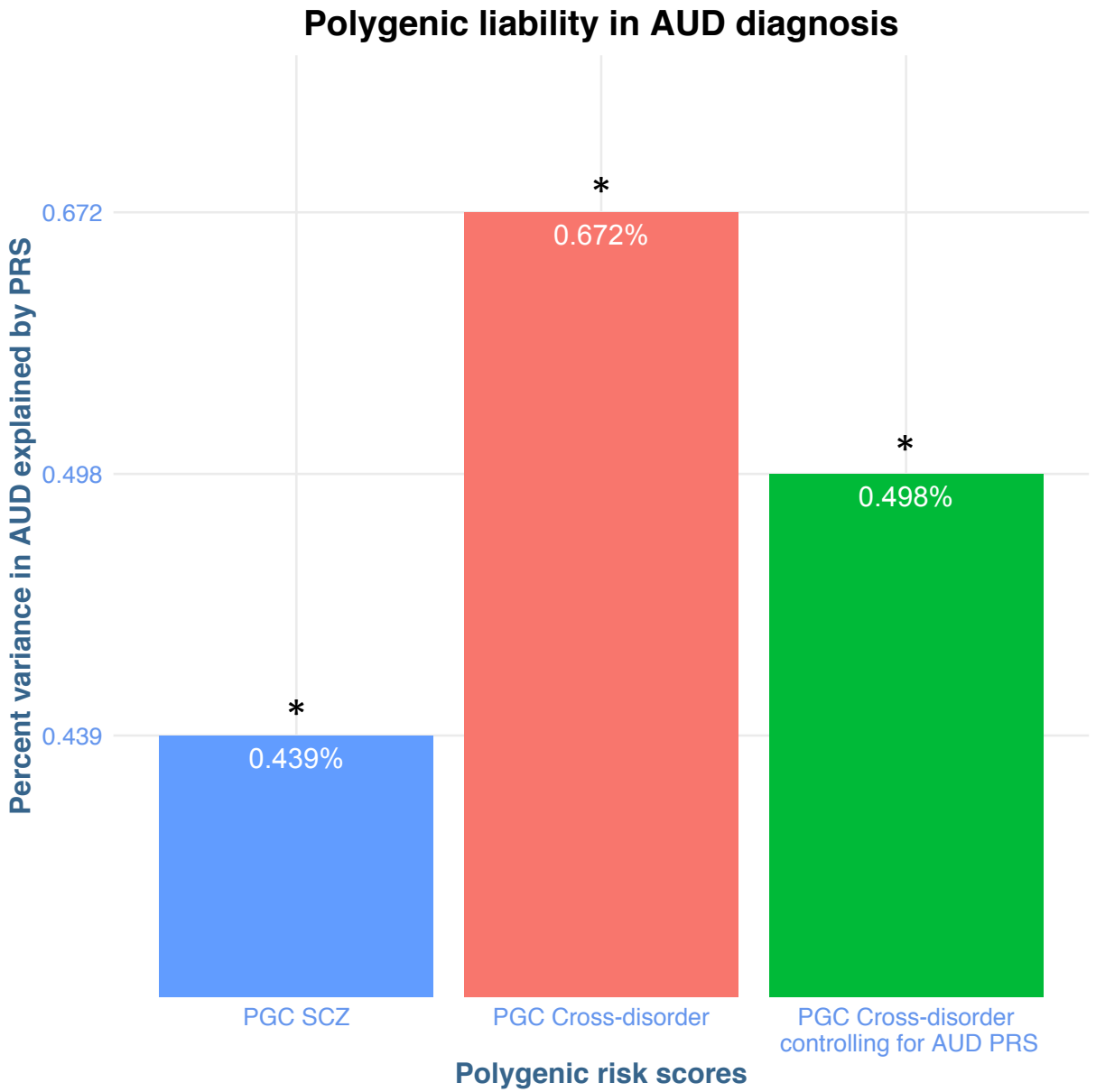
- Independent target sample: Collaborative Studies on the Genetics of Alcoholism (COGA)
  - Number of beers/wine/liquor a week, maximum drinks in 24 hours, maximum drinks per week, age first got drunk, mother or father with AUD, max AUD symptom count, AUD diagnosis

