Controlling and Testing Horizontal Pleiotropy with Probabilistic Mendelian Regression for Transcriptome-wide Association Studies

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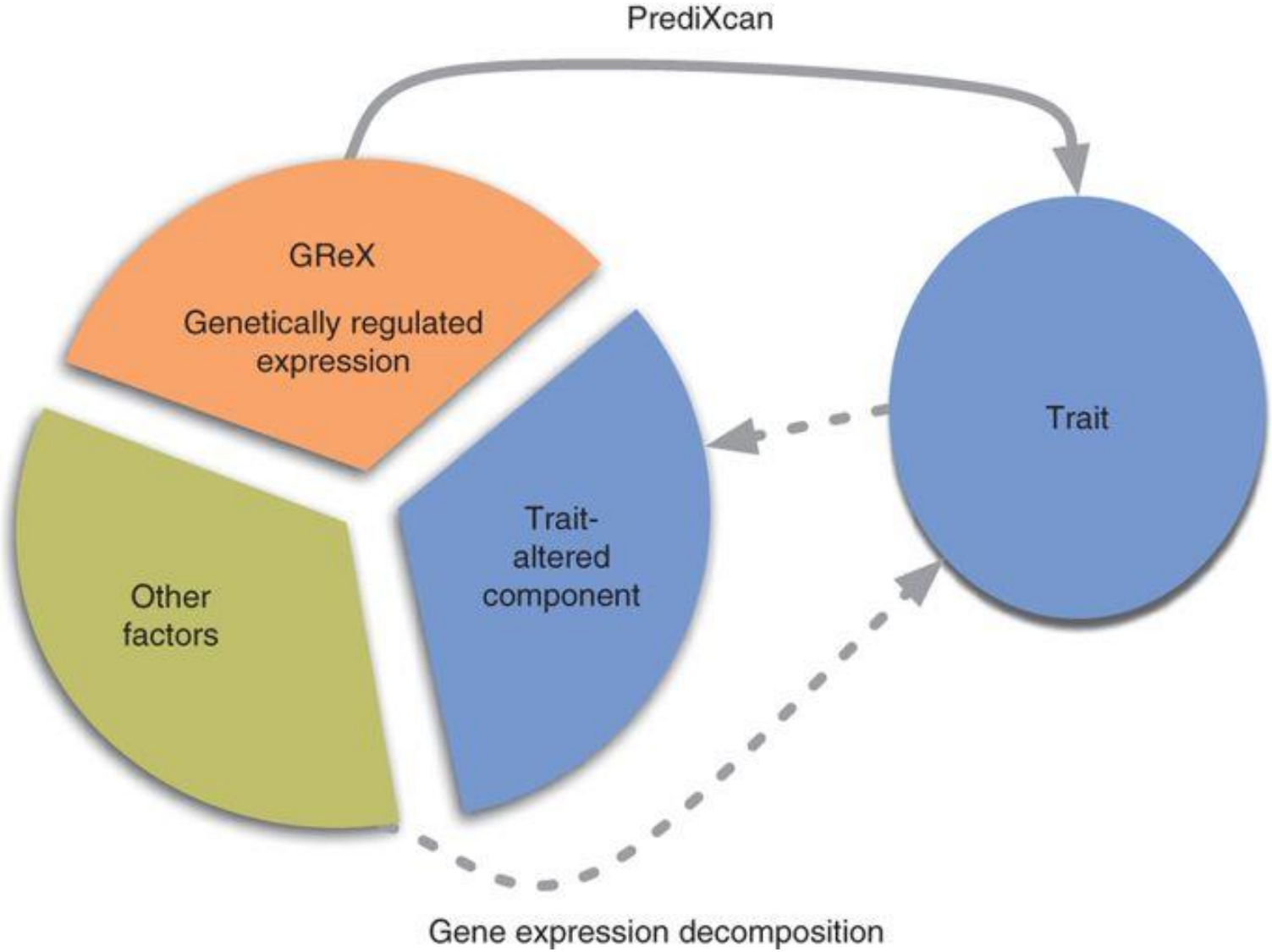
Transcriptome-wide Association Studies

- Genome-wide association studies (GWASs) have identified many genetic variants associated with diseases and complex traits.
- Expression quantitative trait loci (eQTL) mapping studies have also identified enabled accurate measurements of gene expression levels.
- Integrative analysis of GWASs and eQTL mapping studies has the potential to yield insight into the causal relationship between genes and complex traits.

Existing Integrative Approaches: PrediXcan



Gamazon et al., Nature Genetics, 2015

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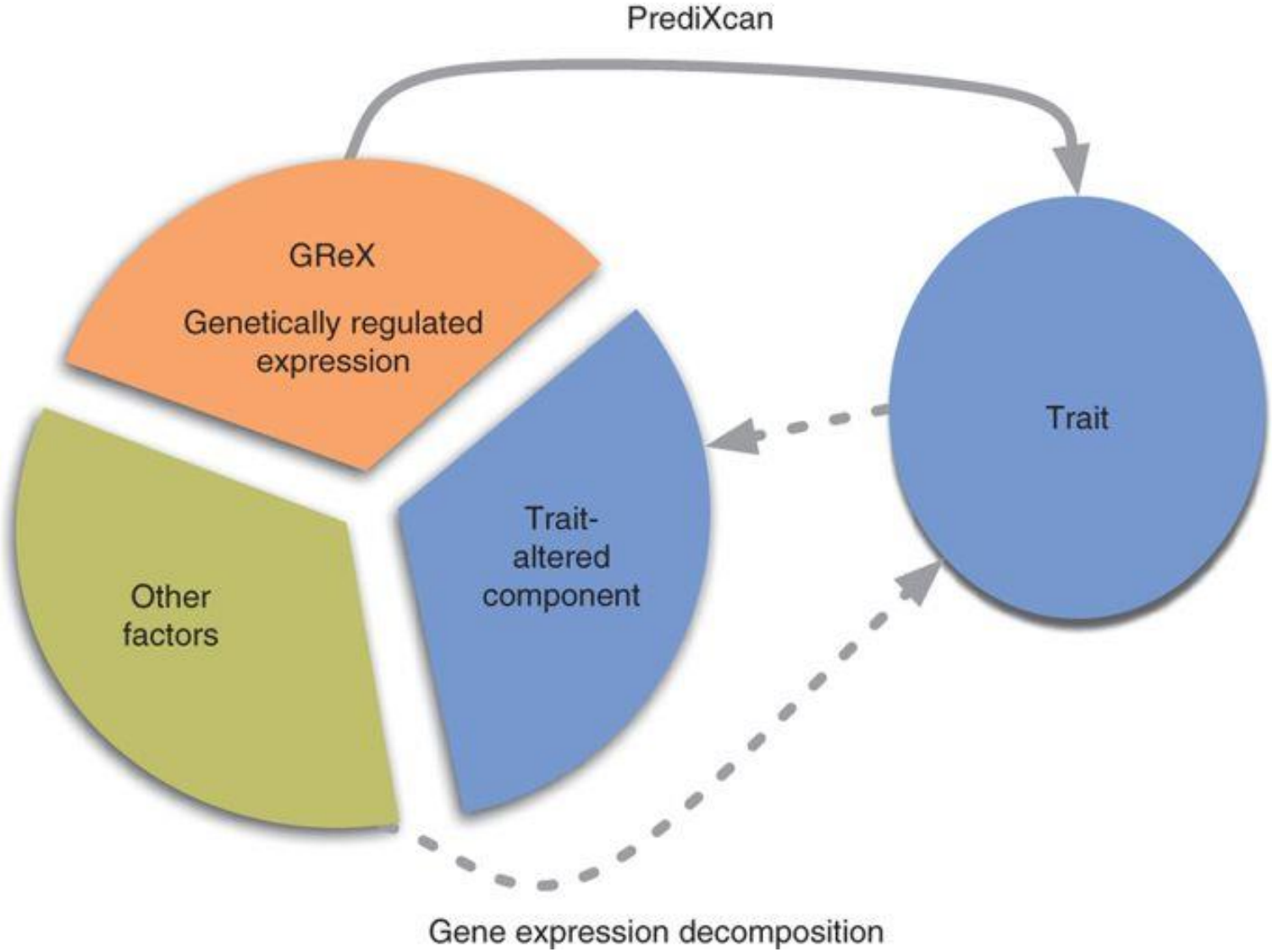

“SNP aggregation approach”

Gamazon et al., Nature Genetics, 2015

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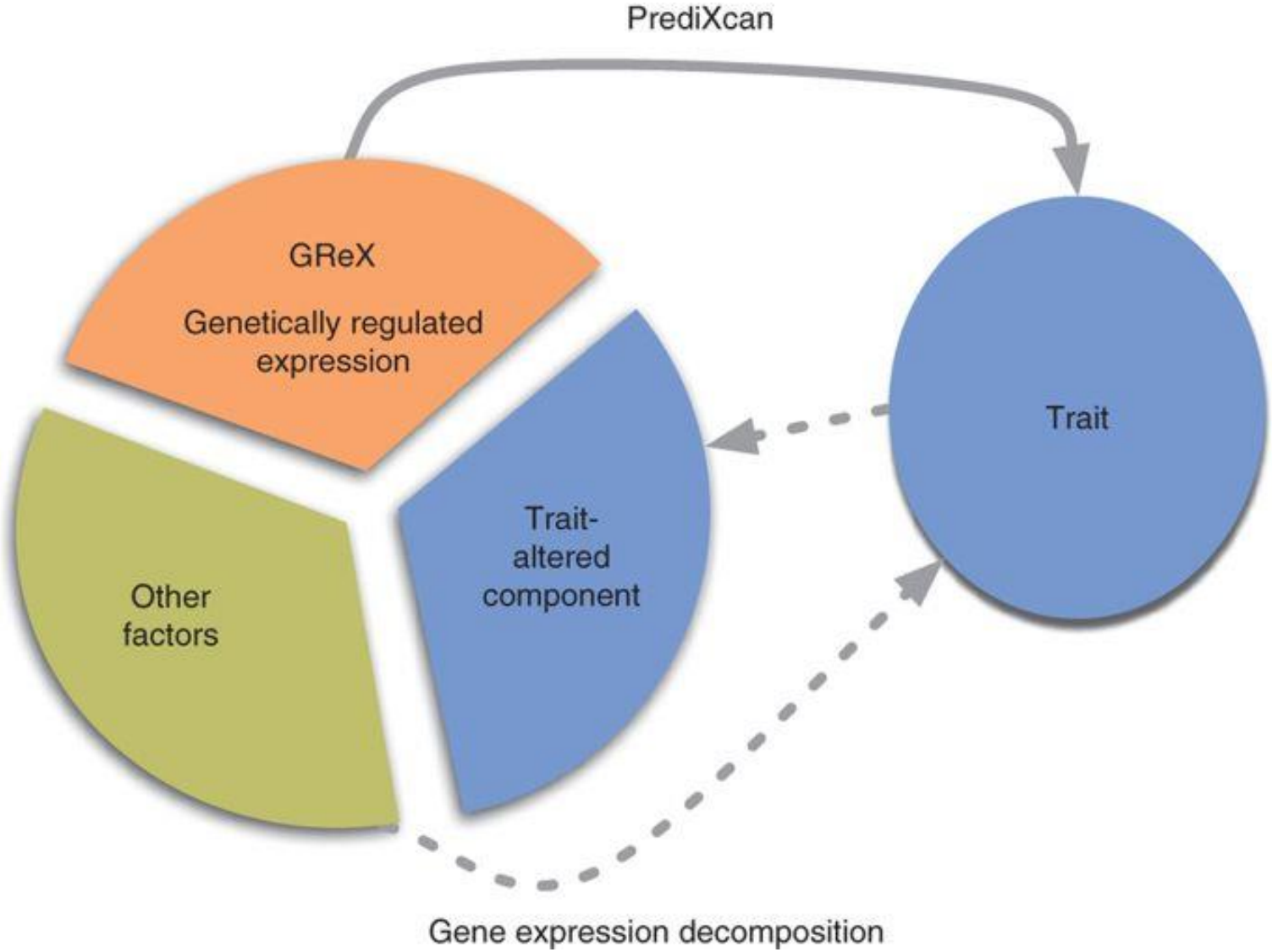

"SNP aggregation approach"

Step 1: Construct a genetic predictor of gene expression using ElasticNet

Gamazon et al., Nature Genetics, 2015

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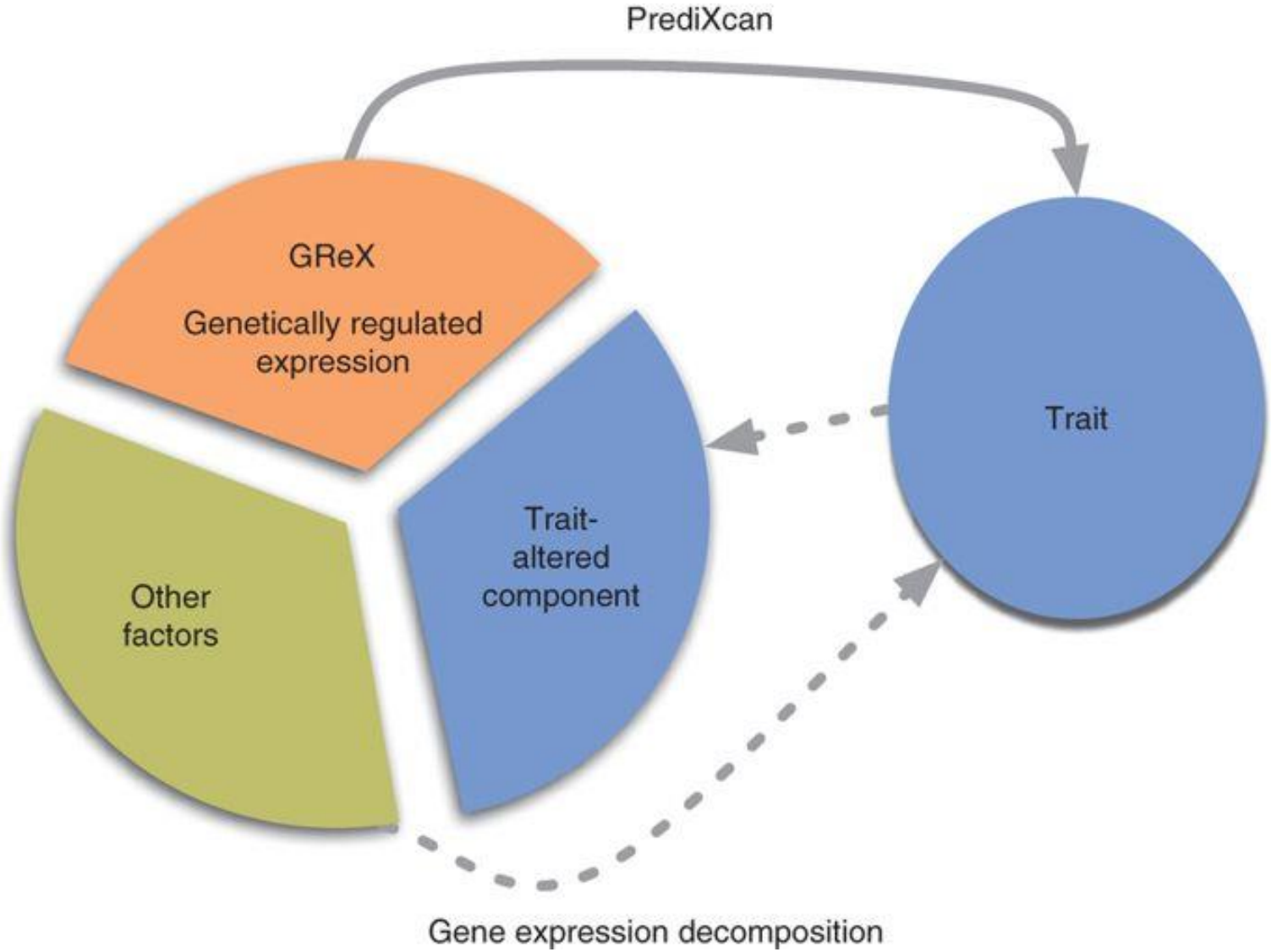


