Nothing to disclose

Distinct explanations underlie gene-environment interactions in the UKBiobank

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Center for Genetic Epidemiology

Outline

1. Background on gene-environment interactions
2. Methods
3. Results
4. Summary

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1. **Background on gene-environment interactions**
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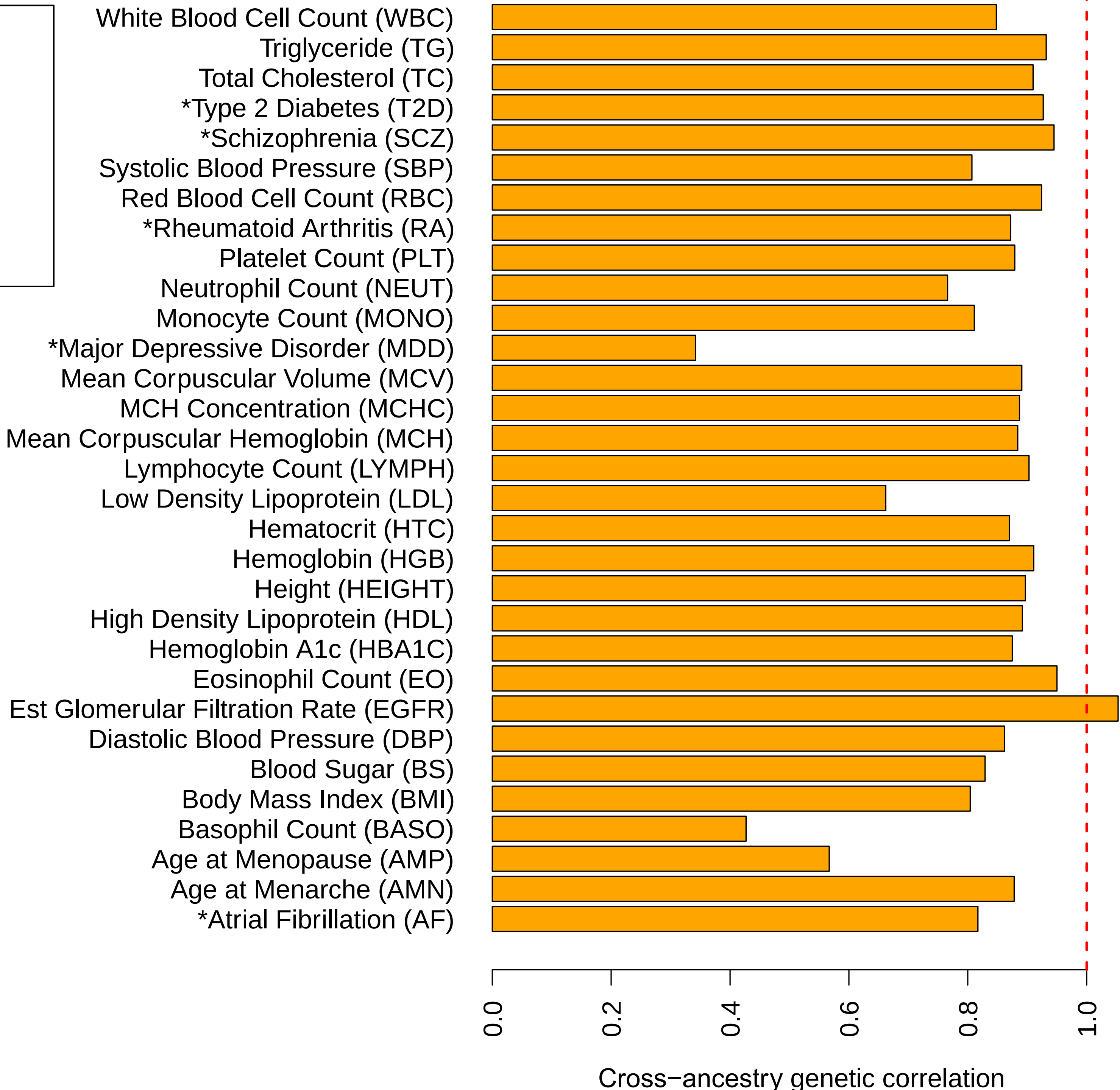
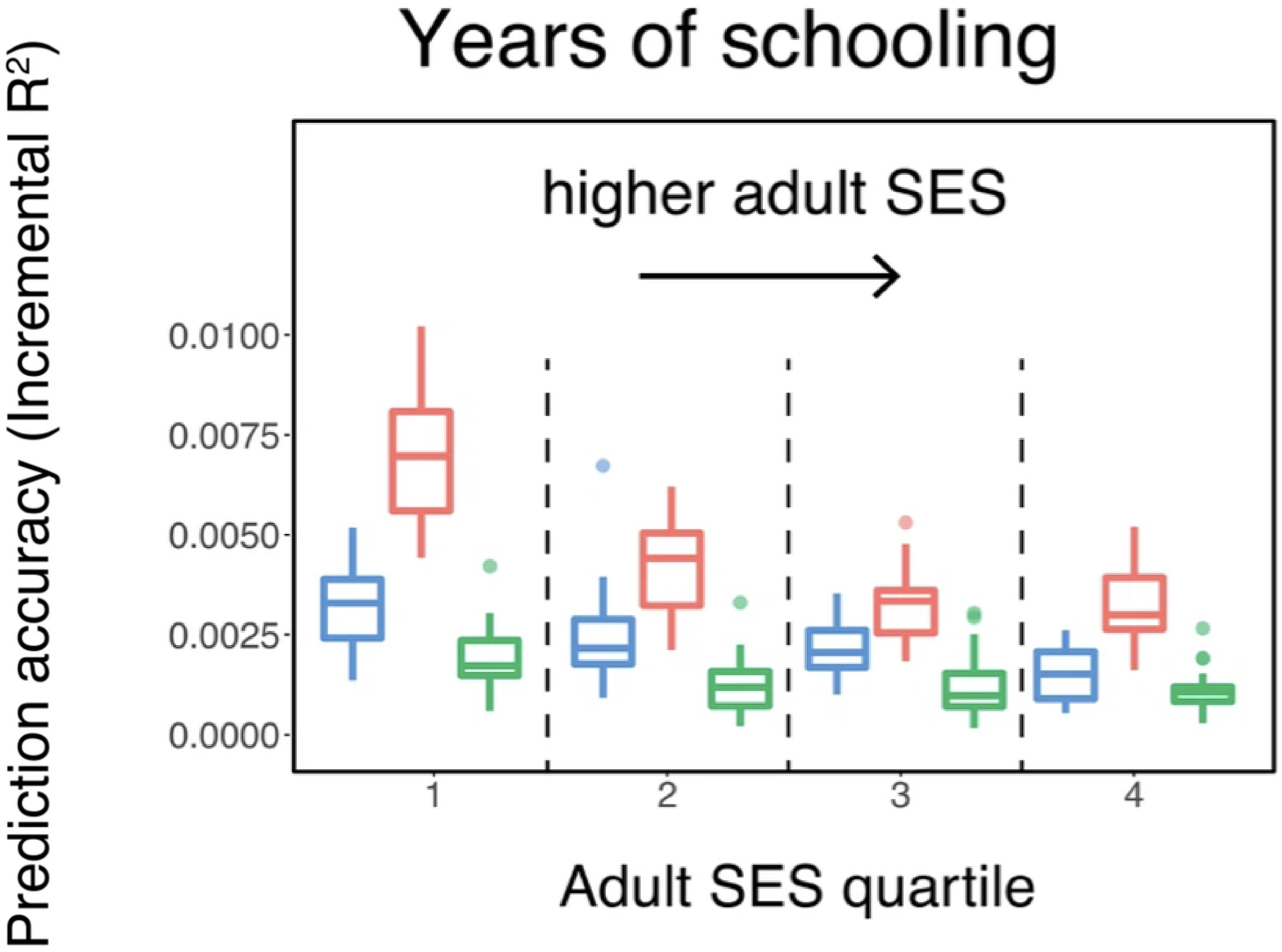
Genetic effects across the genome may exhibit context dependence

