Bayesian Genome-wide TWAS method integrating both cis- and trans- eQTL with GWAS summary statistics

Jingjing Yang, PhD

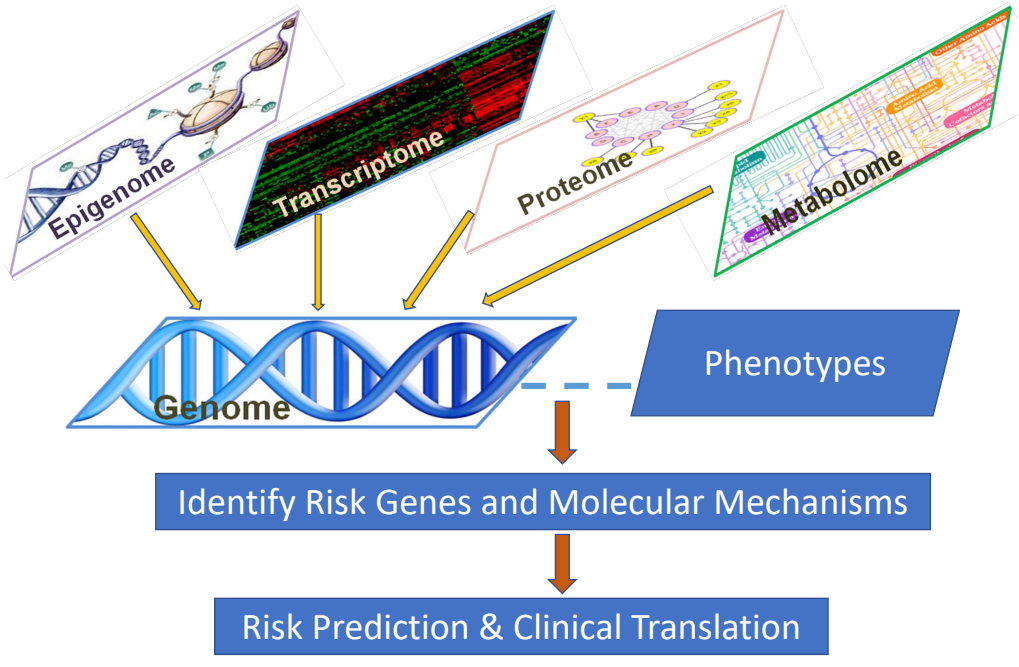
EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

CCQG
CENTER FOR COMPUTATIONAL
AND QUANTITATIVE GENETICS

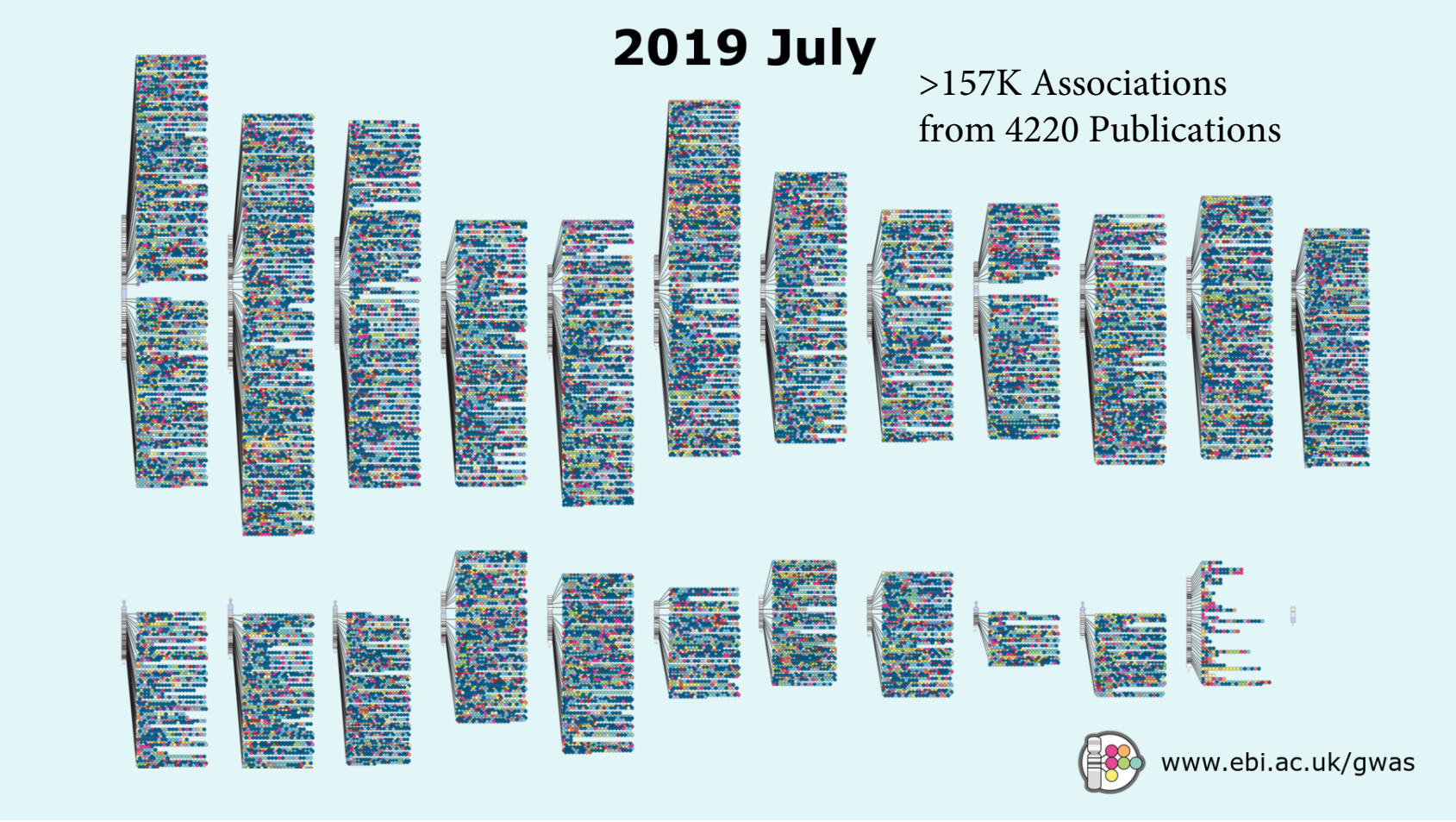
Outline

Genetic Etiology of Complex Diseases

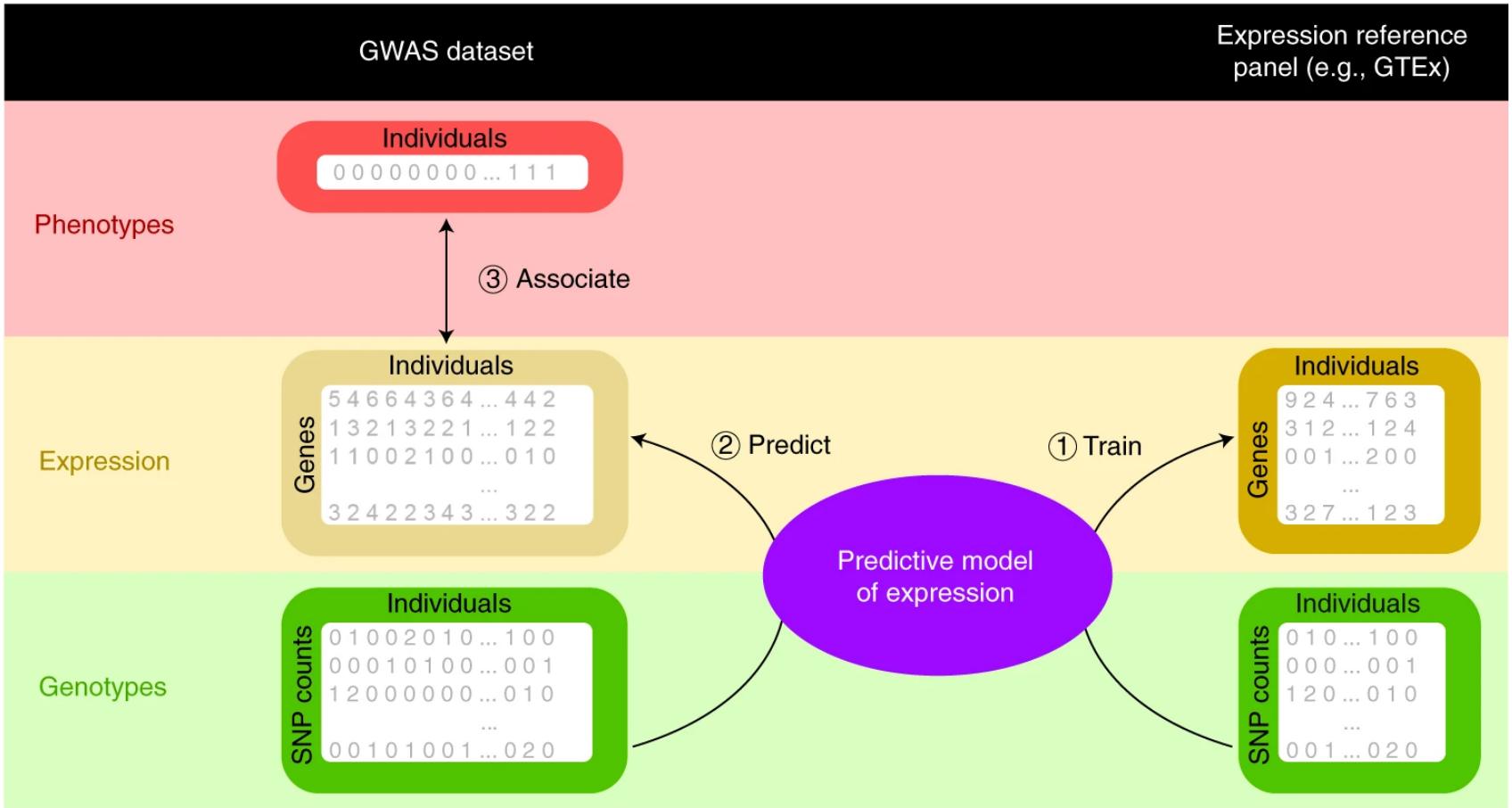
- Polygenic with low penetrance by individual genes
- Affected by multi-layers of Omics data
- Largely unknown genomic etiology