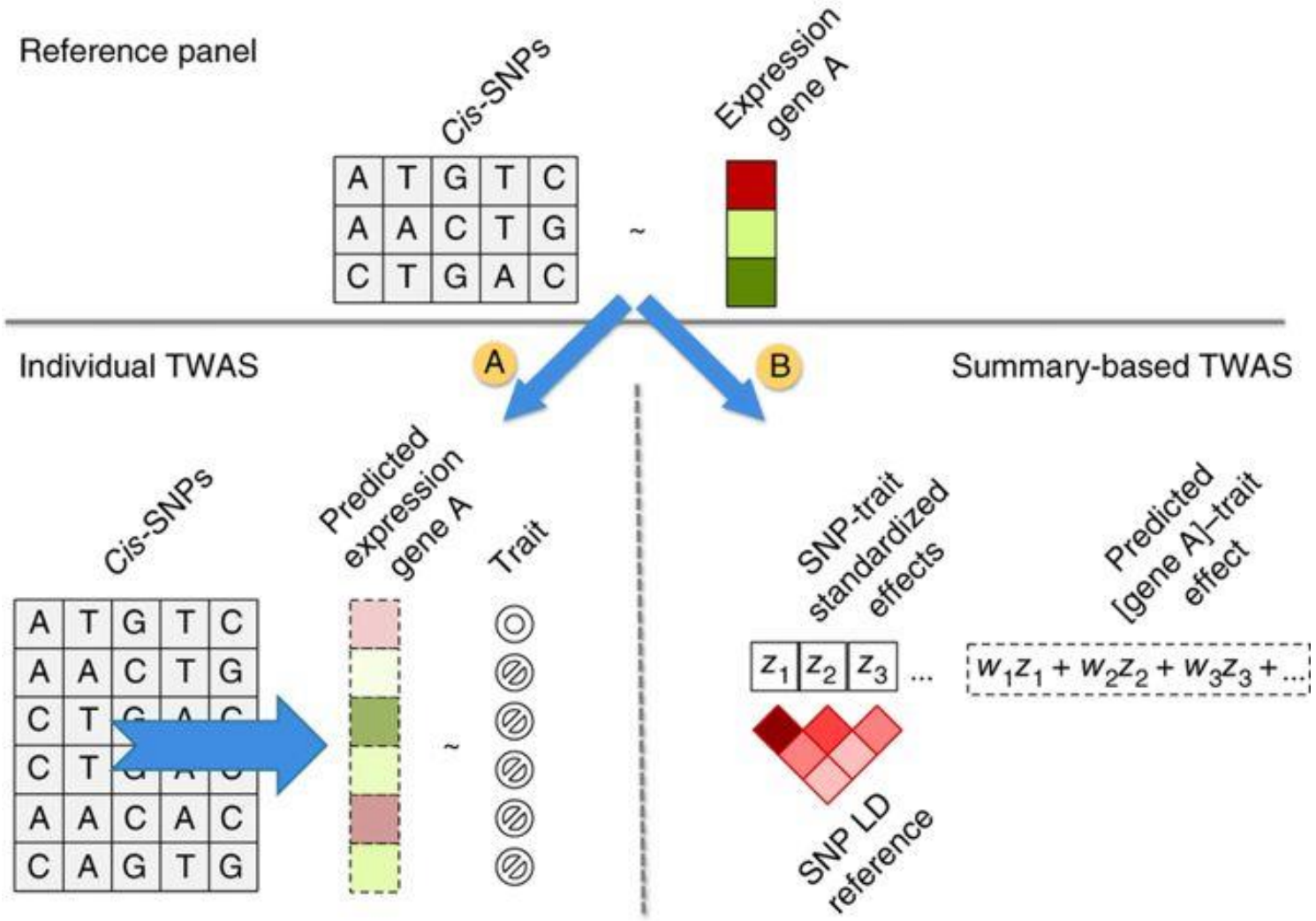
"SNP aggregation approach"

Step 1: Construct a genetic predictor of gene expression using ElasticNet

Step 2: Test the association between genetic predictor of expression and trait

Gamazon et al., Nature Genetics, 2015

Existing Integrative Approaches: TWAS



Gusev et al., Nature Genetics, 2016

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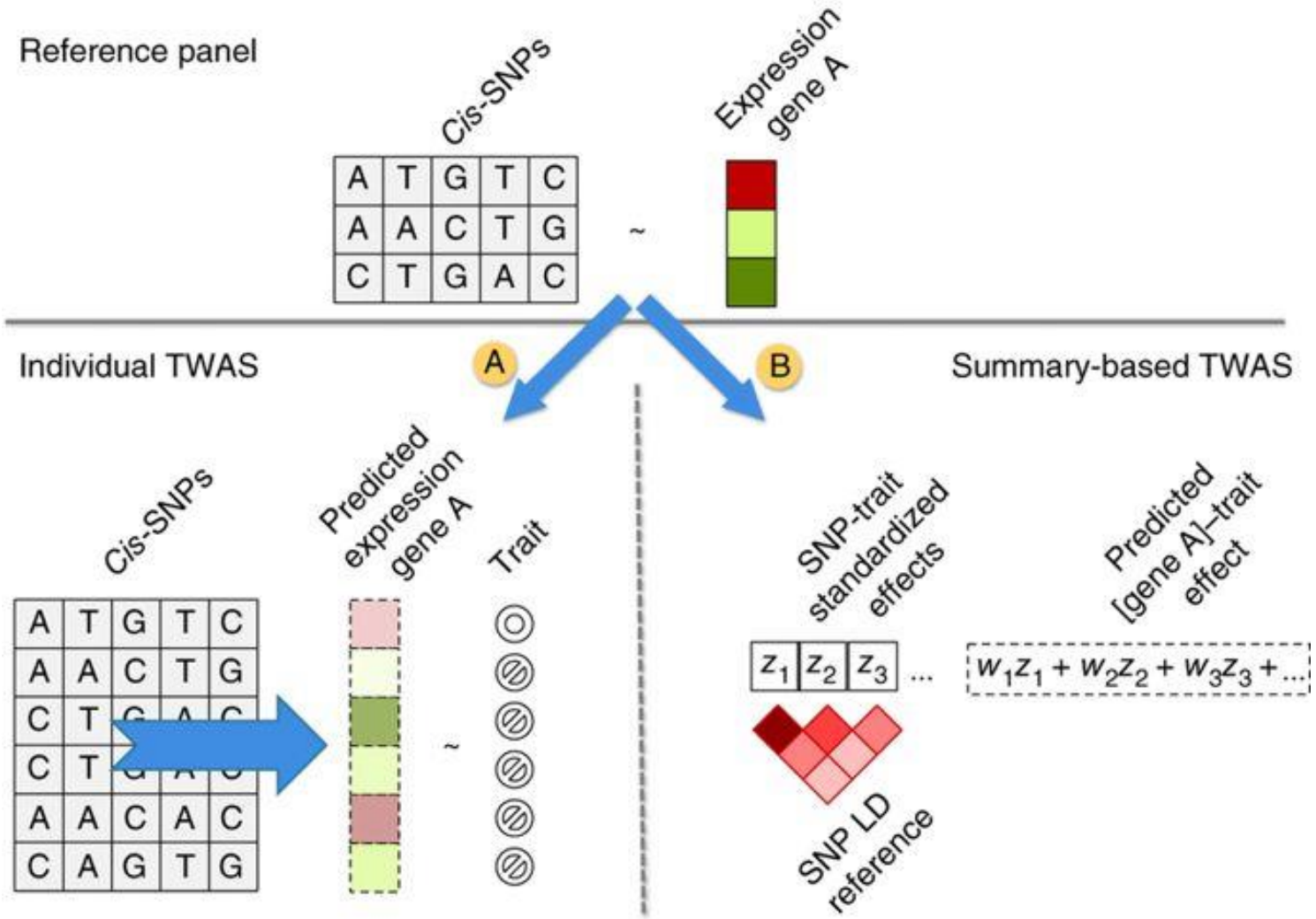

“expression-trait associations”

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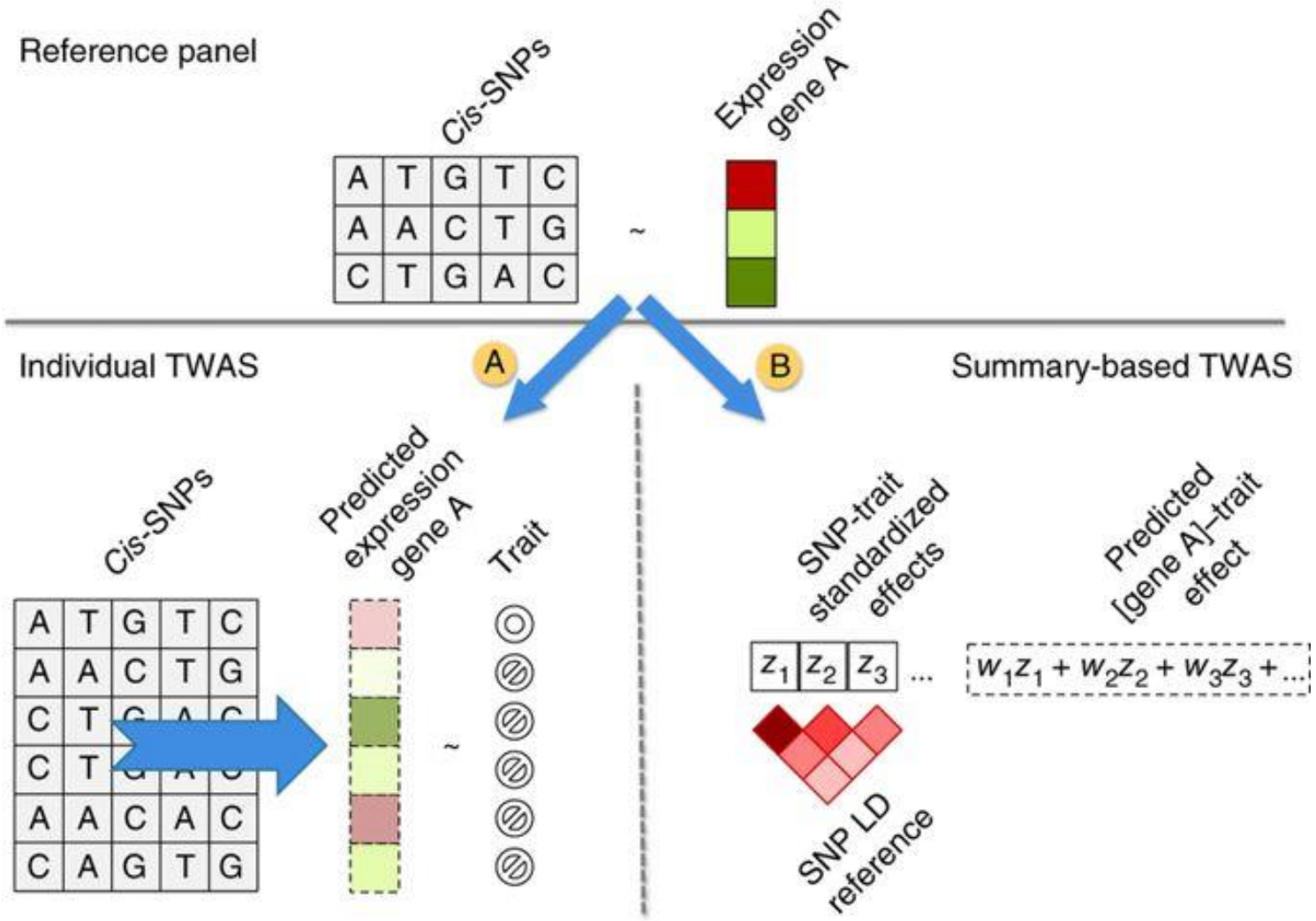

“expression-trait associations”