SCZ PRS predicts variance in more severe alcohol phenotypes

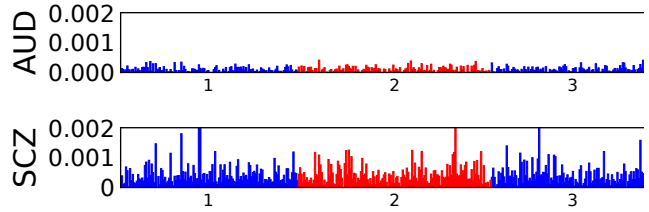


Significant after correction for multiple testing

- Compared with PRS created from the PGC's latest cross-disorder effort (SCZ, MDD, BPD, AN, ADHD, ASD, OCD, TD)
- Cross-disorder PRS out-performs SCZ, *even after controlling for a PRS of AUD*
- Suggests that variants pleiotropic for other disorders also overlap with AUD



Next steps and future directions



- AUD is highly polygenic trait – need larger sample sizes!
- Use more informative samples to disentangle possible confounders (how many SCZ cases also have AUD?)
- Would still like to know more about underlying biology
- Examine which clusters of psychiatric disorders (e.g., mood disorders) associate most strongly with AUD

Summary: Dissecting AUD-SCZ genetics

- No support for causal relationships
- Cross-disorder analyses show some differences in convergent and divergent SNPs
  - Pathways for convergent SNPs, possible enrichment in differentially expressed genes of SCZ vs control
  - Less obvious what divergent SNPs represent
  - African ancestry samples currently underpowered (but it's a start)
- Genetic Covariance
  - Enriched in genes expressed in brain tissues
  - SCZ appears to share less overlap with alcohol consumption than with disordered drinking
  - Somewhat replicated in polygenic score analyses in COGA

Next steps for me

- F32 (2018 – 2020): genetic overlap of AUD and SCZ
  - Identify convergent and divergent pleiotropy, partition the genetic covariance
  - Examine whether SCZ is associated more strongly with certain aspects of AUD
- Young Investigator Grant from the American Foundation for Suicide Prevention (2019 – 2021): genetic (and non-genetic) relationships between substance use, cognition, psychiatric disorders, and suicidal thoughts and behaviors (STB)
  - Use polygenic scores to dissect the contributions of negative affect, cognition, impulsivity, and substance use to increased risk of STB
  - Does family history of AUD increase risk of STB even after accounting for polygenic liability for AUD?
- K01: examine genetic overlap of cannabis use/use disorder and SCZ (A1 submission due July 2020)
  - Evidence of causality? Pleiotropy?
  - Integrate multi-omics data across model organisms to bolster our findings, identify genes with greatest potential for functional follow-up studies

Washington University in St. Louis
School of Medicine

Thanks!

PGC
Psychiatric Genomics Consortium

- PGC SUD working group
  - **Raymond Walters, Renato Polimanti, Alex Hatoum, Hang Zhou, Jeanette McClintick, Dongbing Lai**
  - PIs: **Arpana Agrawal, Howard Edenberg, Joel Gelernter**
- PGC SCZ working group
  - Mick O'Donovan, James Walters
- Million Veteran Program, Genomic Psychiatry Cohort, GSCAN
- Manav Kapoor, Tim Bigdeli, Sarah Hartz, Ayman Fanous, Jacquelyn Meyers, Stephan Ripke, Roseann Peterson
- F32 co-mentors: Arpana Agrawal and Elliot Nelson
- Funding from NIAAA (F32AA027435) and NIDA/NIMH (U01MH109532 to PGC)

NIH National Institute on Drug Abuse

NIH National Institute on Alcohol Abuse and Alcoholism

NIH National Institute of Mental Health