- European-East Asian cohort genetic correlation is less than 1 (average: **85%** SE: 1%) across a wide range of traits
- Polygenic GxE is one possible explanation



Data replotted from Shi et al 2021 Nat Commun

Polygenic GxE may explain variable prediction accuracy of polygenic scores within an ancestry



- Incremental R^2 changes as a function of E variables
- Could be due to interactions, among other explanations

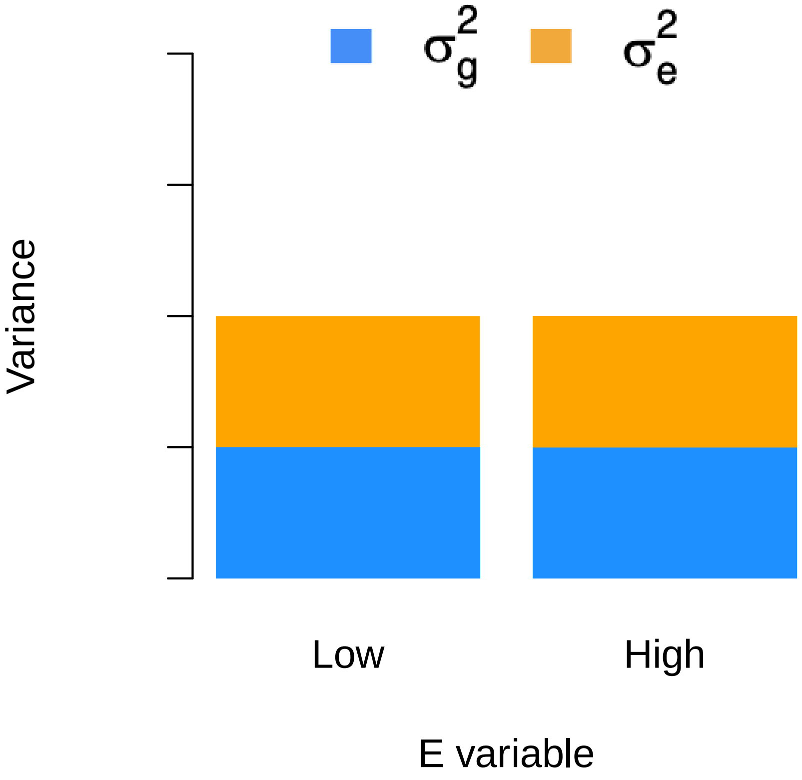
Mostafavi et al 2020 eLife

Major questions remain about the contribution of GxE to disease heritability

- How widespread are context dependent genetic effects?
- What is the contribution of polygenic GxE to disease heritability?

GxE can arise through different scenarios

Imperfect genetic correlation



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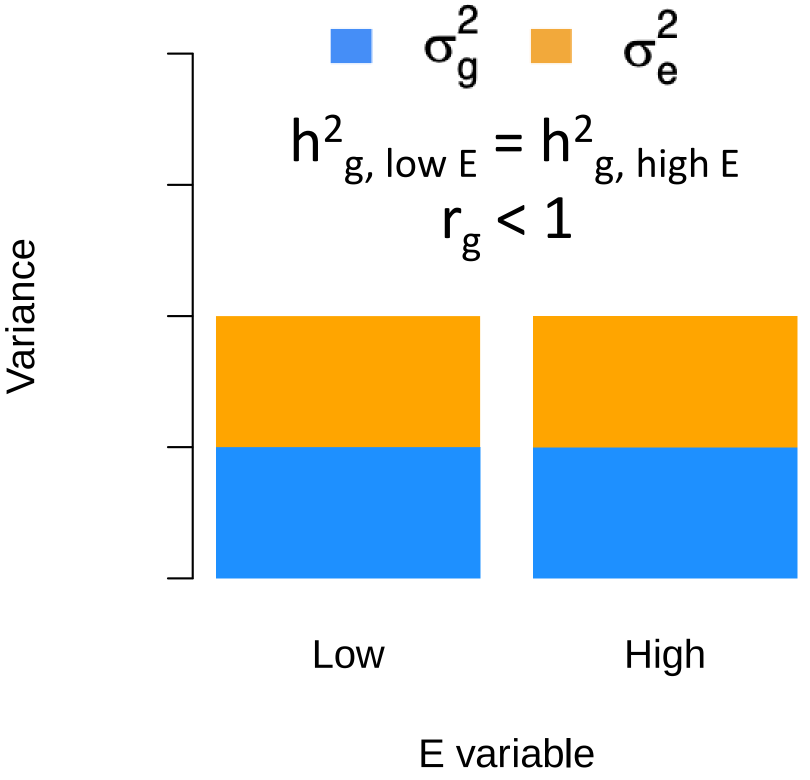