Step 1: Construct a genetic predictor of gene expression using BSLMM

Gusev et al., Nature Genetics, 2016

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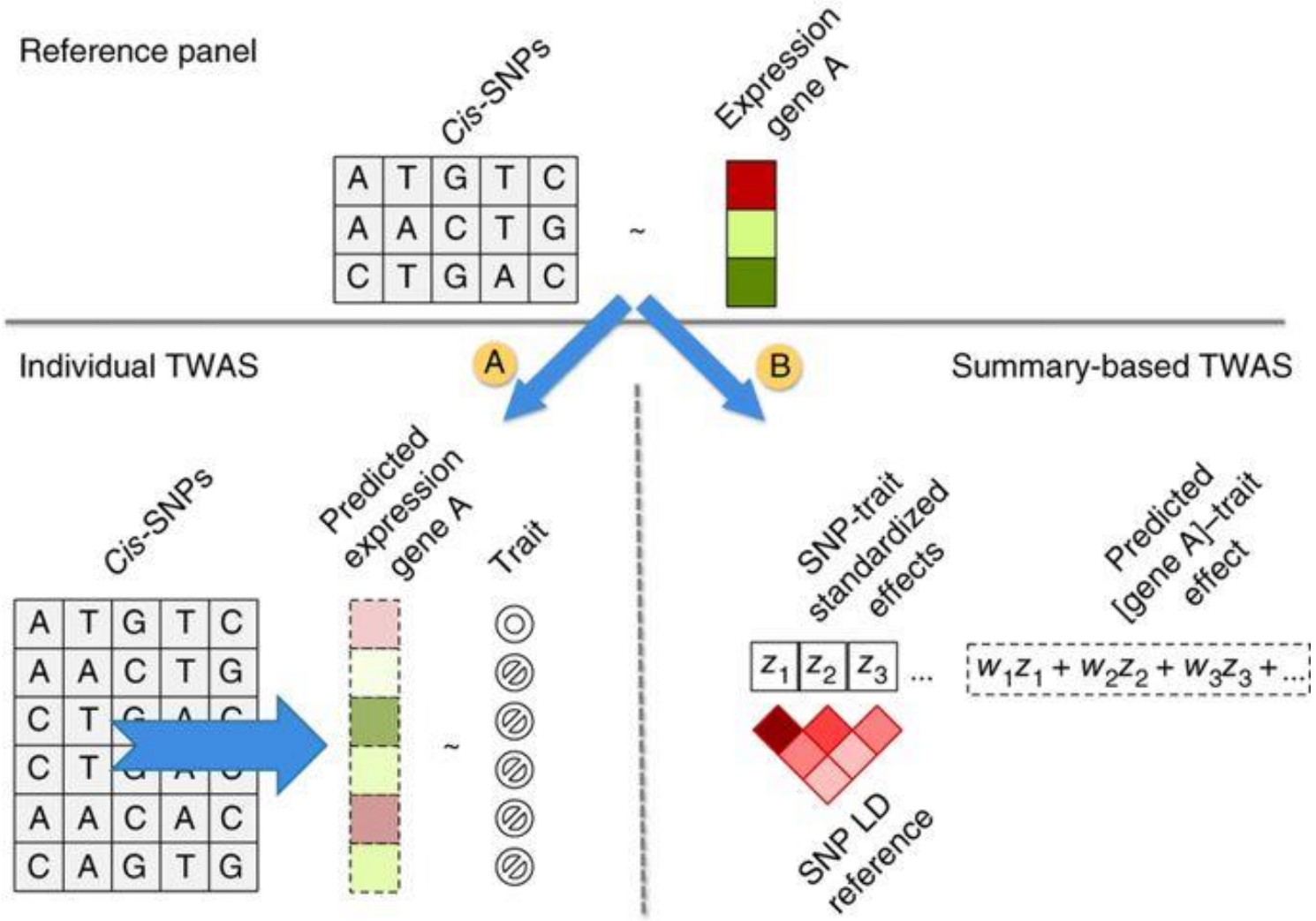

"expression-trait associations"

Step 1: Construct a genetic predictor of gene expression using BSLMM

Step 2: Test the association between genetic predictor of expression and trait

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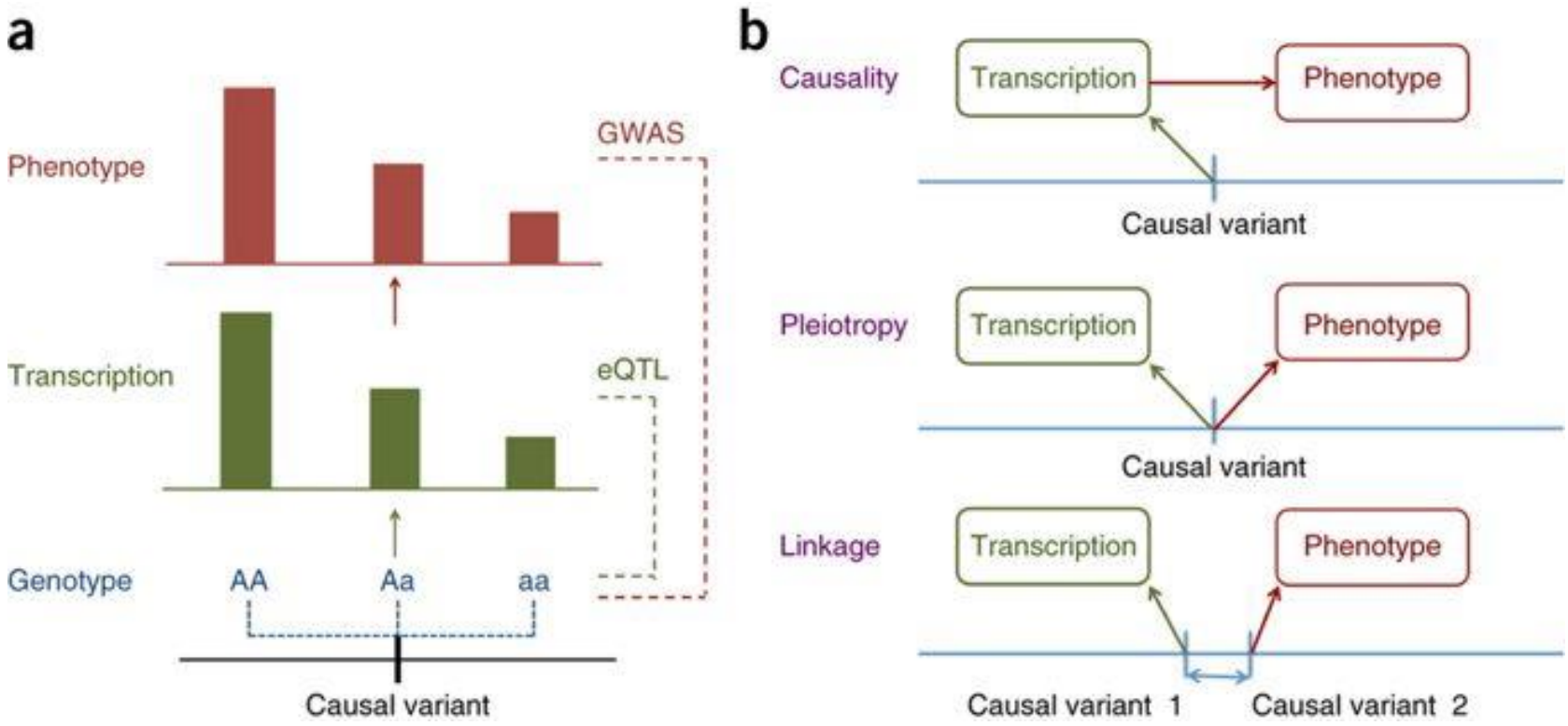
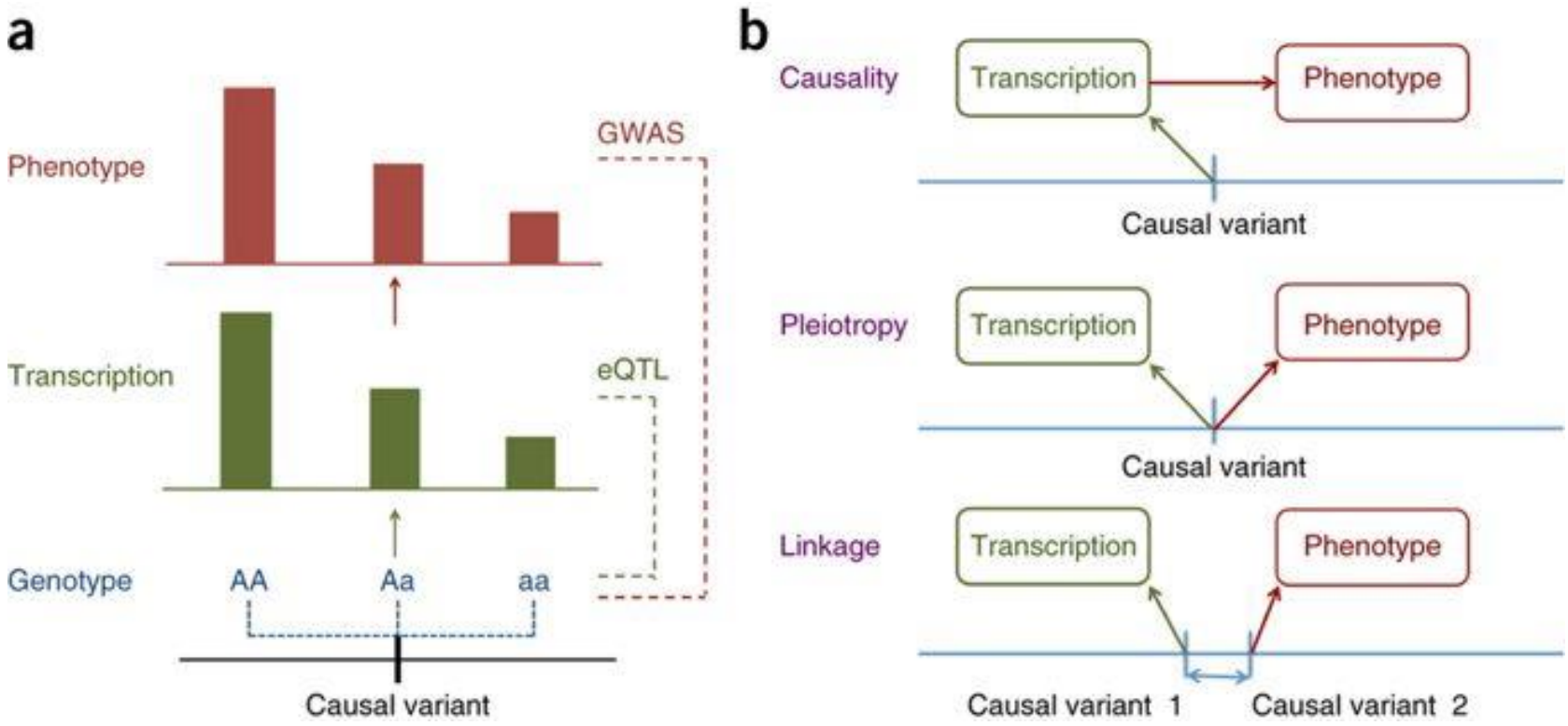
Existing Integrative Approaches: SMR



Zhu et al., Nature Genetics, 2016

Existing Integrative Approaches: SMR

“identify causal genes”



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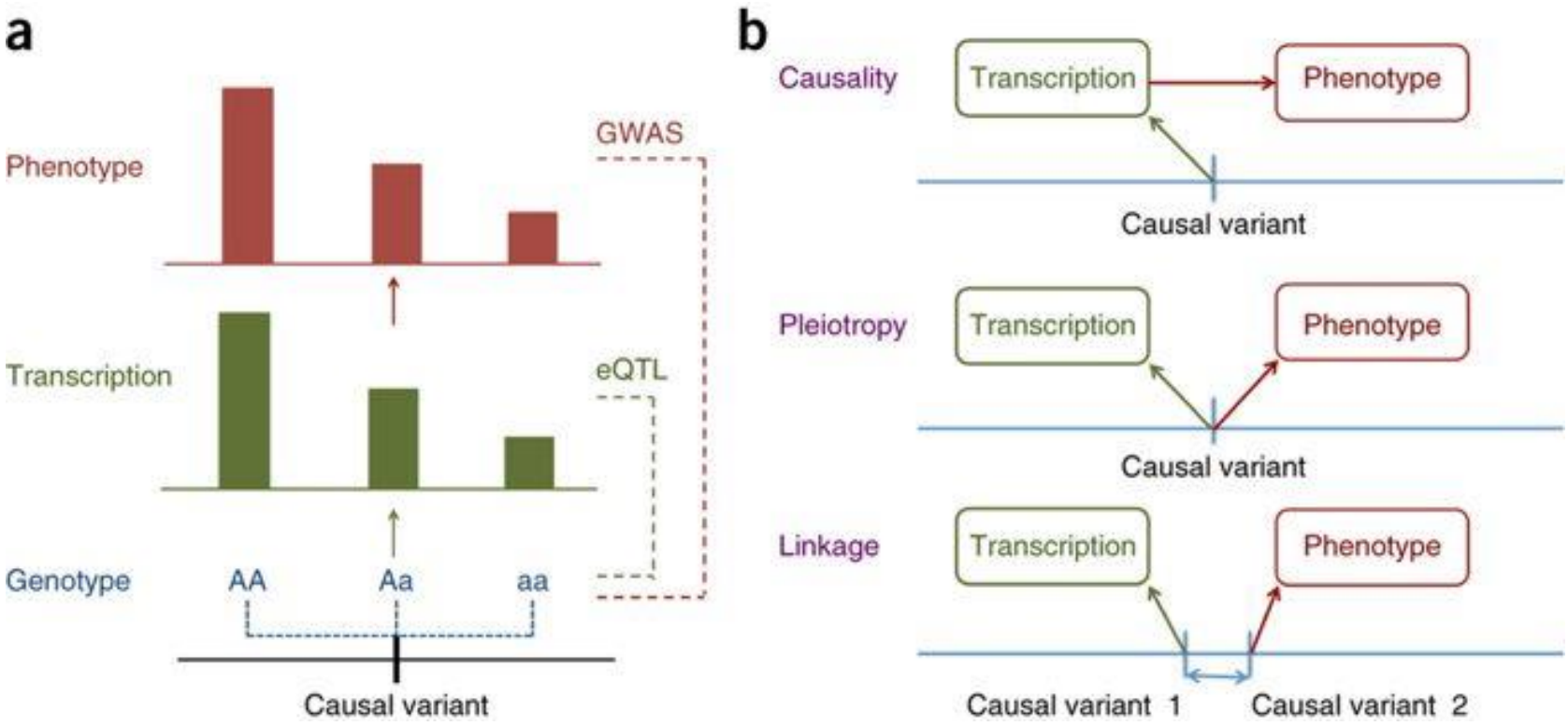

“identify causal genes”

Step 1: Construct a genetic predictor of gene expression using linear regression with one SNP