GWAS Findings



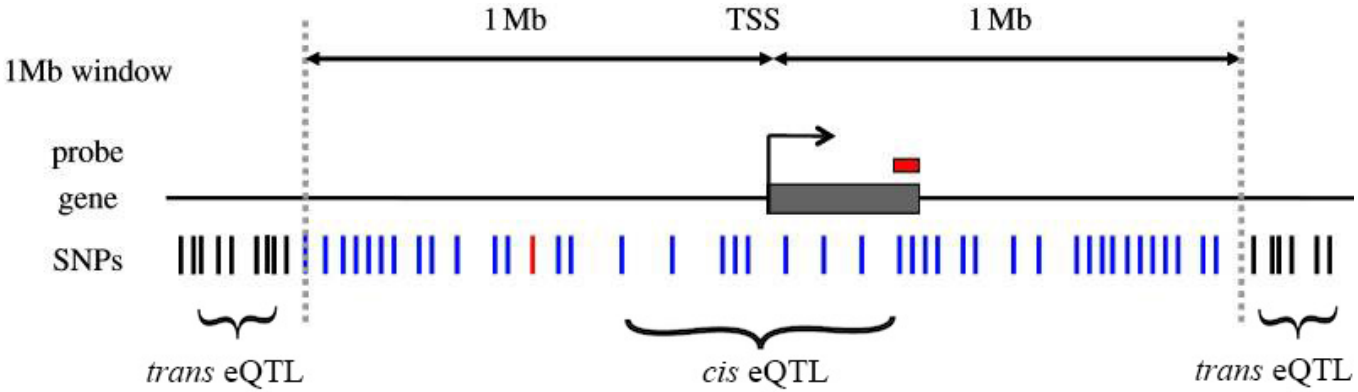
Transcriptome-wide Association Study (TWAS)



[Wainberg M. et. al. Nat. Genetics. 2019.]

Existing TWAS Tools

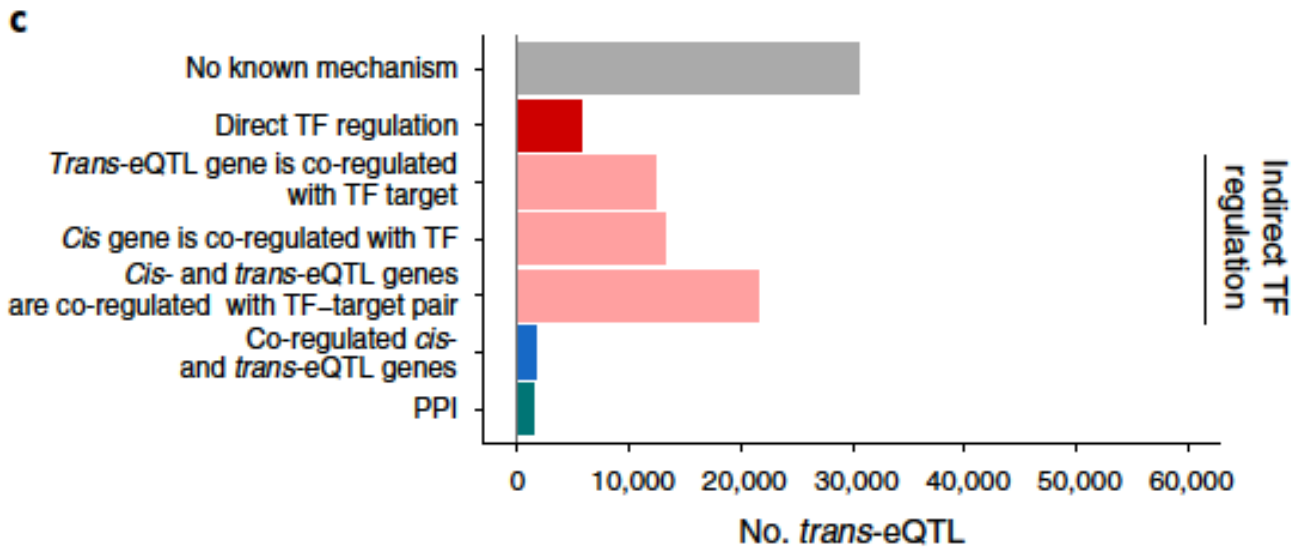
- Tools for TWAS:
  - PrediXcan. *[Gamazon et al., Nat. Genetics. 2015]*
  - FUSION. *[Gusev et al., Nat. Genetics. 2016]*
  - TIGAR. *[Nagpal et al., AJHG. 2019]*
- Caveat: utilize only *cis*-eQTL, defined by proximity to gene



Variants around a transcription starting site, *cis* or *trans* acting. *[Nica & Dermitzakis, Philos Trans R Soc Lond B Biol Sci. 2013.]*

Importance of *trans*-eQTL

- Both *cis* and *trans*-eQTL contribute to expression heritability. *[Gusev et al., Nat. Genetics. 2016]*.
- In whole blood tissue, >30% genes have significant *trans*-eQTL. *[Lloyd-Jones et al., AJHG, 2017]*.
- Distal *trans*-eQTL were detected for 37% of 10,317 trait-associated GWAS signals in eQTLGen Consortium of 31,684 blood samples, primarily working through regulation by transcription factors. *[Vosa U. et al., Nat. Genetics. 2021]*.



Bayesian Variable Selection Regression (BVSR)

- Consider quantitative gene expression trait $\boldsymbol{T}_g$ and "spike-and-slab" prior for eQTL effect size w_i

$$\boldsymbol{T}_g = \boldsymbol{X}\boldsymbol{w} + \boldsymbol{\varepsilon}$$
$$w_i \sim \pi_q N(0, \sigma_\varepsilon^2 \sigma_q^2) + (1 - \pi_q)\delta_0(w_i)$$
$$\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$$

- Consider an indicator variable γ_i per SNP

$$\gamma_i \sim Bernoulli(\pi_q) \text{ such that } w_i \sim \begin{cases} N(0, \sigma_\varepsilon^2 \sigma_q^2) & \text{if } \gamma_i = 1 \\ 0 & \text{if } \gamma_i = 0 \end{cases}$$

  for variant i and cis or $trans$ assignment q.
- Allow respective prior distribution for effect sizes of cis and $trans$ eQTL.