$h^2_{g,\ \text{low E}} = h^2_{g,\ \text{high E}}$

$r_g < 1$

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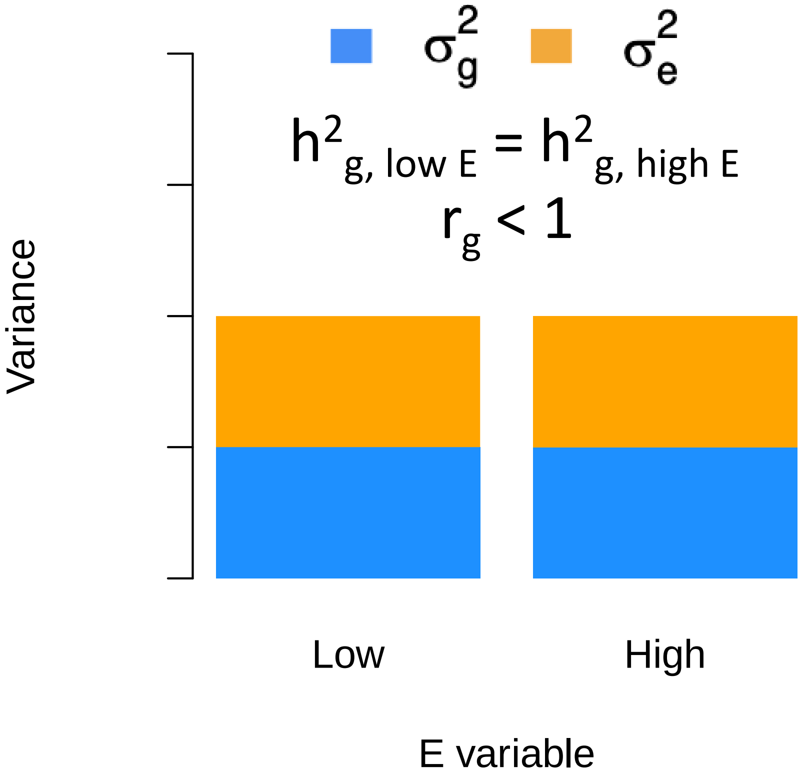

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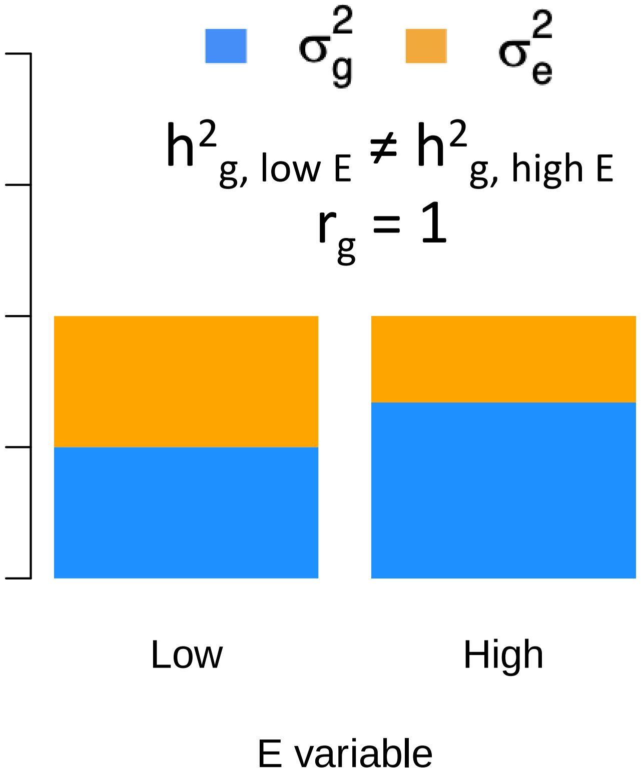
Varying genetic variance