Zhu et al., Nature Genetics, 2016

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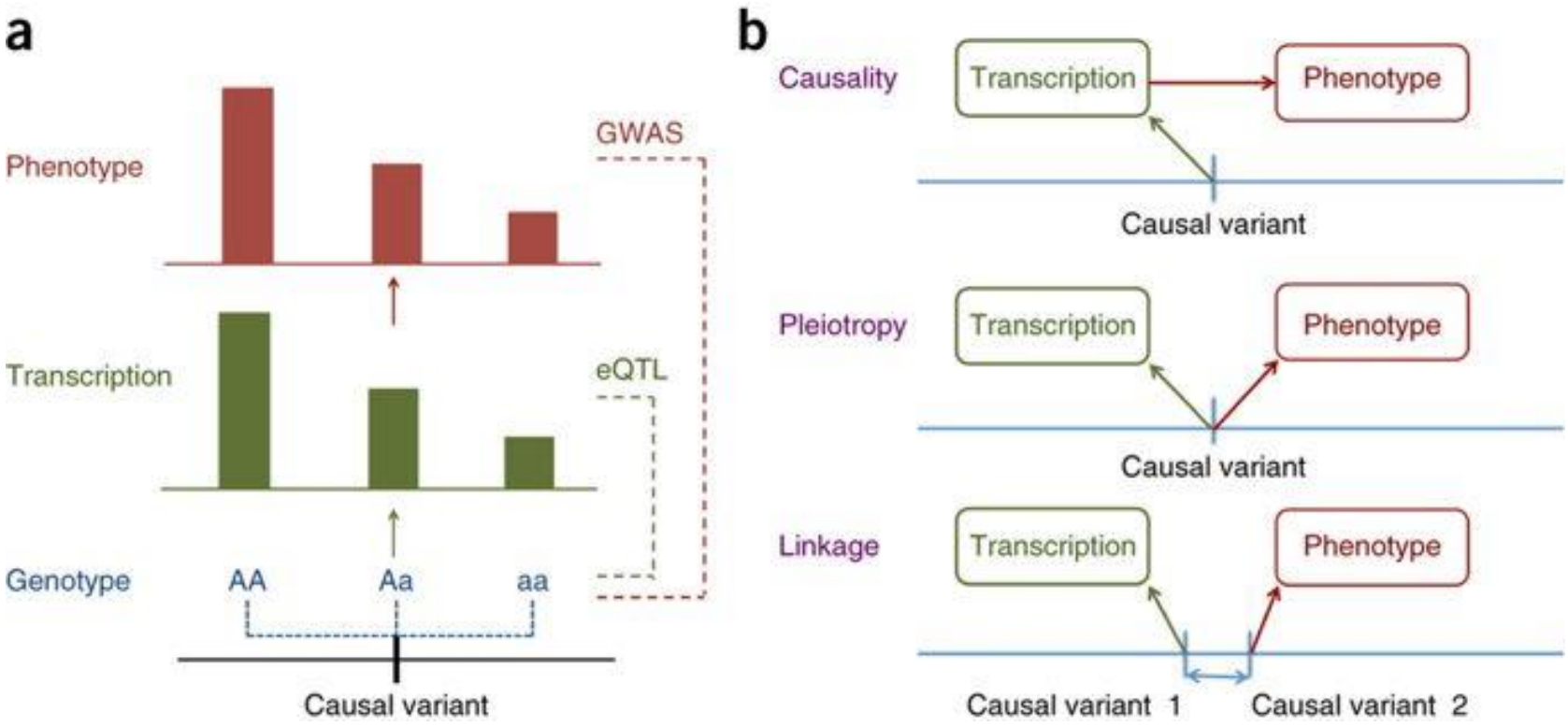


"identify causal genes"

Step 1: Construct a genetic predictor of gene expression using linear regression with one SNP

Step 2: Test the association between genetic predictor of expression and trait

Zhu et al., Nature Genetics, 2016

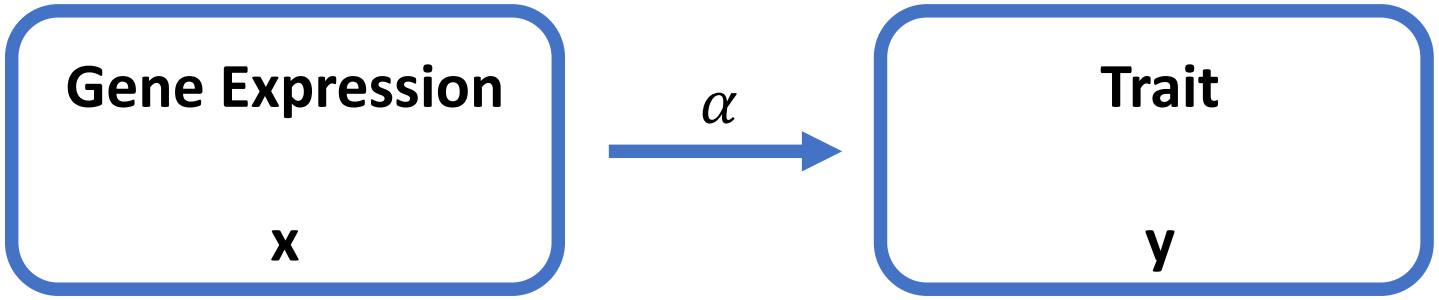
Mendelian Randomization

- These existing approaches can all be thought of as a two-stage regression version of Mendelian randomization (MR) analysis.

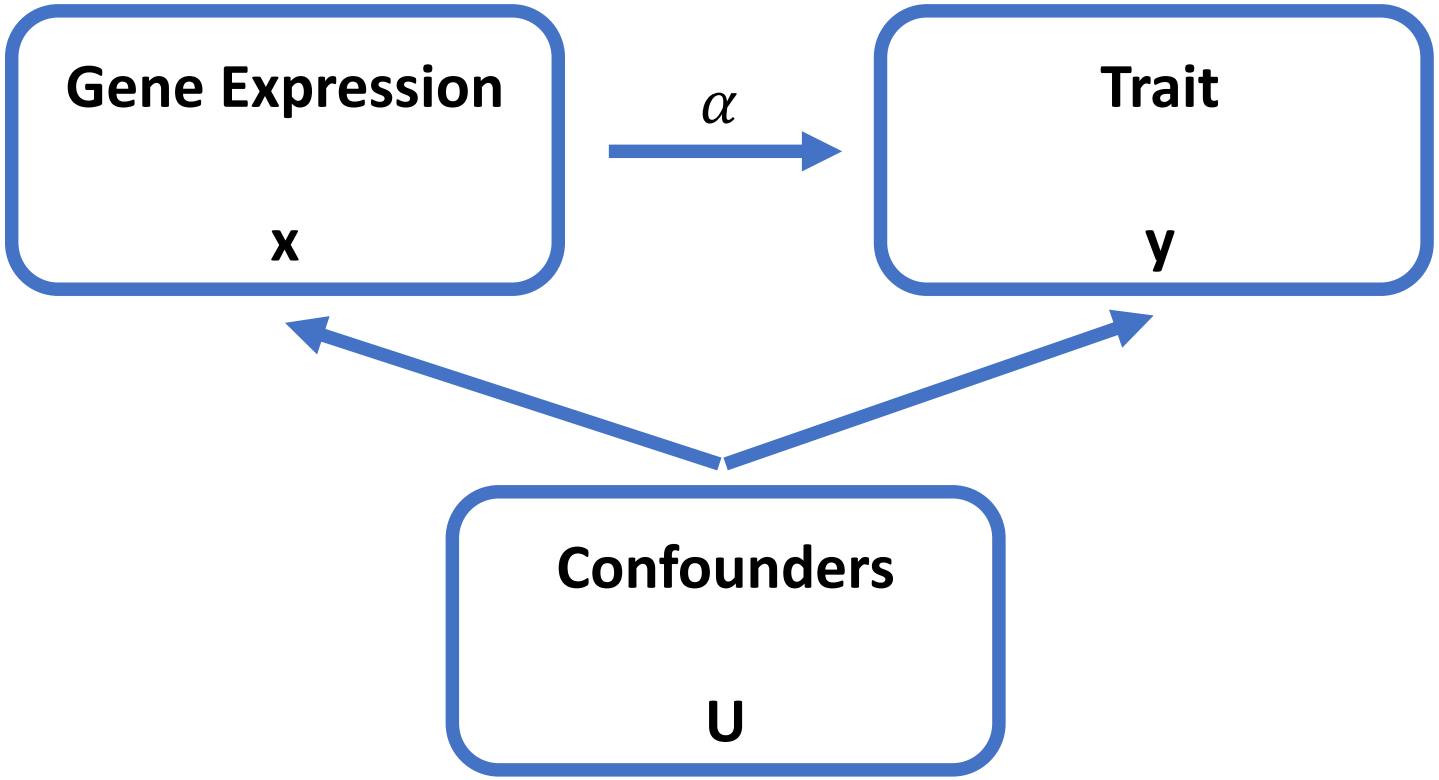
- MR is a form of instrumental variable analysis with SNPs serving as instruments.

- MR is a powerful statistical tool to determine causal relationship between an exposure variable (in this case, gene expression) and an outcome variable (in this case, complex trait) in observational studies

Mendelian Randomization



Mendelian Randomization



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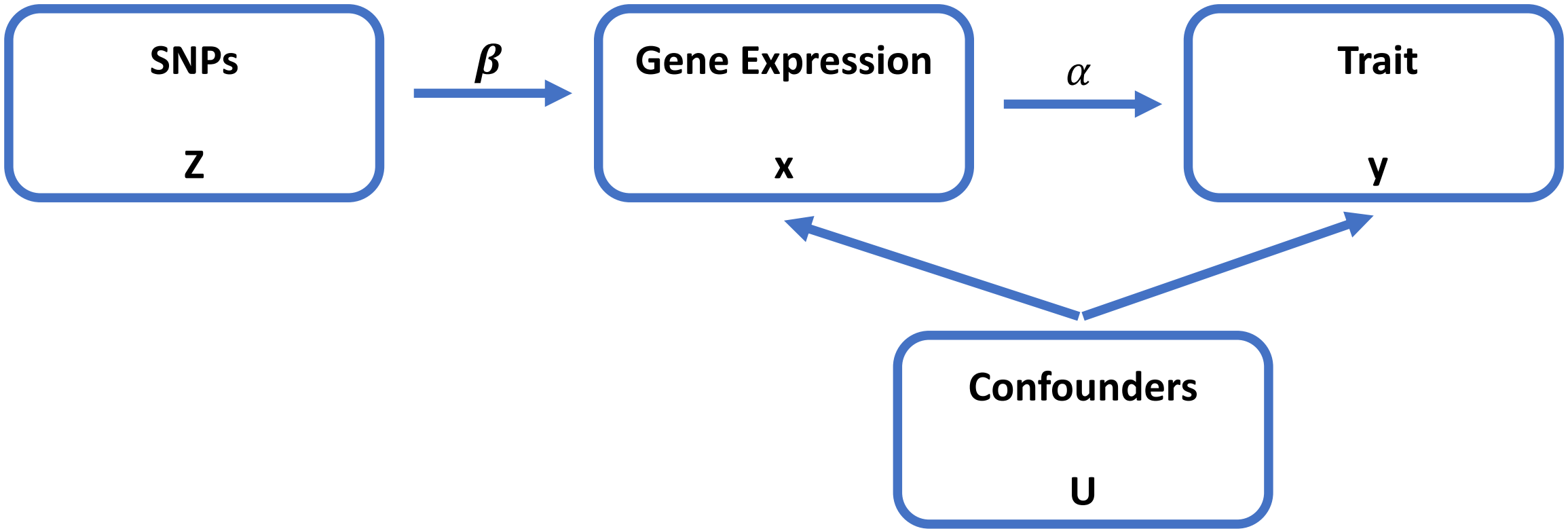

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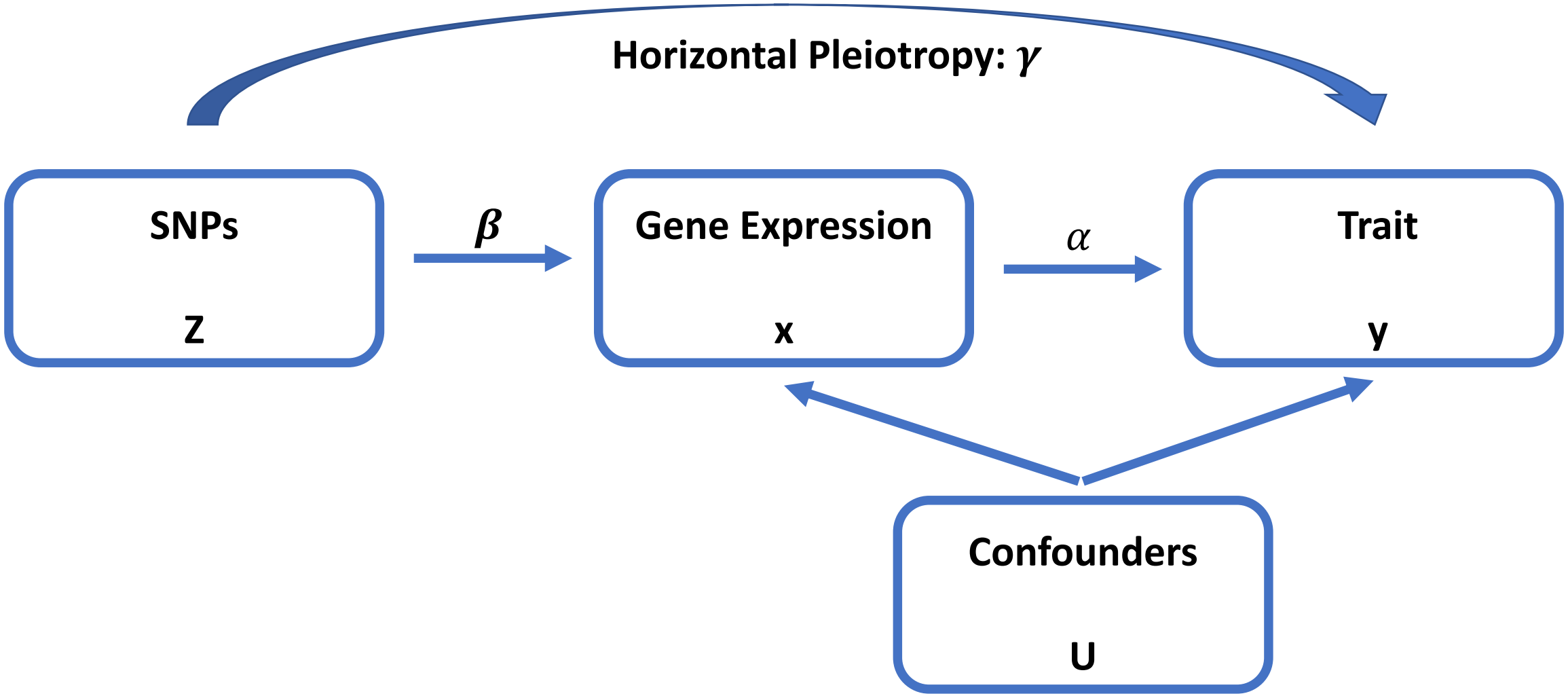