Bayesian Genome-Wide TWAS (BGW-TWAS)

$$\mathbf{T}_g = \mathbf{X}\mathbf{w} + \boldsymbol{\varepsilon}$$

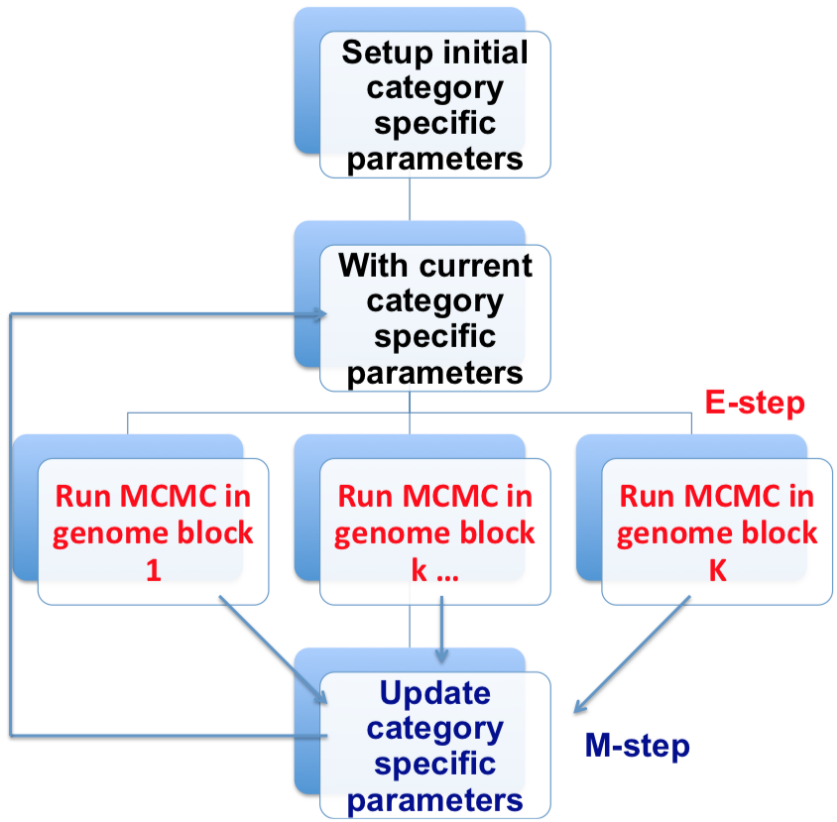
$$\widehat{GReX}_g = \sum_{i=1}^{m} \hat{\gamma}_i \hat{w}_i x_i^*$$

$$E[g(\mathbf{Y}_{pheno}|\mathbf{X}, \hat{\mathbf{w}}, \hat{\gamma})] = \beta \widehat{GReX}_g = \beta \left(\sum_{i=1}^{m} \hat{\gamma}_i \hat{w}_i x_i^* \right)$$

- *Posterior Causal Probability* (PP): $\hat{\gamma}_i = E[\gamma_i] = Prob(\gamma_i = 1)$
- $H_0 : \beta = 0$

Estimate $\mathbf{w}$ and $\mathbf{E}[\gamma]$

1. Employ EM-MCMC algorithm *[Yang et al., AJHG 2017]*
2. Use pre-calculated summary statistics from single variant model, $T_g = \boldsymbol{x}_i w_i + \varepsilon$
3. Pre-calculate LD correlation coefficients
4. Parallelize over segmented genome blocks



[*Yang et al., AJHG 2017*]

Segment and Prune Genome Blocks

- Genome-wide SNPs segmented into blocks with $\sim$ 3,000 - 10,000 variants based on block-wise LD structure
- Prune to genome blocks that:
  - have variants in cis
  - have potential marginally significant (p-value $< 10^{-5}$) variant by single variant tests
  - up to 50 blocks, ranked by top significant p-values by single variant tests

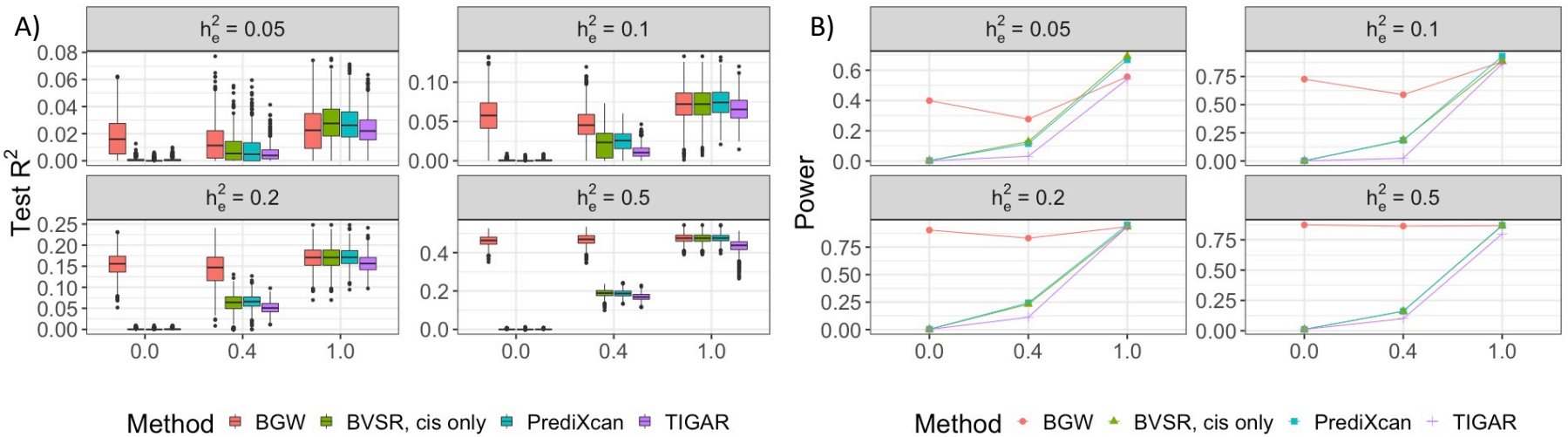
Simulation Study Design

- Use real genotype data of an arbitrarily selected genome region (22,641 common variants - 1,269 cis and 21,372 $trans$) of 1,708 ROS/MAP samples
- Simulate quantitative gene expression traits from selected true eQTL
- Train **BGW** (BVSR), **PrediXcan** (Elastic-Net), and **TIGAR** (non-parametric Bayesian Dirichlet process regression) gene expression imputation models using 499 training samples
- Predict $GReX$ values and conduct gene-based association tests (TWAS) using 1,209 test samples

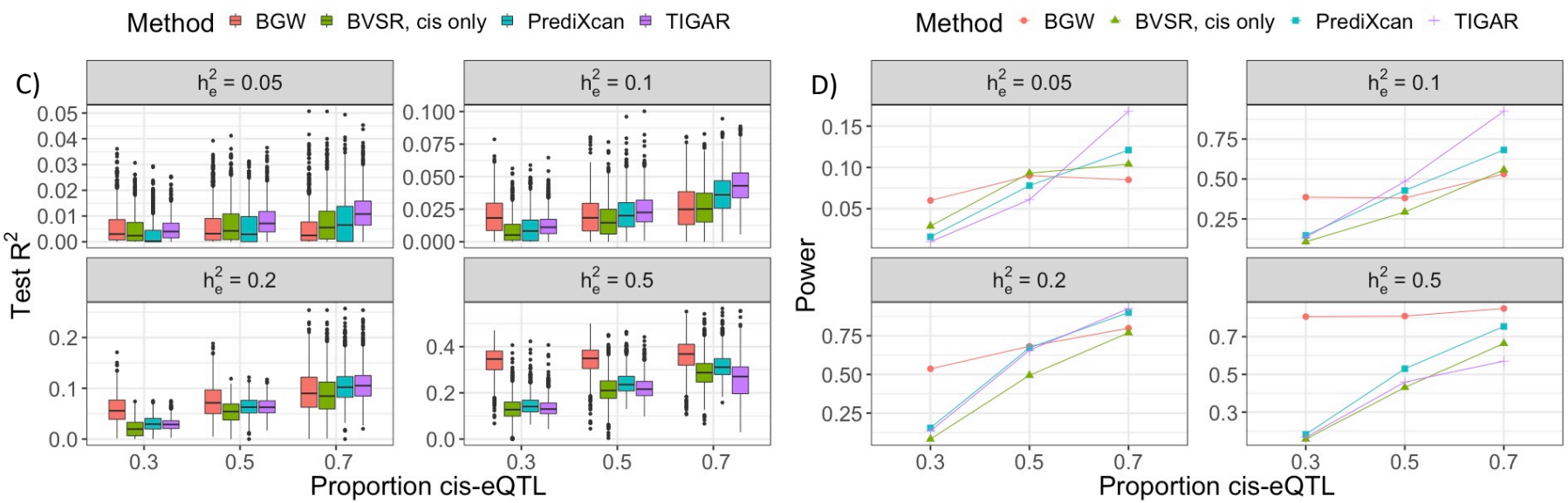
Simulation Study Design

- Consider the following scenarios:
  - 5 true causal eQTL and various proportions of cis variants, $(0\%, 40\%, 100\%)$
  - 22 true causal eQTL and various proportions of cis variants, $(30\%, 50\%, 70\%)$
  - Various heritability for quantitative gene expression traits $h_e^2 = (0.05, 0.1, 0.2, 0.5)$
- Repeat simulation for 1,000 times to compare both imputation R^2 and TWAS power per scenario