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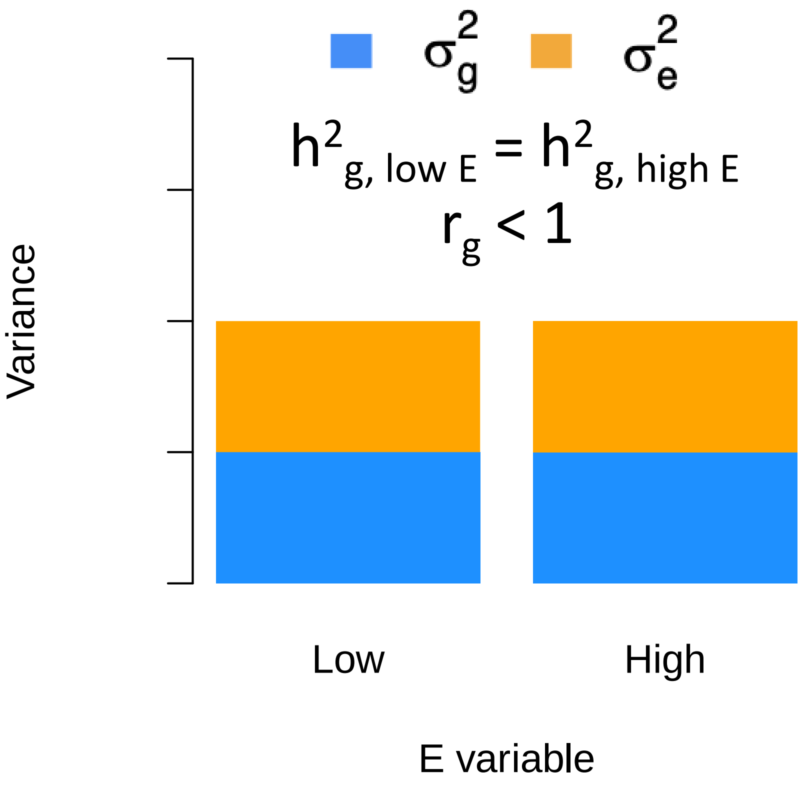