Pervasive Horizontal Pleiotropy

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-018-0099-7

Corrected: Publisher Correction

Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases

Marie Verbanck[1,2,3,7], Chia-Yen Chen[4,5,6,7], Benjamin Neale[4,5,6,8*] and Ron Do[1,2,3,8*]

MR with Horizontal Pleiotropy Accounted for

- Sample I, the observed gene expression data:

$$\boldsymbol{x} = \mu_{\mathrm{x}} + \mathbf{Z}_{\mathrm{x}}\boldsymbol{\beta} + \boldsymbol{\varepsilon}_{\mathrm{x}} \qquad (1)$$

MR with Horizontal Pleiotropy Accounted for

- Sample I, the observed gene expression data:

$$\boldsymbol{x} = \mu_{\mathrm{x}} + \mathbf{Z}_{\mathrm{x}}\boldsymbol{\beta} + \boldsymbol{\varepsilon}_{\mathrm{x}} \qquad (1)$$

- Sample II, the unobserved gene expression data:

MR with Horizontal Pleiotropy Accounted for

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- Sample II, the unobserved gene expression data:

$$\tilde{\boldsymbol{x}} = \mu_{\mathrm{x}} + \mathbf{Z}_{\mathrm{y}}\boldsymbol{\beta} + \boldsymbol{\varepsilon}_{\mathrm{y}} \qquad (2)$$

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- Sample II, the observed GWAS data:

MR with Horizontal Pleiotropy Accounted for

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$$\tilde{\boldsymbol{x}} = \mu_{\mathrm{x}} + \mathbf{Z}_{\mathrm{y}}\boldsymbol{\beta} + \boldsymbol{\varepsilon}_{\mathrm{y}} \qquad (2)$$

- Sample II, the observed GWAS data:

$$\boldsymbol{y} = \mu_{\mathrm{y}} + \tilde{\boldsymbol{x}}\alpha + \mathbf{Z}_{\mathrm{y}}\boldsymbol{\gamma} + \boldsymbol{\epsilon} \qquad (3)$$

Additional Modeling Assumptions

- Because the number of SNPs (*p*) is often larger than the sample size (*n*), we need to make additional modeling assumption for model identifiability.

- For $\boldsymbol{\beta}$, we follow standard polygenic models to assume $\beta_j \sim N(0, \sigma_\beta^2)$.

- For $\boldsymbol{\gamma}$, we follow Egger regression to assume $\gamma_1 = \cdots = \gamma_p = \gamma$

Probabilistic Mendelian Randomization

- Instead of the usual two-stage regression procedure, we rely on the maximum likelihood estimation procedure for inference.
- We develop a computationally efficient fitting algorithm, based on a parameter expansion version of the expectation maximization algorithm (PX-EM).
- We test causal effect $H_0: \alpha = 0$ through LRT.
- We test horizontal pleiotropic effect $H_0: \gamma = 0$ through LRT.
- We refer to our method as PMR-Egger.

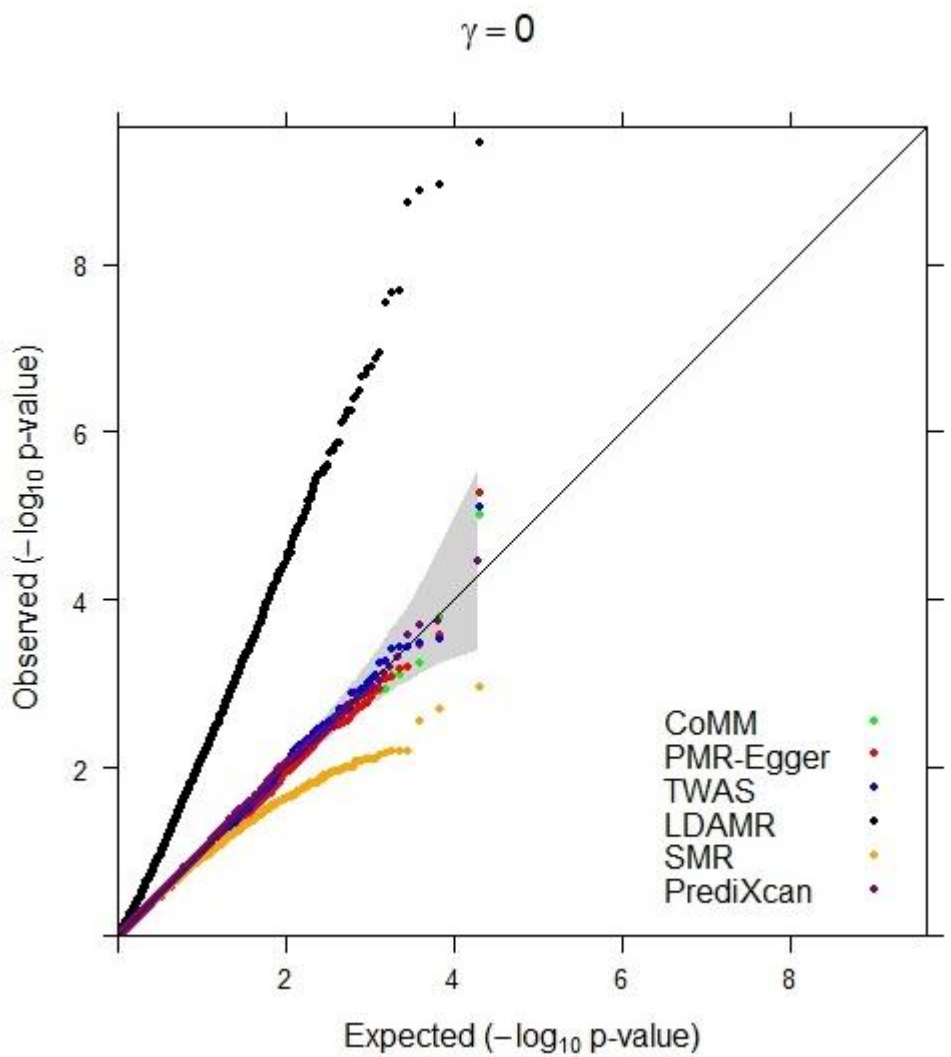
Simulations

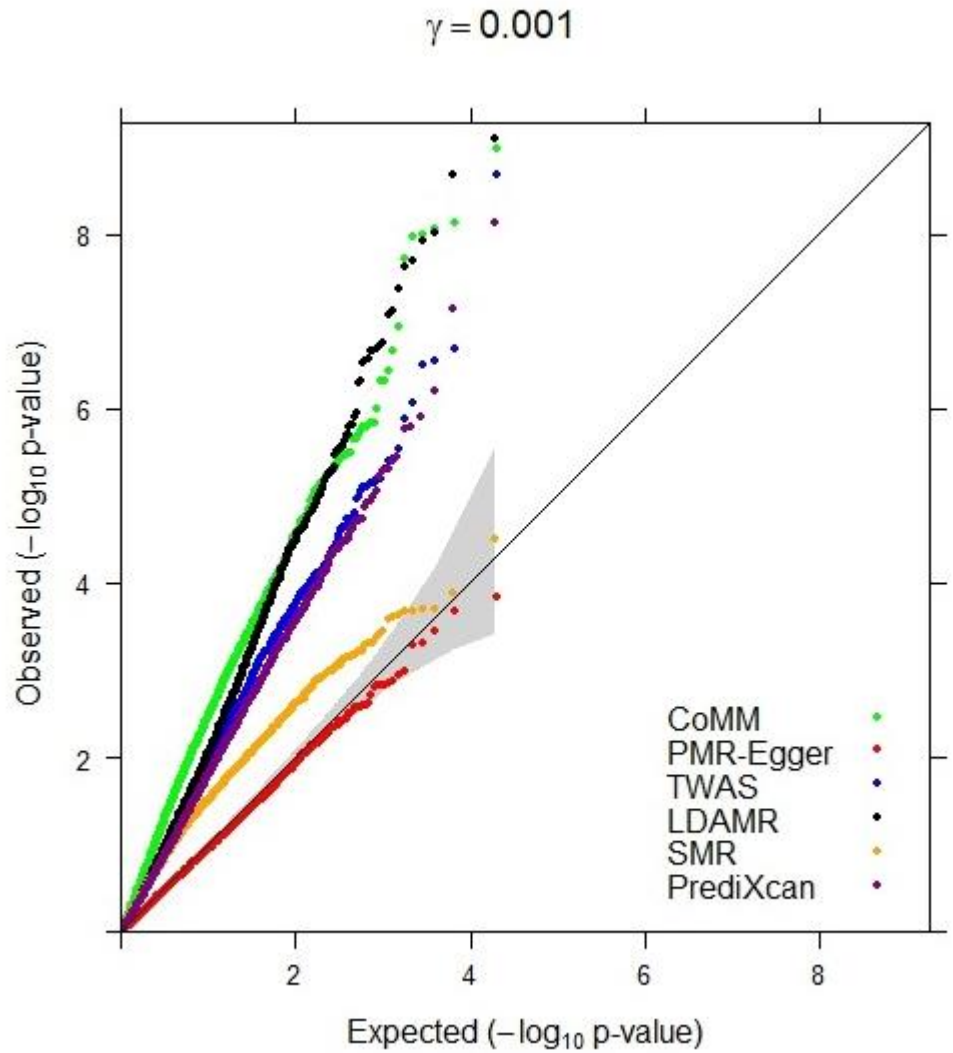
- We extracted $p = 556$ cis-SNPs of a gene from the GEUVADIS data ($n_1 = 465$) and simulated gene expression.
- We extricated the same SNPs from 2,000 controls in the Wellcome trust case control consortium (WTCCC) and simulated trait.
- We examined various scenarios, with 10,000 replicates for each scenario.

Compared Methods: Testing α

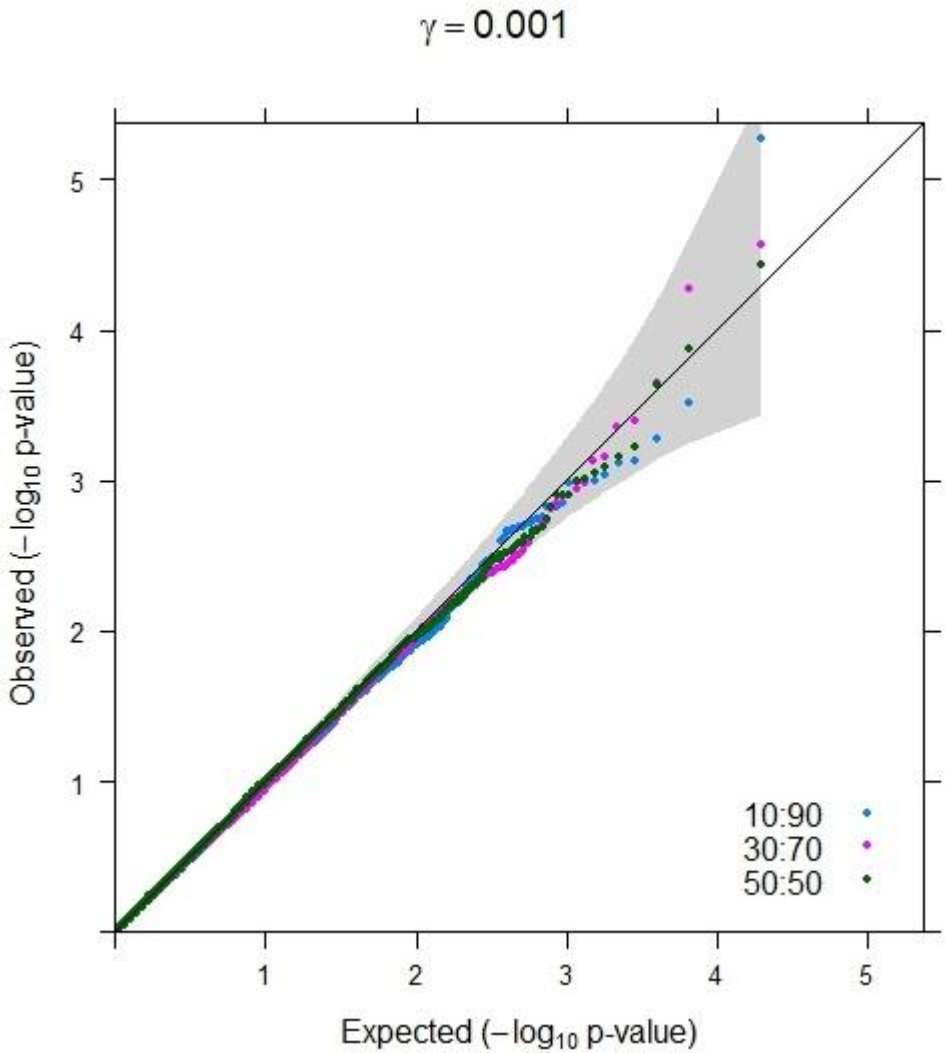
- PrediXcan: Elastic Net prior on $\boldsymbol{\beta}$; no $\boldsymbol{\gamma}$; two-stage inference
- TWAS: BSLMM prior on $\boldsymbol{\beta}$; no $\boldsymbol{\gamma}$; two-stage inference
- SMR: Single $\boldsymbol{\beta}$; no $\boldsymbol{\gamma}$; two-stage inference
- CoMM: Normal prior on $\boldsymbol{\beta}$; no $\boldsymbol{\gamma}$; maximum likelihood inference
- LDA MR Egger: Fixed effects of $\boldsymbol{\beta}$; Egger assumption on $\boldsymbol{\gamma}$; two-stage inference
- PMR-Egger: Normal prior on $\boldsymbol{\beta}$; Egger assumption on $\boldsymbol{\gamma}$; maximum likelihood inference