With 5 True Causal eQTL



With 22 True Causal eQTL



Average sums of posterior probabilities of having non-zero eQTL effect sizes, for simulation scenarios with 3/5 and 11/22 true trans-eQTL

Gene Expression Heritability		Sum of Posterior Probabilities		
		Whole Genome	Cis-Region	Trans-Region
5 True Causal eQTL	0.05	0.79	0.46	0.33
	0.1	2.28	1.13	1.15
	0.2	3.72	1.44	2.28
	0.5	4.91	1.56	3.35
22 True Causal eQTL	0.05	0.05	0.02	0.03
	0.1	0.21	0.11	0.10
	0.2	1.43	0.87	0.56
	0.5	6.46	3.89	2.57

Application Studies of Alzheimer's Dementia (AD)

ROS/MAP

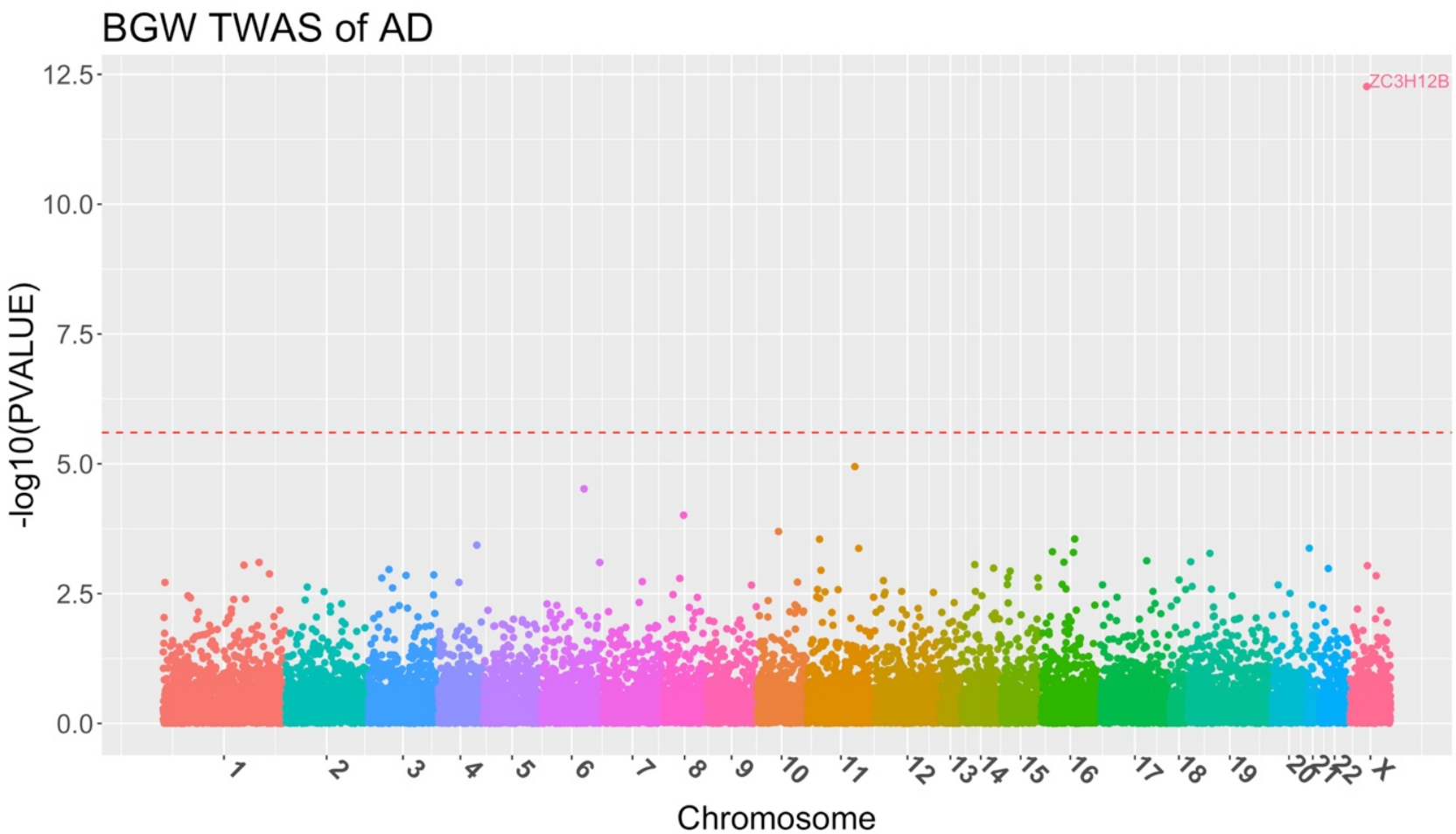
- Training data: 499 subjects with both genotype and transcriptomic data (14,156 genes)
- TWAS data: 2,093 individuals with profiled genotype data
- Considered phenotypes of AD clinical diagnosis, β-Amyloid, Tangles, Global AD pathology
- TWAS adjusted for covariates age at death, sex, smoking, ROS or MAP study, education level, top 3 PCs

Mayo Clinic LOAD GWAS Data

- TWAS data: 2,099 individuals with profiled genotype data
- Considered phenotypes of AD clinical diagnosis
- TWAS adjusted for covariates age, sex, top 3 PCs

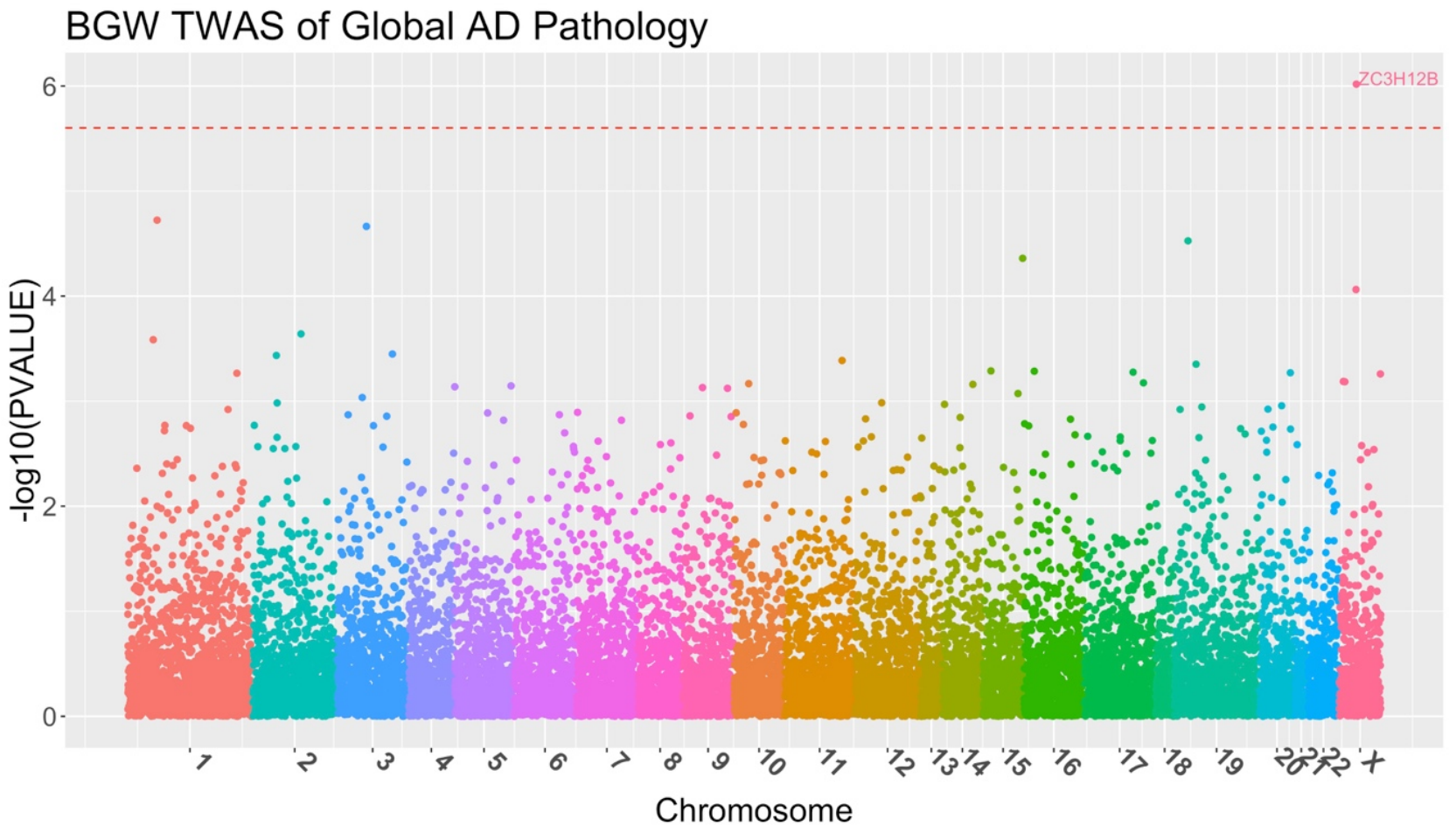
BGW TWAS of AD Clinical Diagnosis

A)