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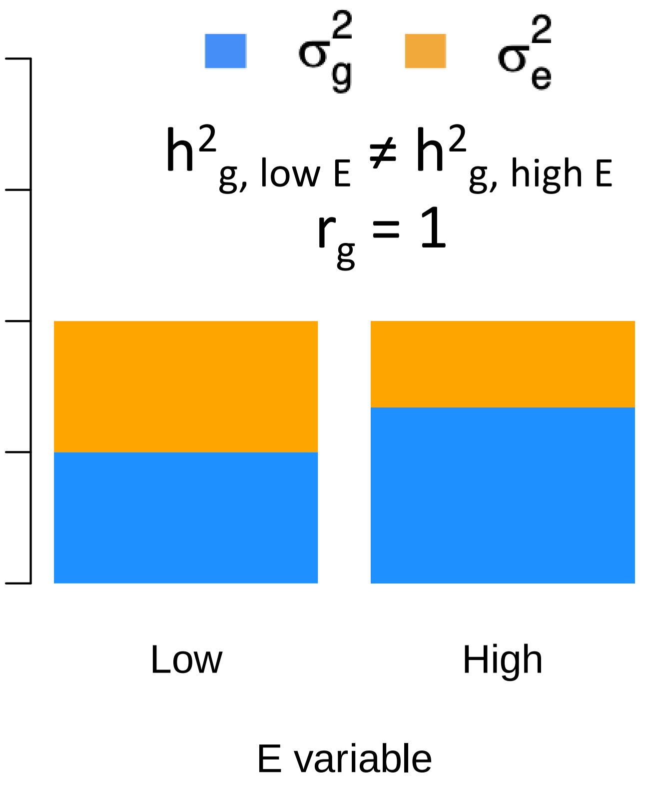
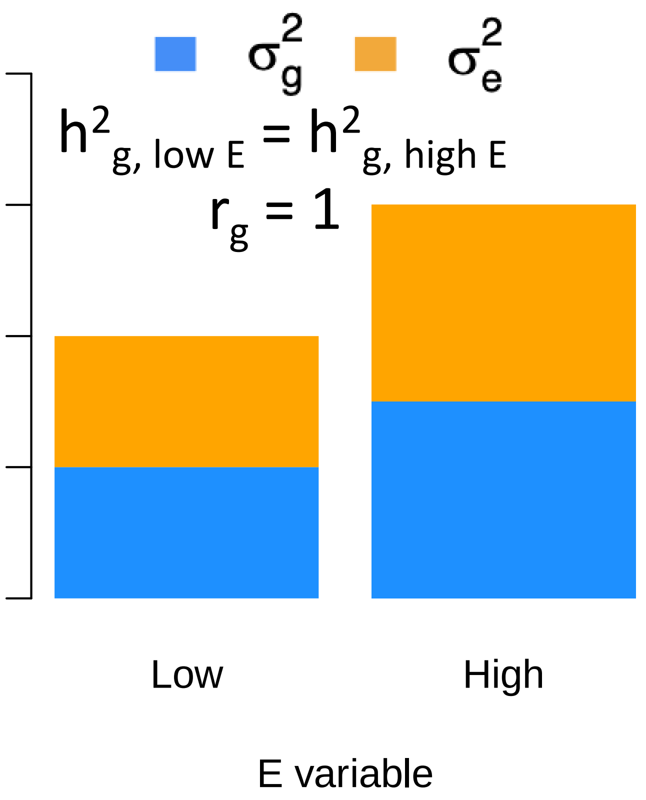


Proportional amplification



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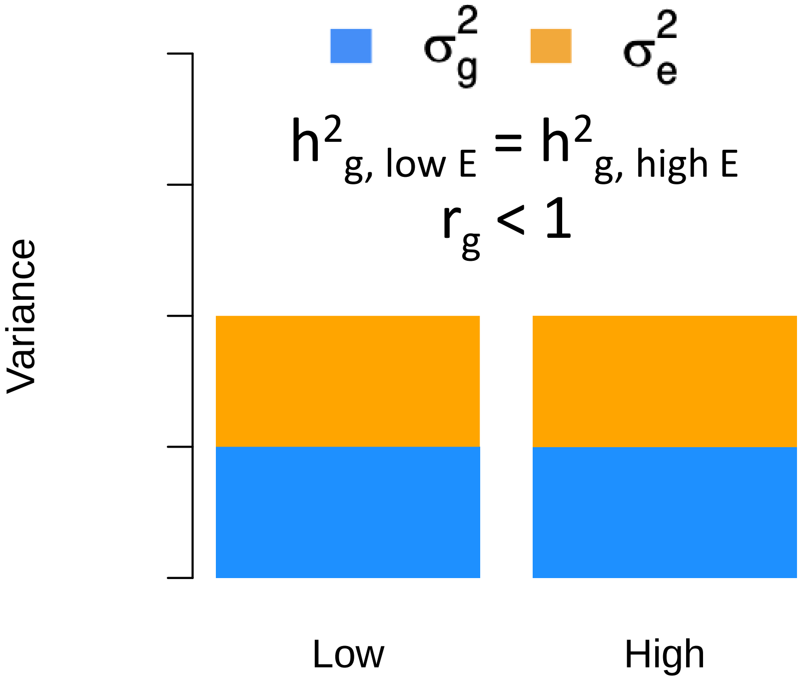