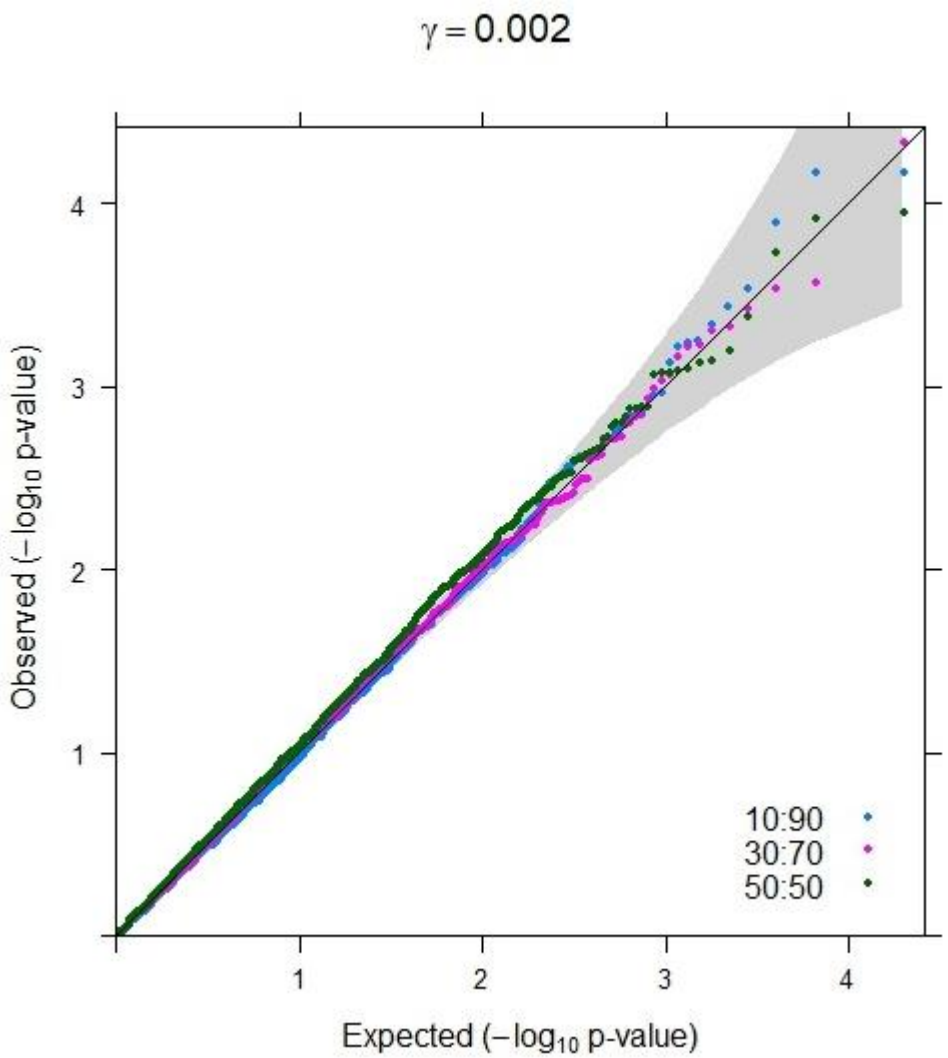
Testing Causal Effect α under the Null



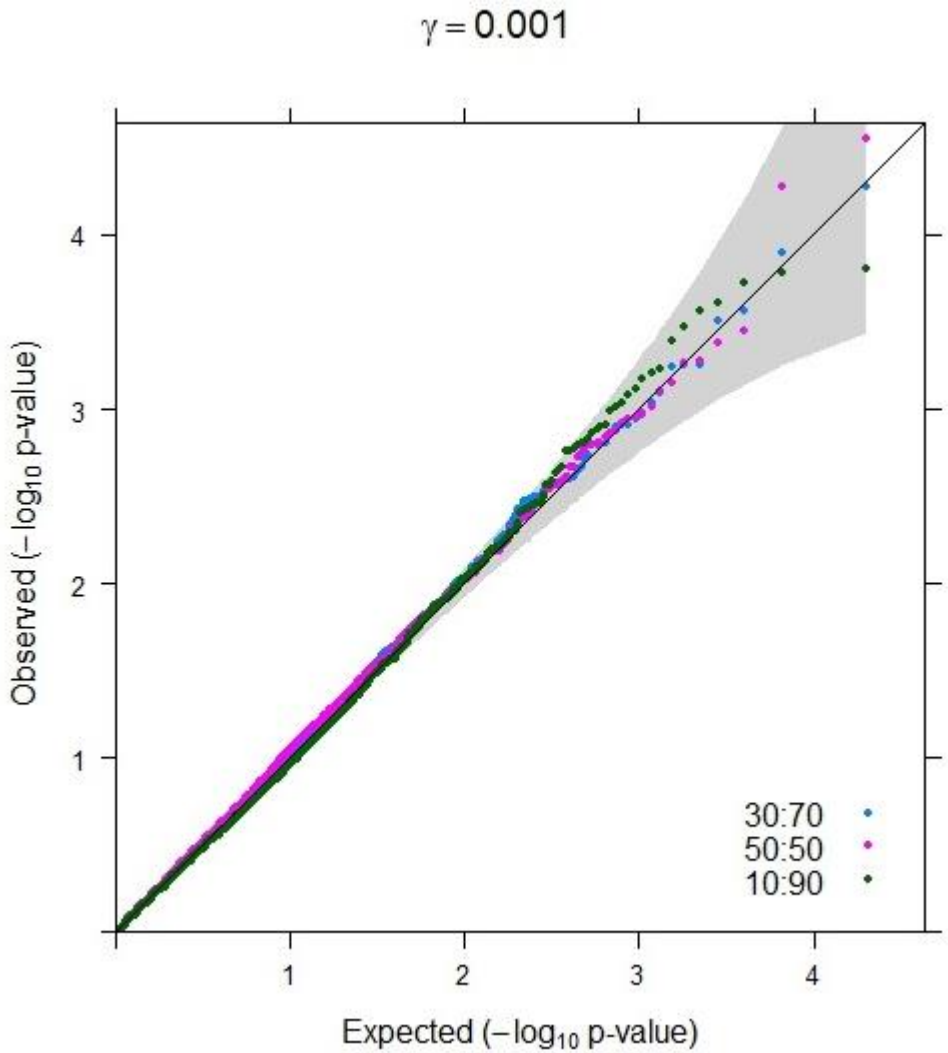


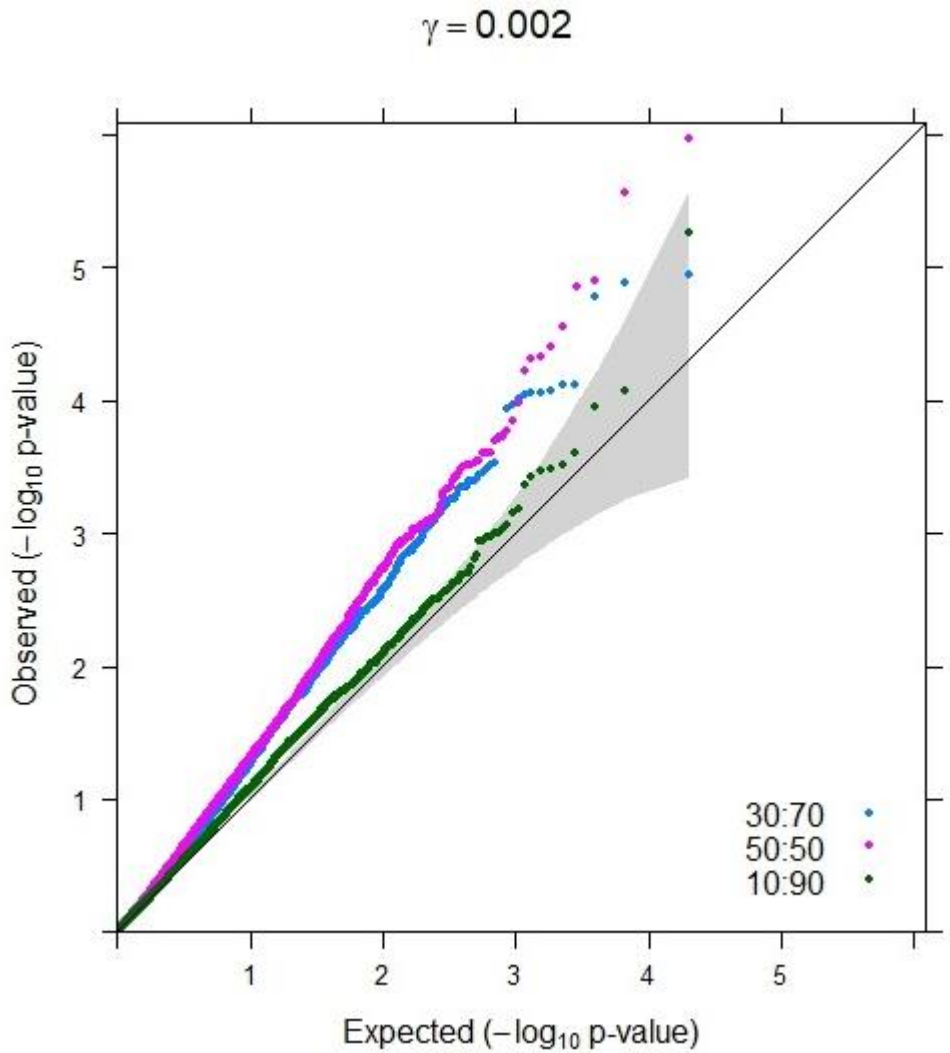
Violation of the Polygenic β Assumption



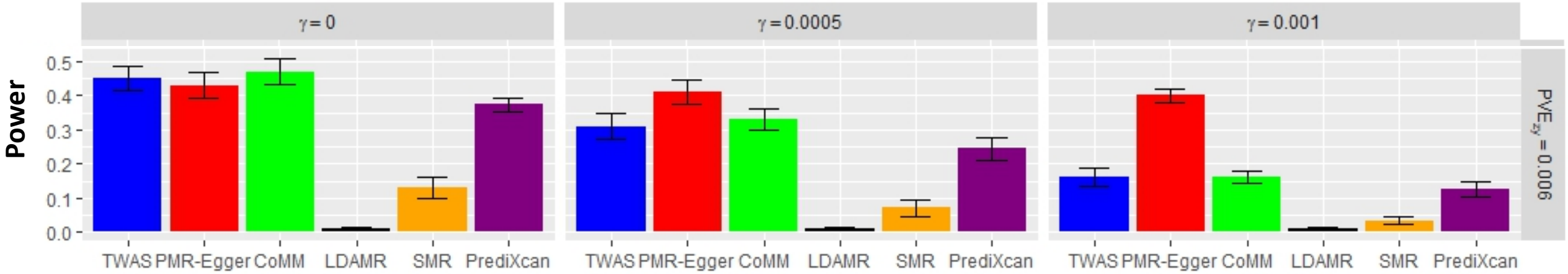


Violation of the Homogeneous γ Assumption





Power of Testing α under Alternative



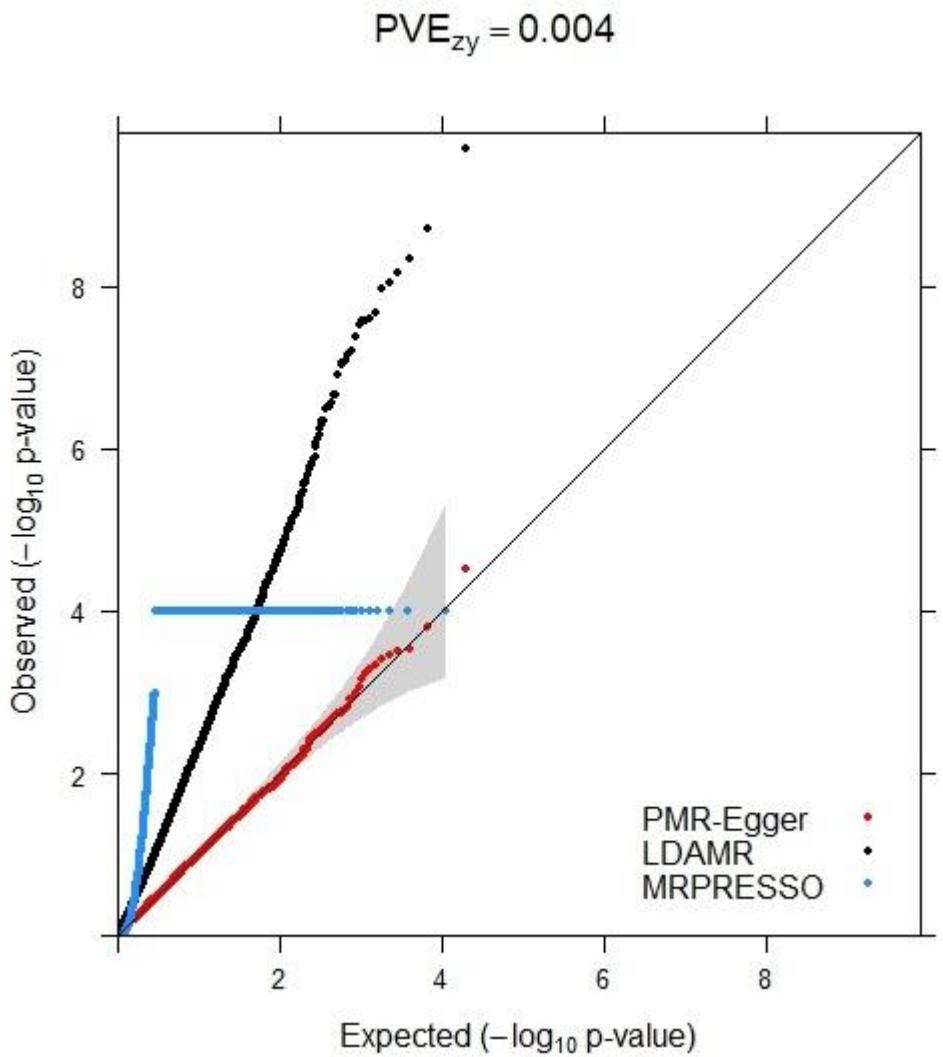
Compared Methods: Testing γ

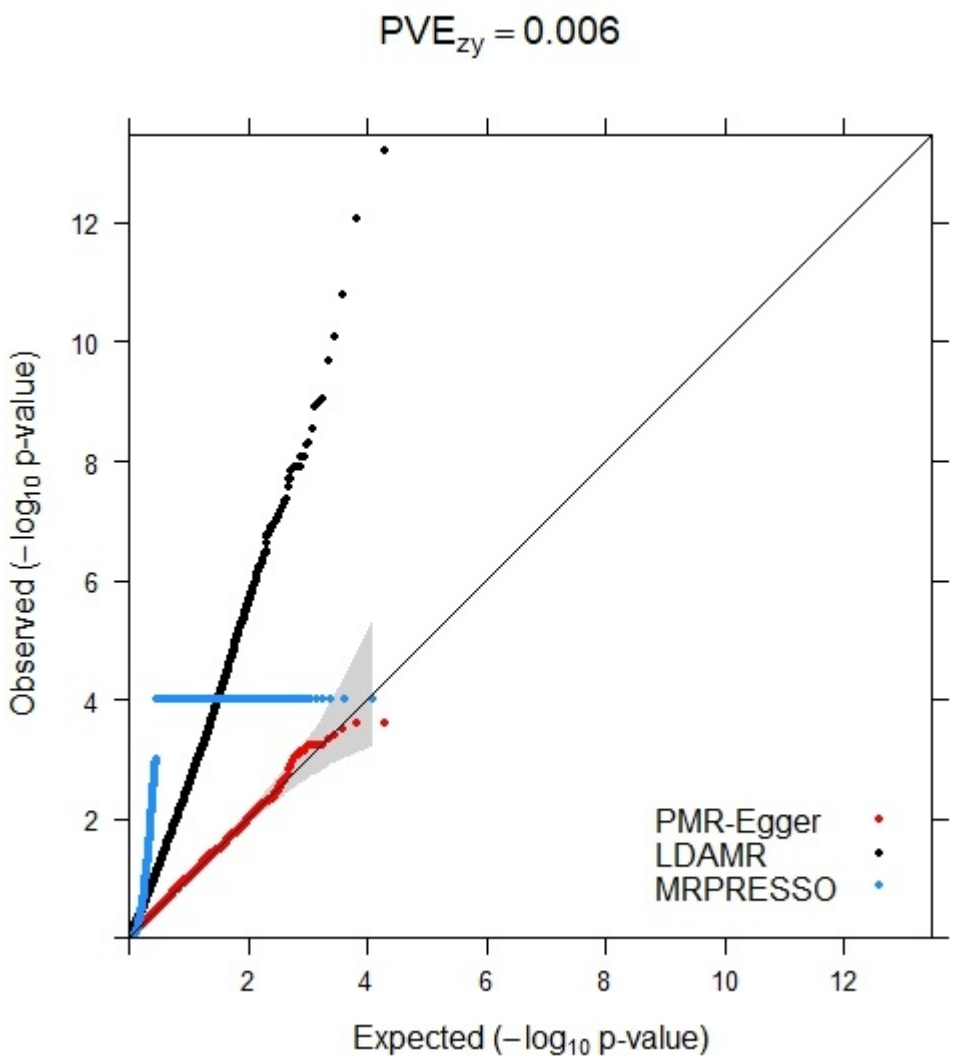