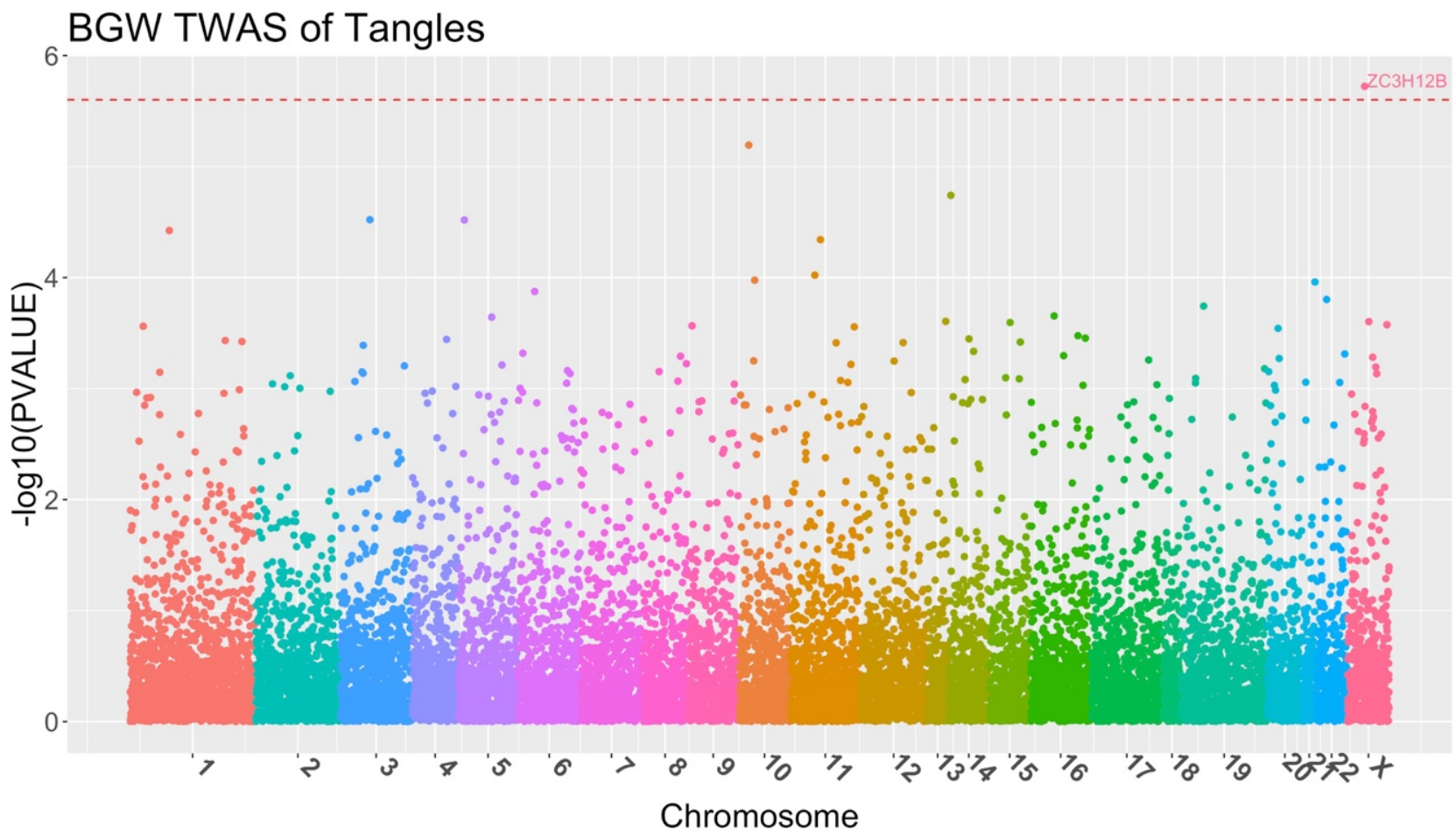
BGW TWAS of Global Pathology

B)

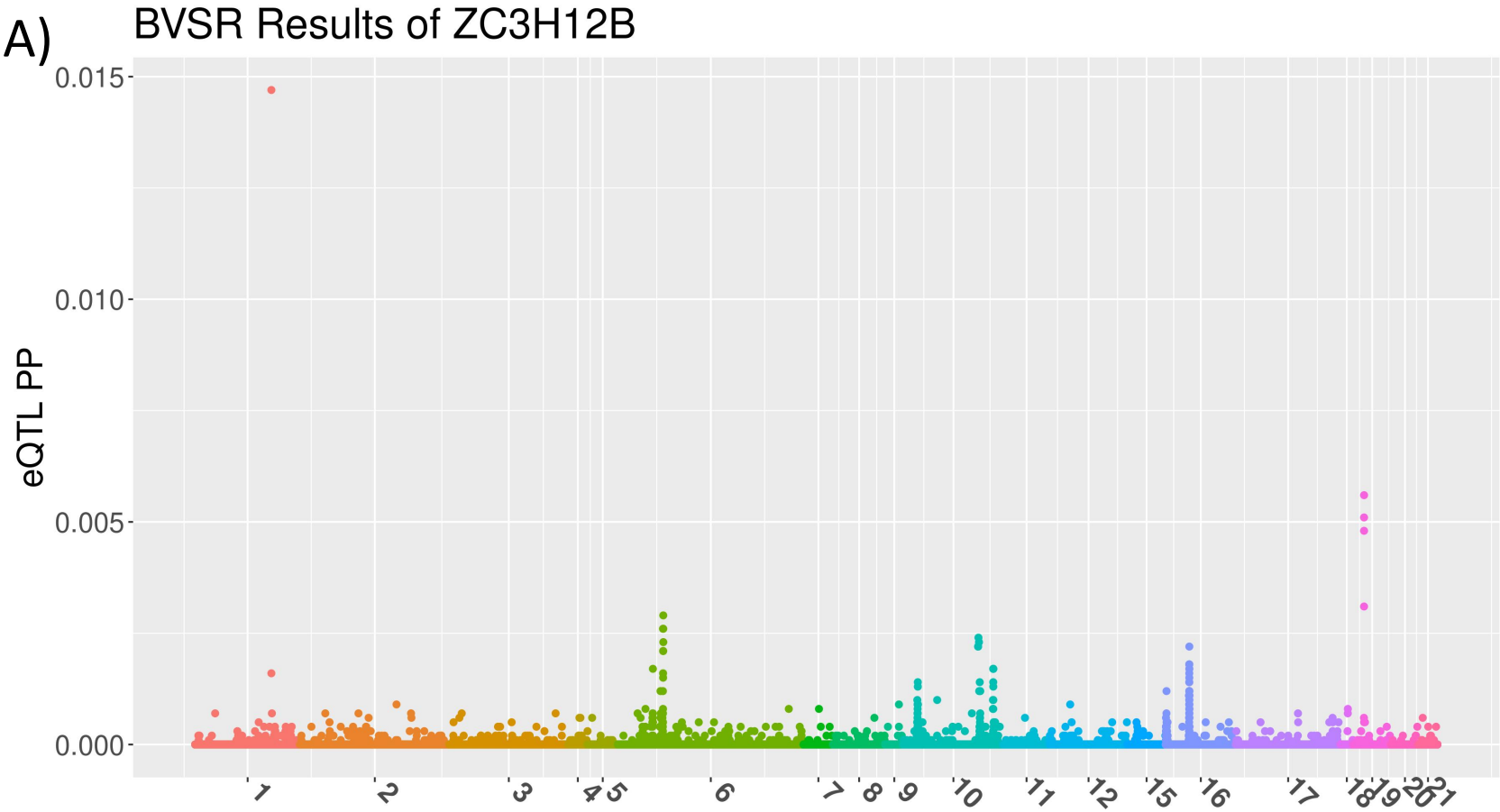


BGW TWAS of Tangles

A)



BVSR Results for Gene *ZC3H12B*



Top Five eQTL for Gene *ZC3H12B*

Table 2. Trans-eQTL with top five PP > 0.003 for gene ZC3H12B.