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Locus dependent GxE

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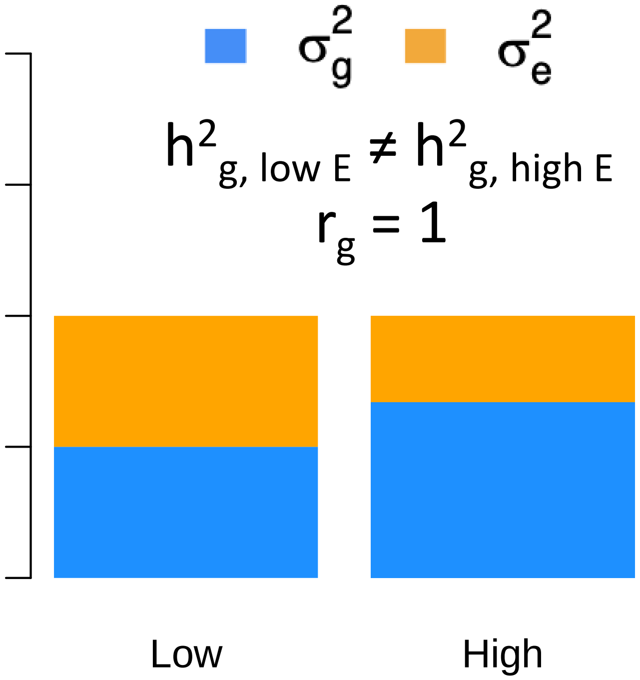

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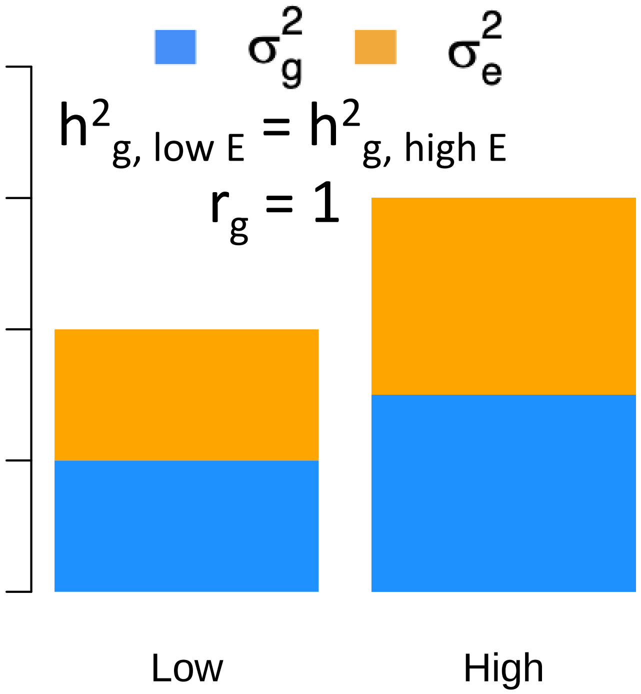

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Non-locus dependent GxE

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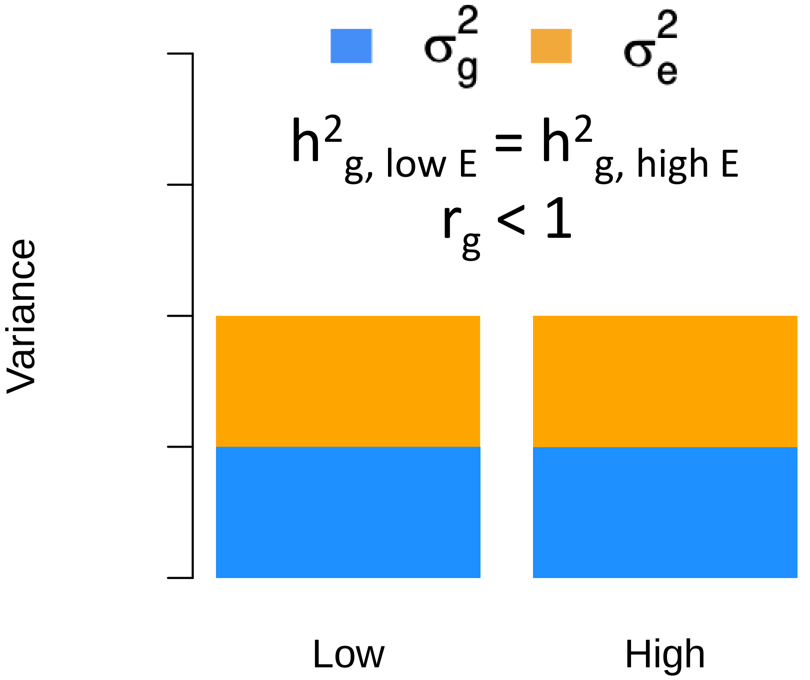