- LDA MR Egger: Fixed effects of $\boldsymbol{\beta}$; Egger assumption on $\boldsymbol{\gamma}$; two-stage inference.

- MR-PRESSO: Permutation based approach; assumes independent instruments.

- PMR-Egger: Normal prior on $\boldsymbol{\beta}$; Egger assumption on $\boldsymbol{\gamma}$; maximum likelihood inference.

Testing Horizontal Pleiotropy γ under the Null





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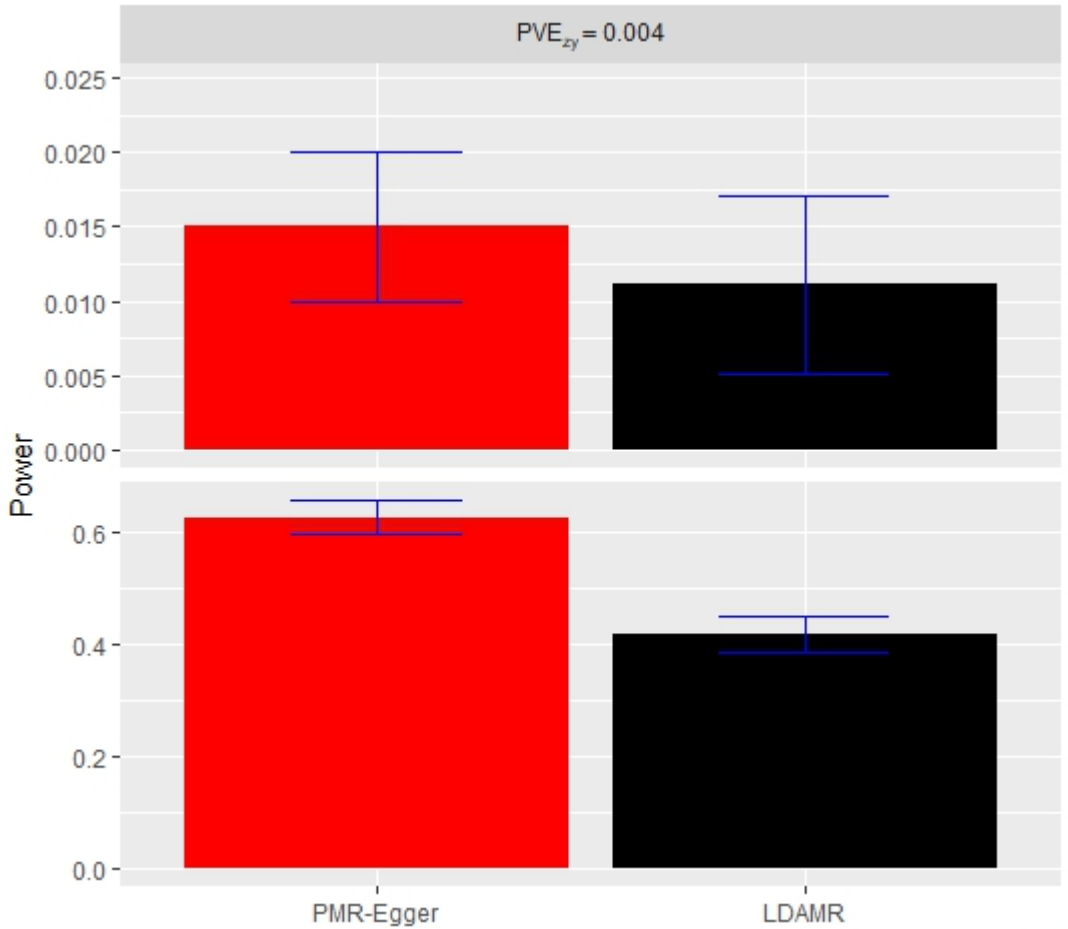
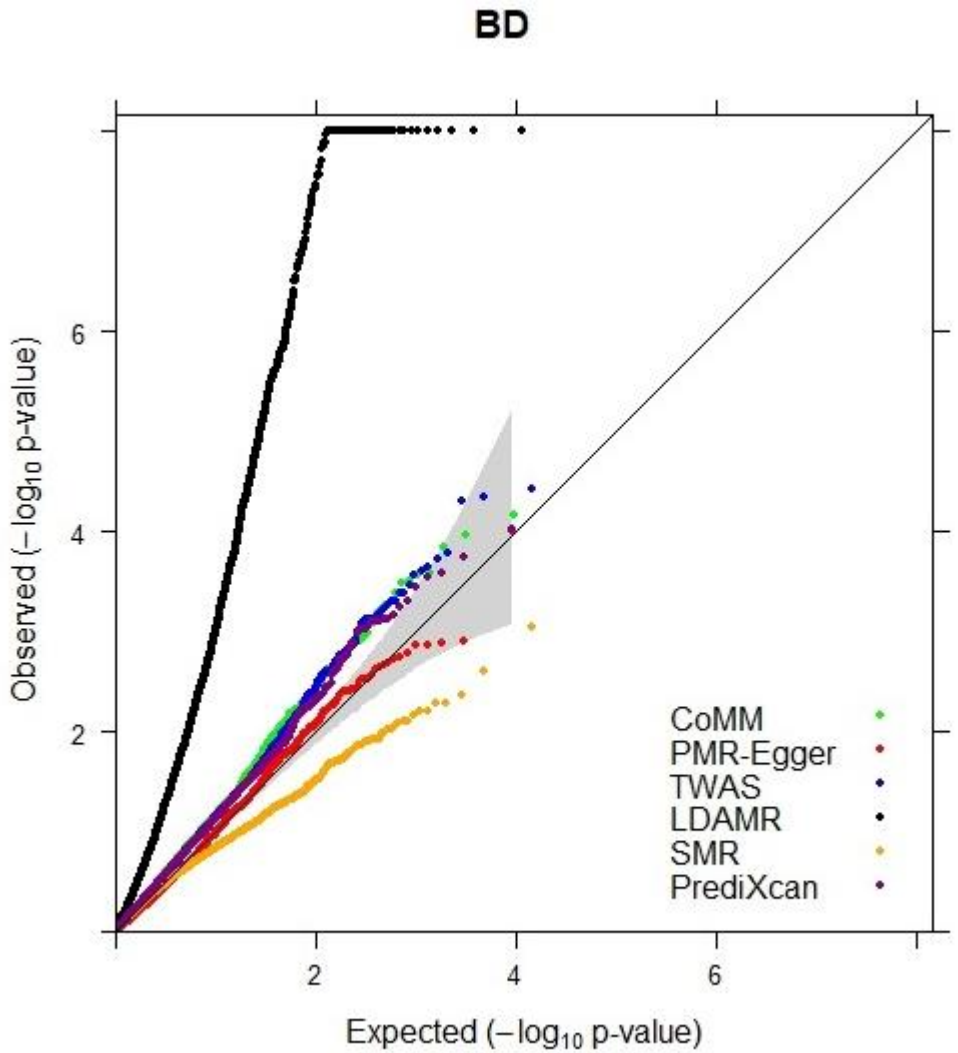
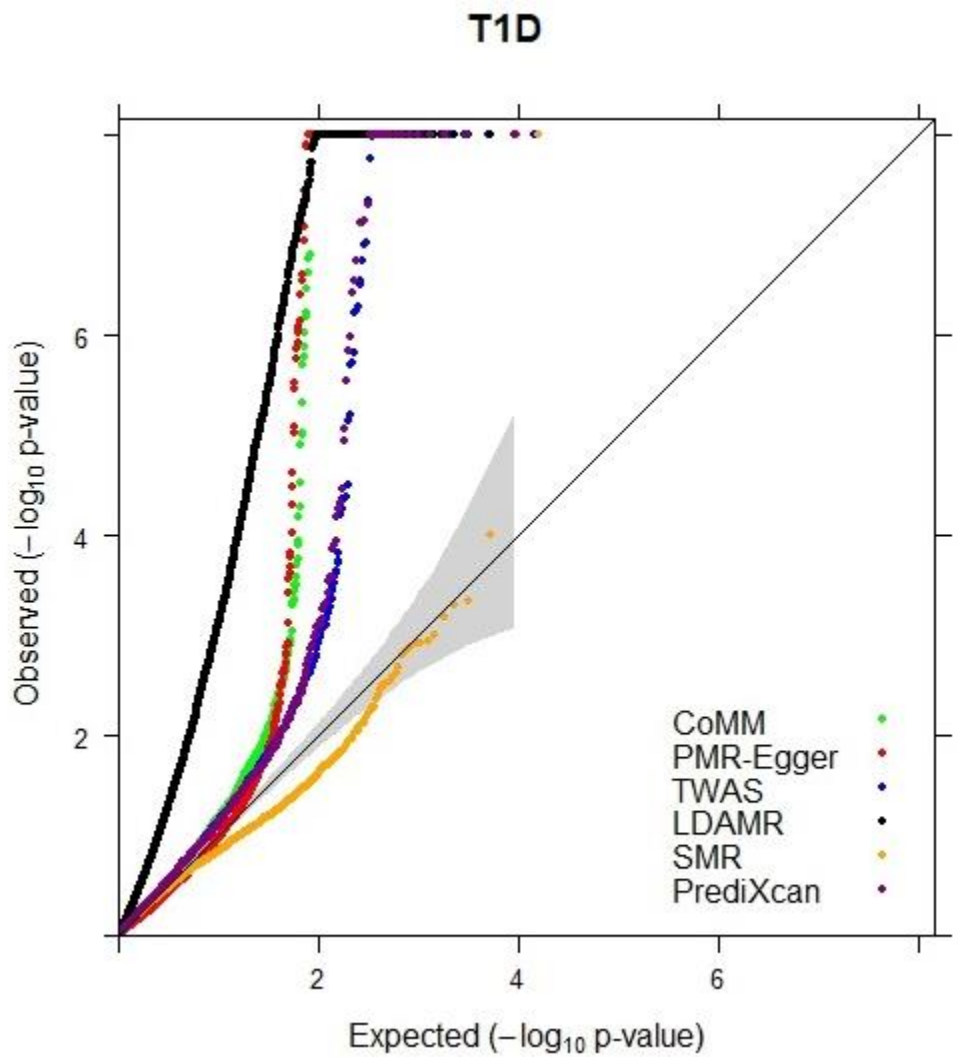