CHR	POS	rsID	Function	MAF	PP	w	p-value
1	159,135,282	rs3026946	Intergenic	0.213	0.0147	-0.071	6.25×10^{-7}
19	45,422,160	rs12721051	3' UTR (APOC1)	0.161	0.0031	0.071	3.94×10^{-6}
19	45,422,846	rs56131196	Downstream (APOC1)	0.173	0.0048	0.069	1.75×10^{-6}
19	45,422,946	rs4420638	Downstream (APOC1)	0.173	0.0051	0.068	1.77×10^{-6}
19	45,424,514	rs157592	Regulatory Region (APOC1)	0.181	0.0056	0.075	1.43×10^{-6}

- *rs12721051* was identified as a GWAS signal of total cholesterol levels
- *rs4420638* is in LD with the *APOE E4* allele (*rs429358*) and was identified to be a GWAS signal of blood lipids
- *rs56131196* and *rs157592* were identified as GWAS signals of AD and independent of *APOE-E4*

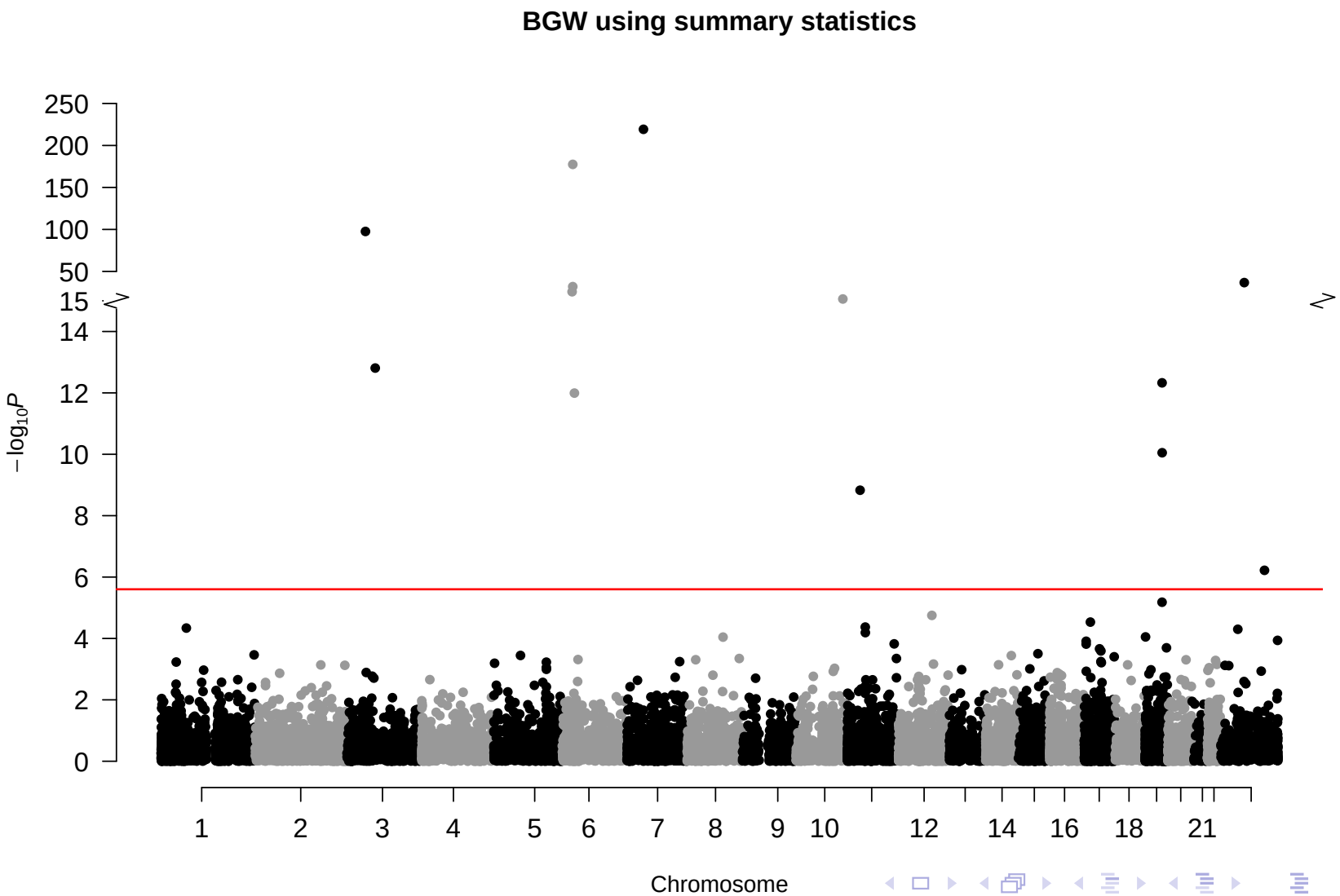
Average sums of posterior probabilities in real ROS/MAP studies.

Train R^2	Sum of Posterior Inclusion Probabilities			Number of Genes
	Whole Genome	Cis- Region	Trans-Region	
(0, 0.05)	6.63	0.60	6.23	1,504
(0.05, 0.1)	1.45	0.13	1.32	1,964
(0.1, 0.25)	2.00	0.17	1.83	6,617
(0.25, 0.5)	2.66	0.22	2.44	3,224
(0.5, 1)	3.04	0.31	2.73	474

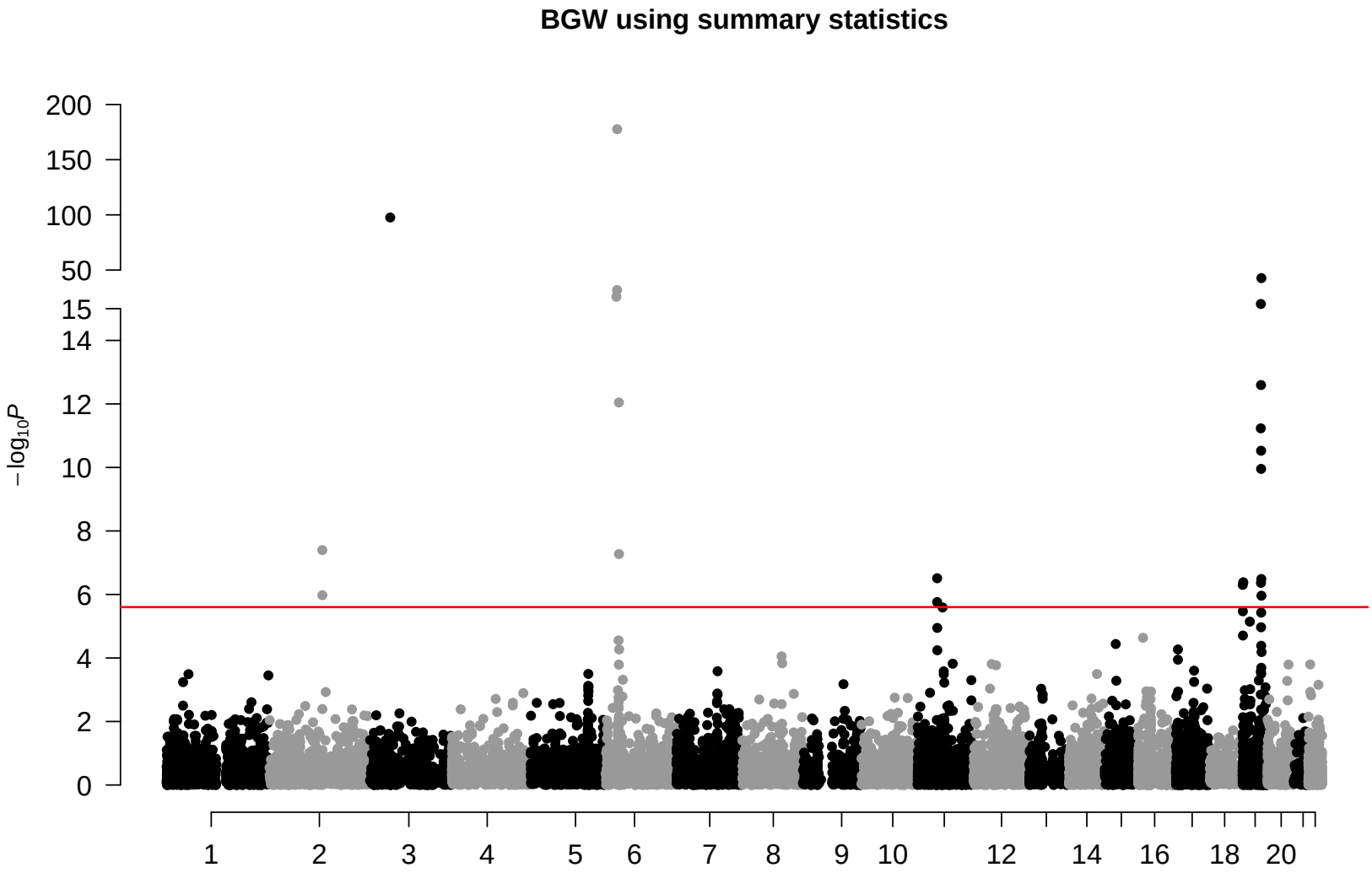
TWAS using IGAP summary-level GWAS data

- GWAS summary statistics for studying AD by International Genomics of Alzheimer's Project (IGAP)
- Generated by meta-analysis of four consortia ($\sim$ 17K cases and $\sim$ 37K controles; European)
  - Alzheimer's Disease Genetic Consortium (ADGC)
  - Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium
  - European Alzheimer's Disease Initiative (EADI)
  - Genetic and Environmental Risk in Alzheimer's Disease (GERAD) Consortium
- Use S-PrediXcan burden test statistic, with variant weights derived by BGW, PrediXcan, and TIGAR.

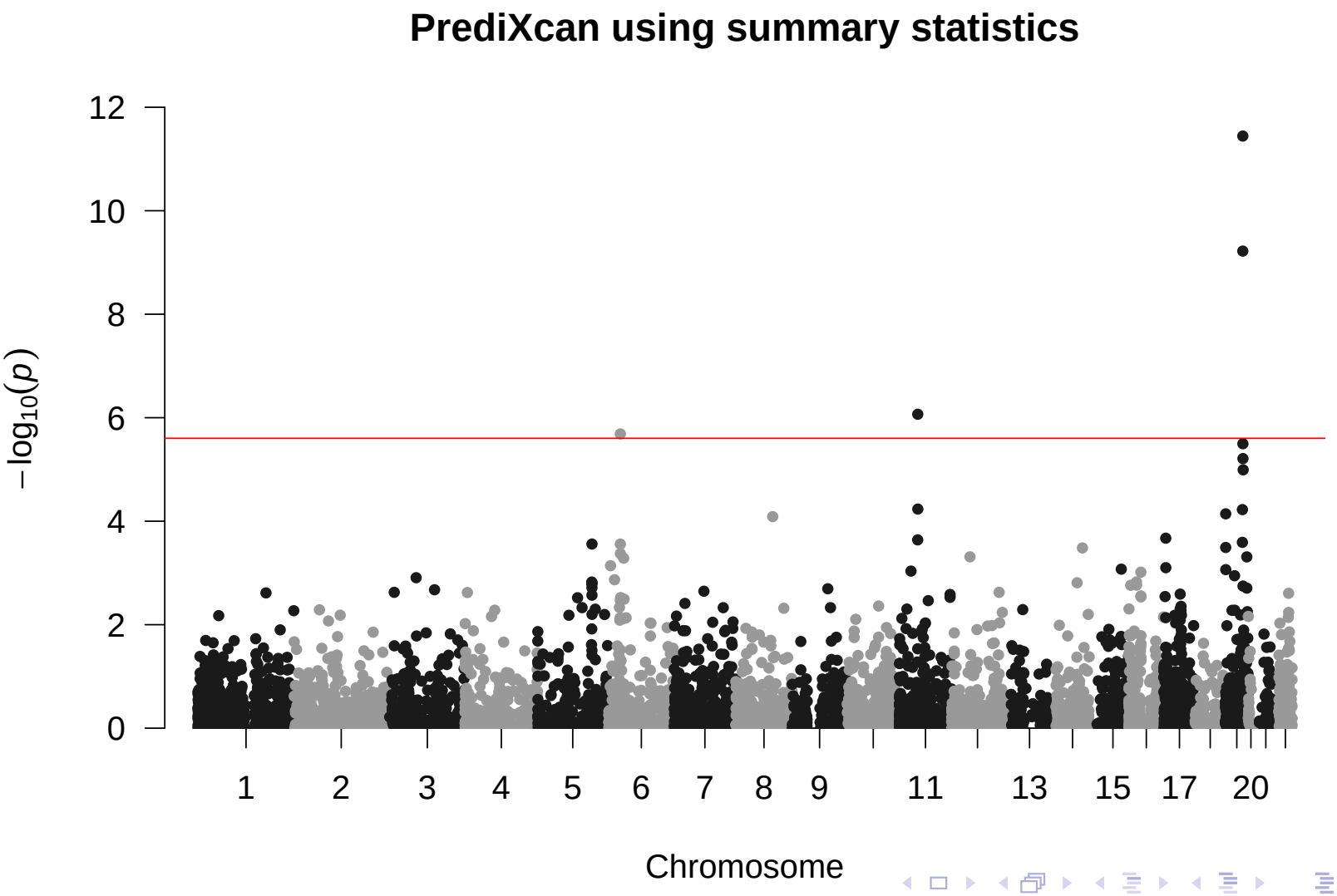
BGW-TWAS


BGW using summary statistics
250
200
150
100
50
15
14
12
10
8
6
4
2
0
$-\log_{10}P$
1
2
3
4
5
6
7
8
9
10
12
14
16
18
21
Chromosome