Real Data Applications

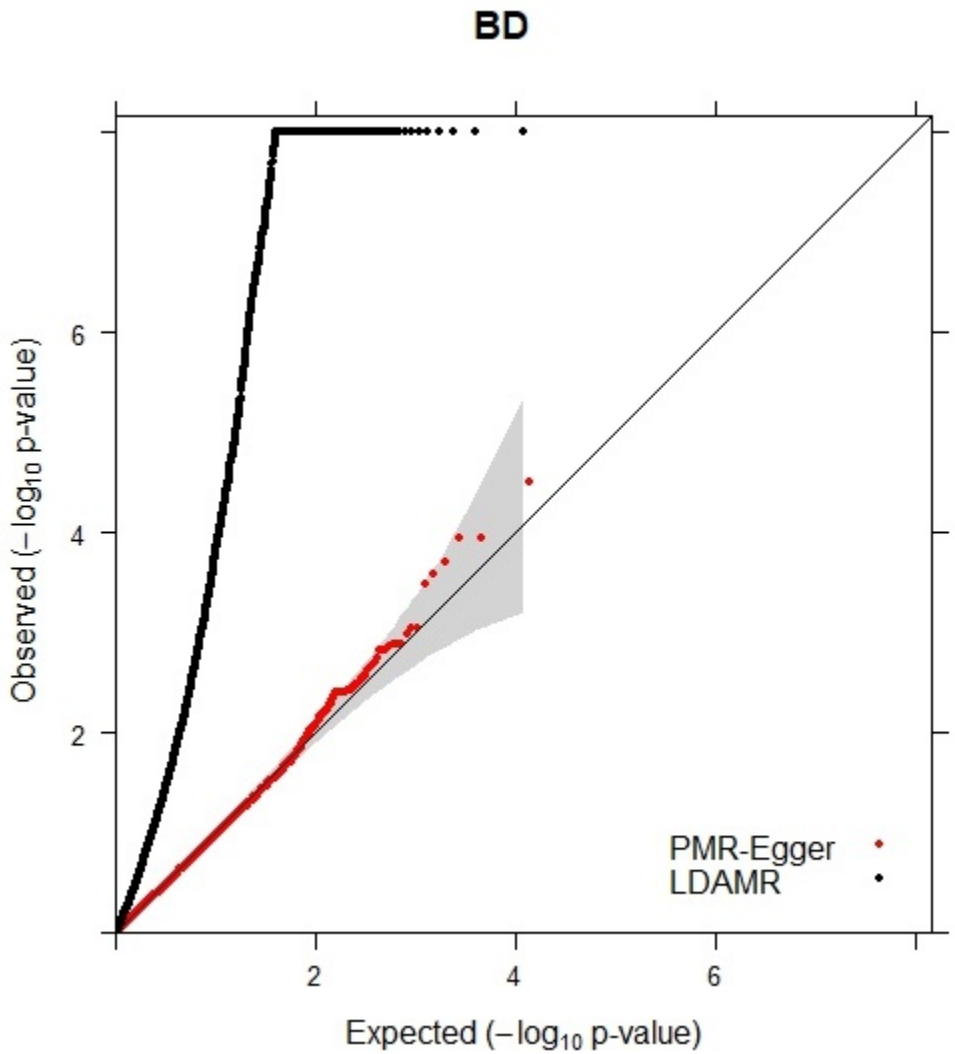
- GEUVADIS Expression Data ($n_1 = 465$), with ~15,000 genes.
- WTCCC: Seven common diseases ($n_2 = \sim 5{,}000$).
- UK Biobank: Ten quantitative traits ($n_2 = \sim 300{,}000$).

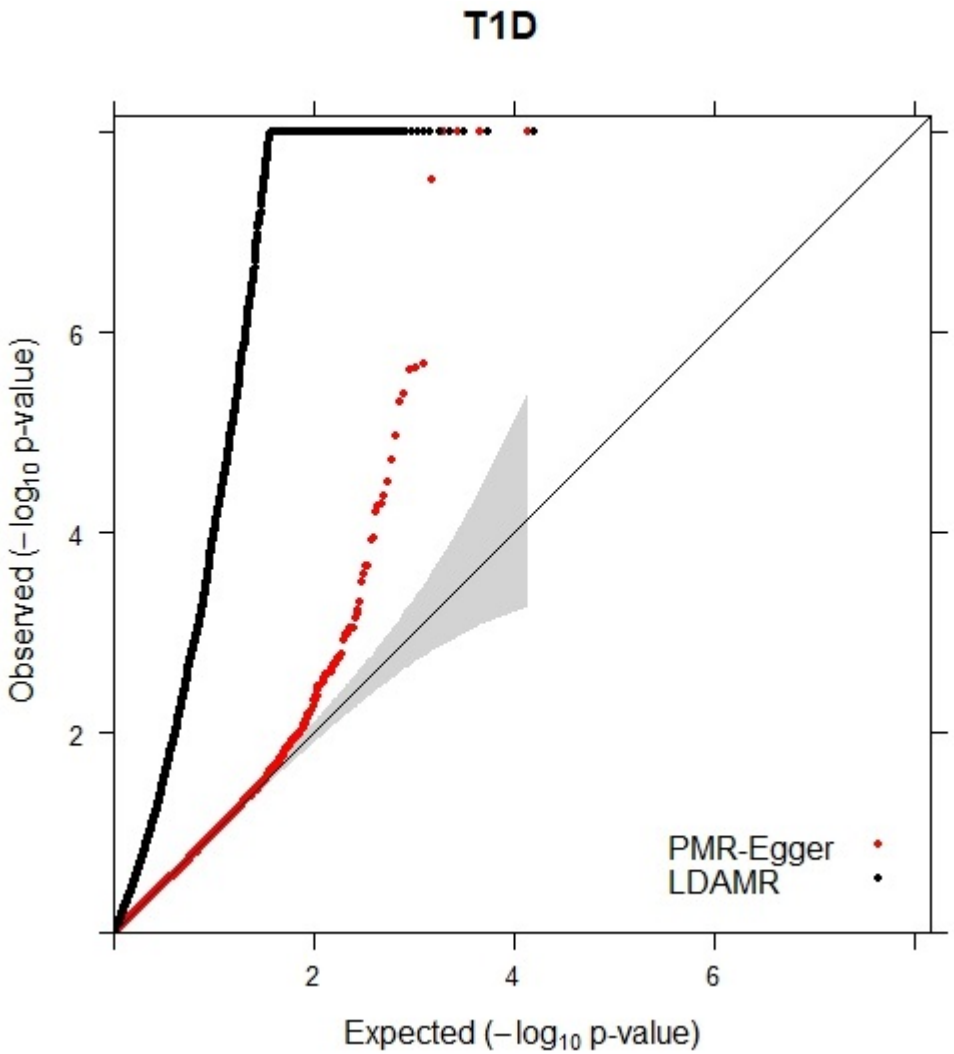
WTCCC: Testing Causal Effects



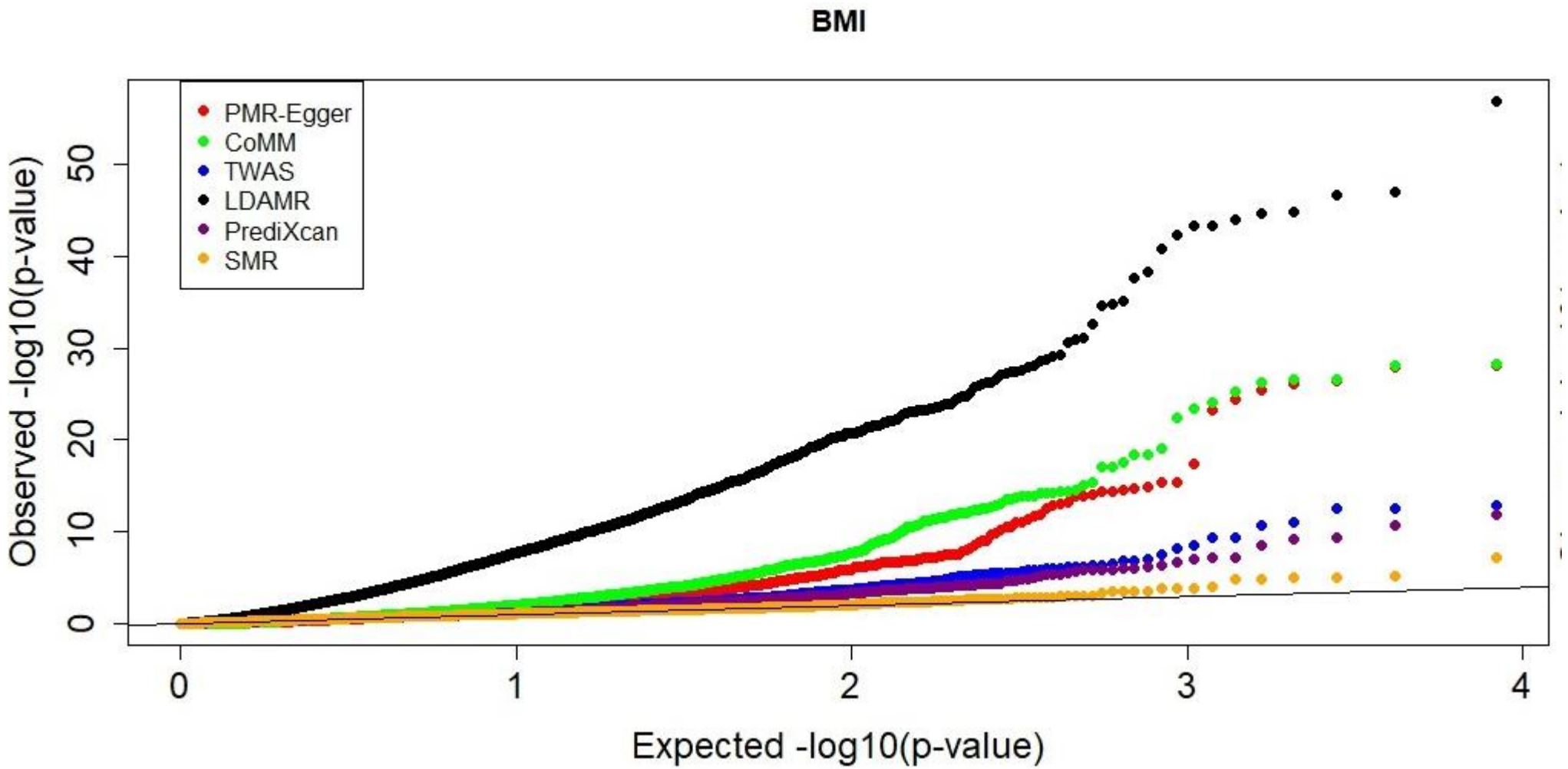


WTCCC: Testing Horizontal Pleiotropy





UK Biobank: Testing Causal Effects



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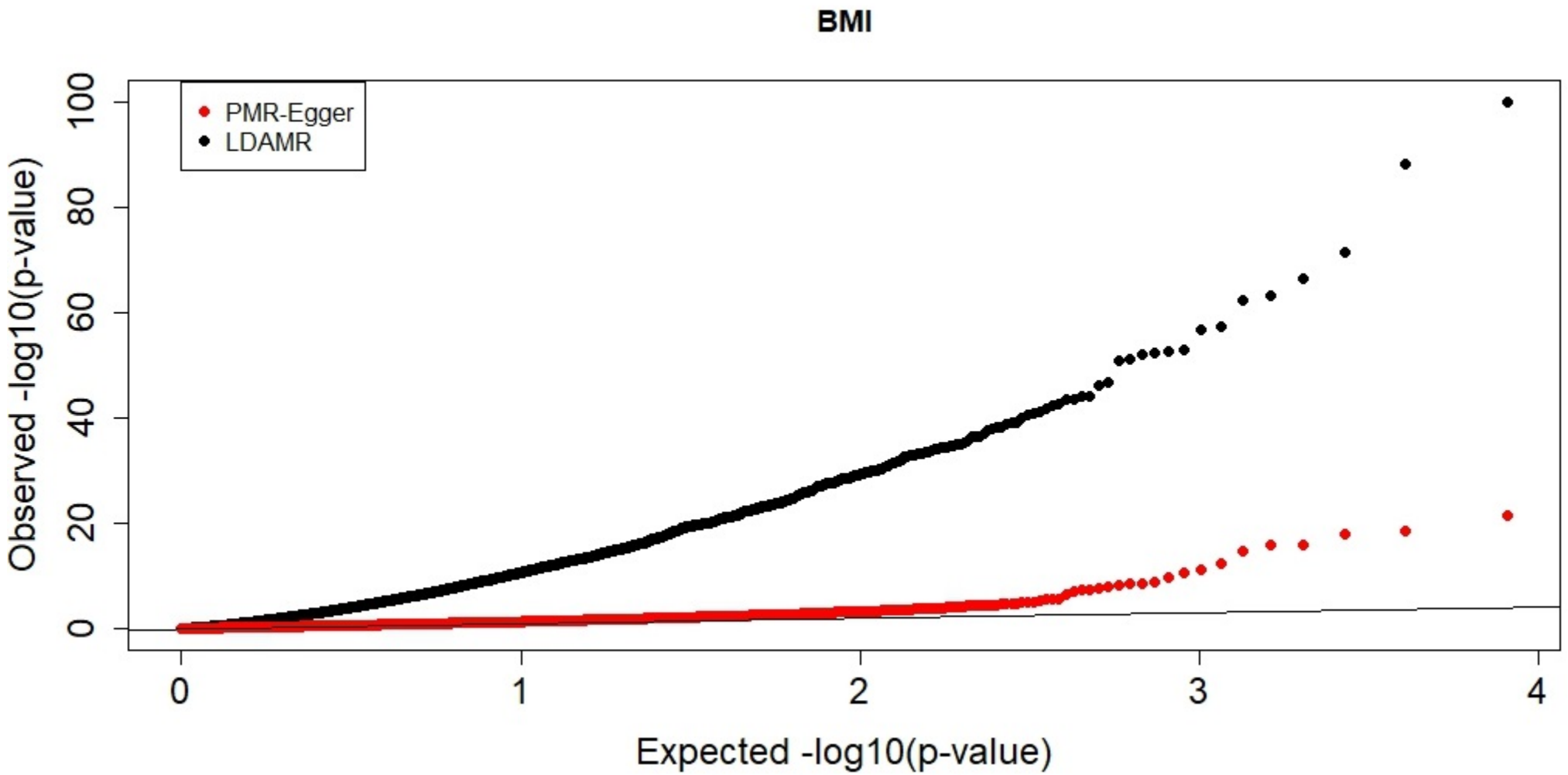

Summary

- We have presented an MR framework that unifies many existing integrative transcriptome wide association analysis method.
- Our method PMR-Egger effectively controls for horizontal pleiotropy through a maximum likelihood/probabilistic inference framework.
- We have demonstrated the effectiveness of PMR-Egger through simulations and real data applications.
- PMR-Egger is implemented in the PMR R package, to be available on www.xzlab.org

Acknowledgements

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- Collaborators: Ping Zeng (Xuzhou Medical University), Can Yang (HKUST) and Jin Liu (Duke-NUS Medical School)

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