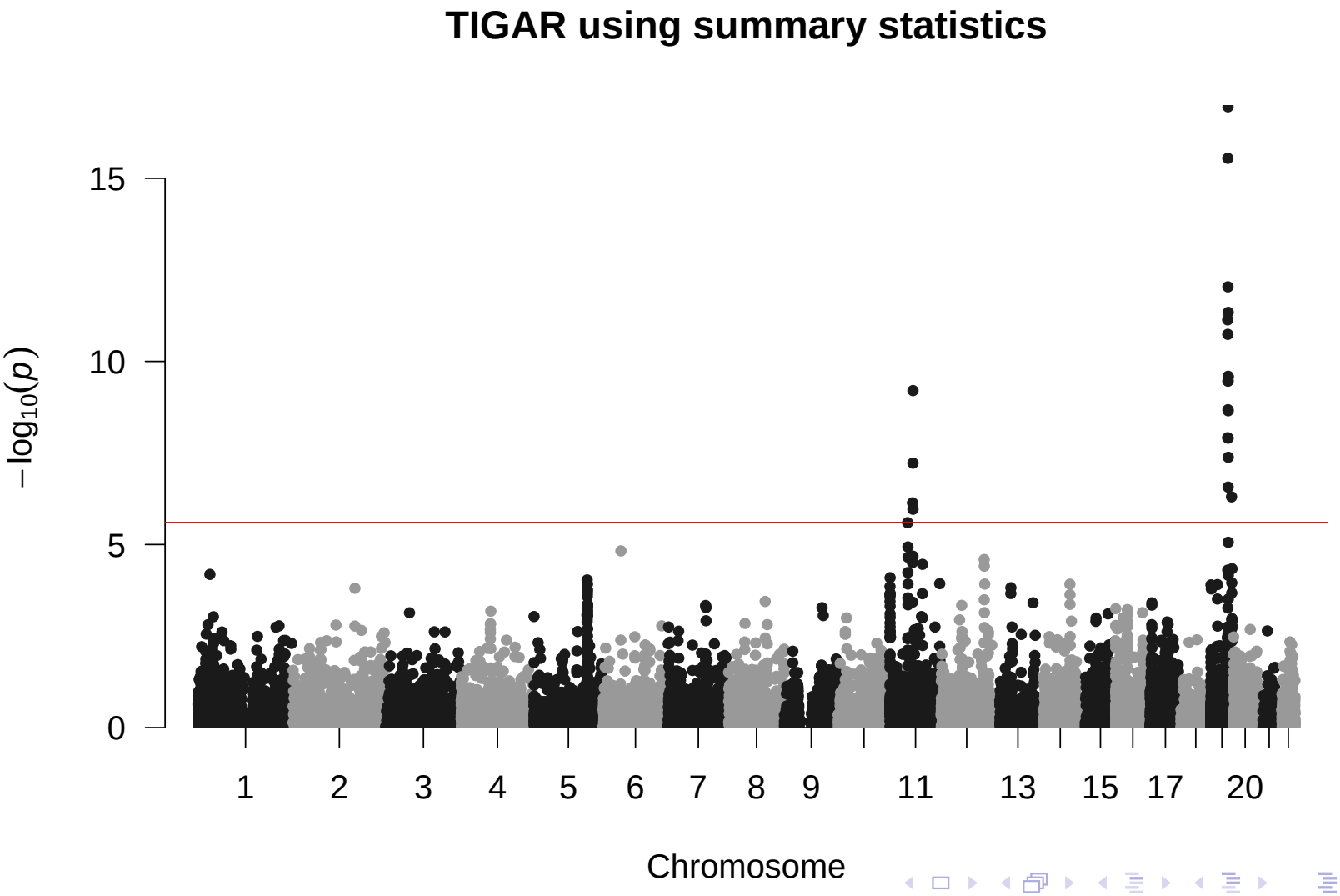
Using BVSR cis-eQTL estimates only



S-PrediXcan


PrediXcan using summary statistics
12
10
8
6
4
2
0
$-\log_{10}(p)$
1
2
3
4
5
6
7
8
9
11
13
15
17
20
Chromosome

TIGAR


TIGAR using summary statistics
15
10
5
0
$-\log_{10}(p)$
1
2
3
4
5
6
7
8
9
11
13
15
17
20
Chromosome

Significant TWAS genes by BGW-TWAS

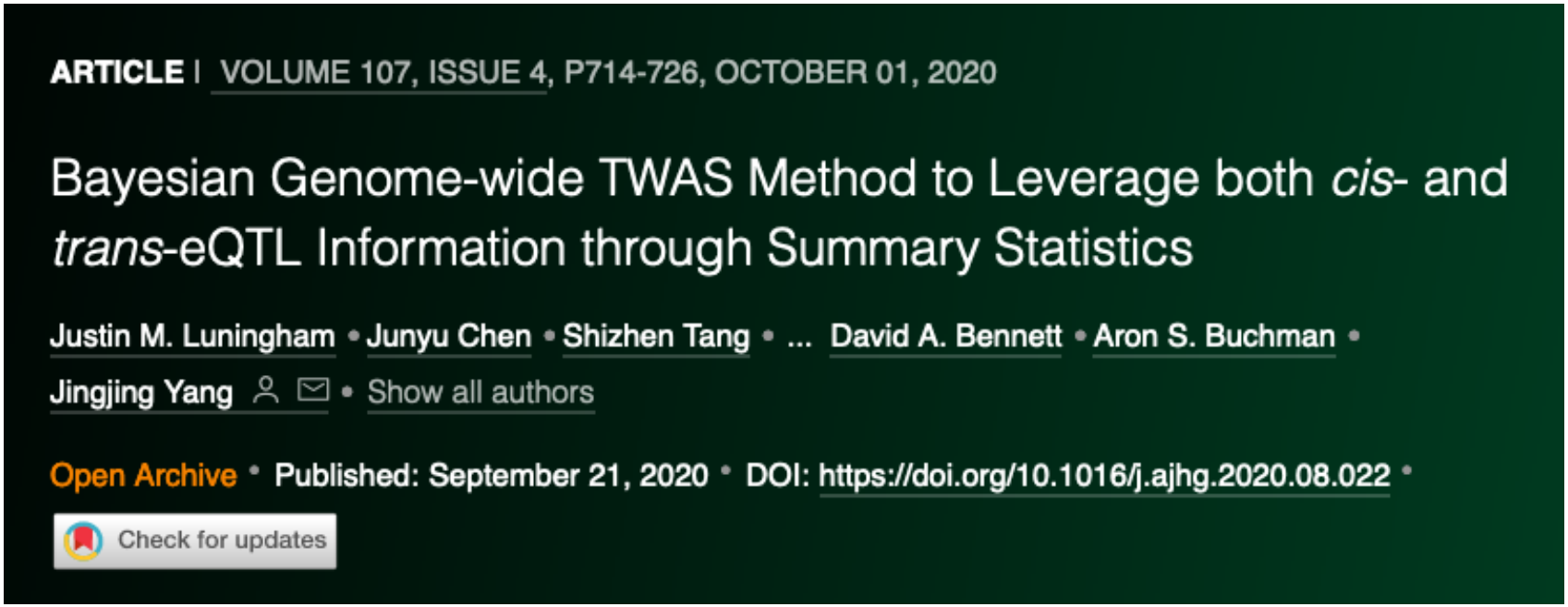
Gene	CHR	Position	TWAS P-VALUE			
			BGW-TWAS	BVSR cis-eQTL	PrediXcan	TIGAR
GPX1[a]	3	49,394,608	2.45×10^{-98}	2.45×10^{-98}	-	3.15×10^{-1}
FAM86DP	3	75,484,261	1.55×10^{-13}	4.81×10^{-1}	5.38×10^{-1}	9.63×10^{-1}
BTN3A2[a]	6	26,378,546	1.59×10^{-26}	1.56×10^{-26}	3.17×10^{-1}	5.04×10^{-1}
ZNF192[a]	6	28,124,089	1.26×10^{-32}	1.25×10^{-32}	8.56×10^{-2}	2.07×10^{-1}
AL022393.7[a]	6	28,144,452	3.25×10^{-178}	2.24×10^{-178}	1.50×10^{-1}	8.36×10^{-2}
HLA-DRB1[ab]	**6**	**32,557,625**	$\mathbf{1.02 \times 10^{-12}}$	$\mathbf{8.99 \times 10^{-13}}$	$\mathbf{2.06 \times 10^{-6}}$	-
AEBP1	7	44,154,161	5.55×10^{-220}	8.62×10^{-1}	6.69×10^{-1}	4.19×10^{-1}
BUB3	10	124,924,886	6.64×10^{-18}	1.05×10^{-2}	-	4.76×10^{-1}
FBXO3	11	33,796,089	1.48×10^{-9}	6.88×10^{-1}	-	1.13×10^{-1}
CEACAM19[abc]	**19**	**45,187,631**	$\mathbf{4.7 \times 10^{-13}}$	$\mathbf{2.54 \times 10^{-13}}$	$\mathbf{3.60 \times 10^{-12}}$	$\mathbf{2.83 \times 10^{-16}}$
APOC1[a]	19	45,422,606	8.9×10^{-11}	1.11×10^{-10}	3.18×10^{-6}	7.2×10^{-3}
ZC3H12B	**X**	**64,727,767**	$\mathbf{2.08 \times 10^{-37}}$	-	-	-
CXorf56	X	118,699,397	6.02×10^{-07}	-	-	-

a. Genes that were also identified as significant by using BVSR cis-eQTL estimates.
b. Genes that were also identified by PrediXcan.
c. Genes that were also identified by TIGAR.

Summary

- Propose a novel BGW-TWAS tool for leveraging both cis- and trans- eQTL to conduct TWAS
- Computationally manageable for modeling genome-wide variants and genes: $\sim$10 minutes per gene
- Gain power when trans-eQTL explain a proportion of gene expression heritability
- Identified that known GWAS signals (*rs4420638, rs56131196, rs157592 on CHR19*) of AD could be mediated through the gene expression levels of *ZC3H12B on CHR X* for affecting AD and AD pathology tangles

Publication



BGW-TWAS Software:

`https://github.com/yanglab-emory/BGW-TWAS.git`

Acknowledgement

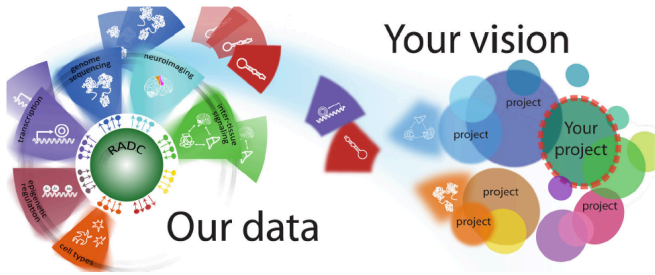
EMORY UNIVERSITY

CCQG CENTER FOR COMPUTATIONAL AND QUANTITATIVE GENETICS

Yang Lab @ Emory

RUSH UNIVERSITY

Rush Alzheimer's Disease Center www.radc.rush.edu



NIH National Institute of General Medical Sciences

Mayo Clinic LOAD GWAS

NIH National Institute on Aging

AMP-AD Knowledge Portal