$h^2_{g,\text{ low E}} = h^2_{g,\text{ high E}}$

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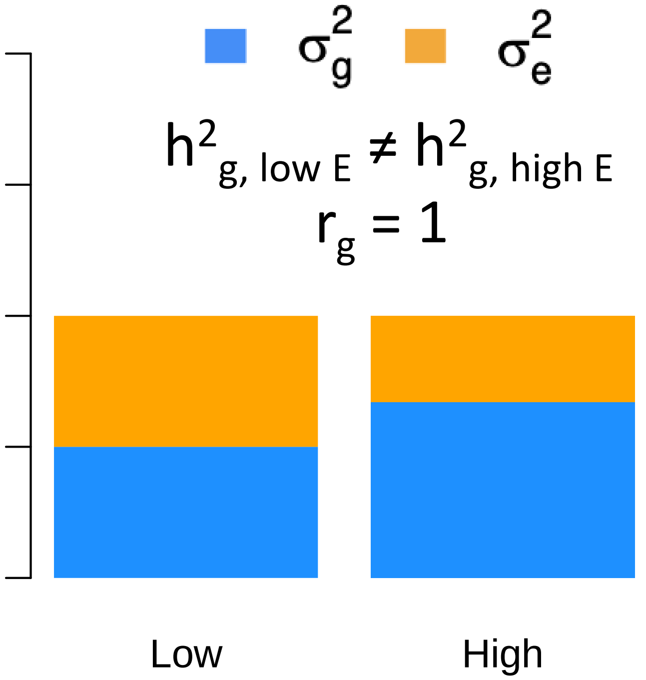
Locus dependent GxE:
Effect sizes are multiplied by a SNP-specific factor

Varying genetic variance



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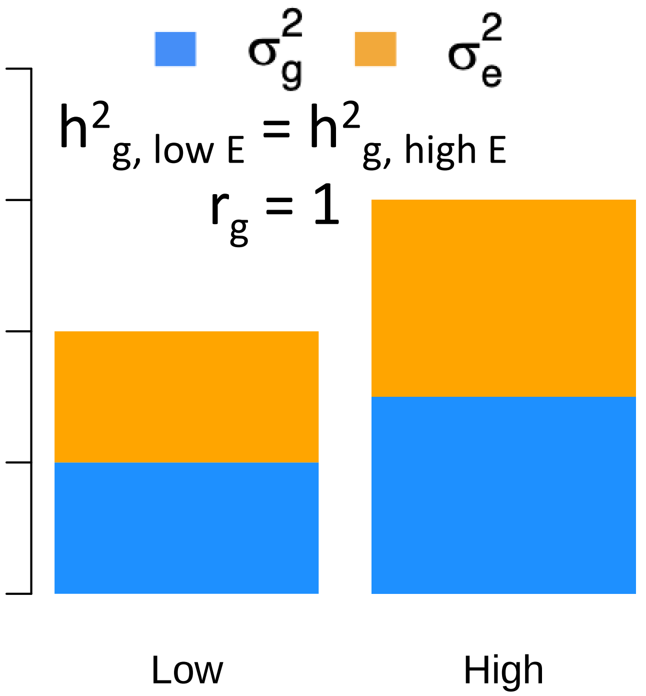

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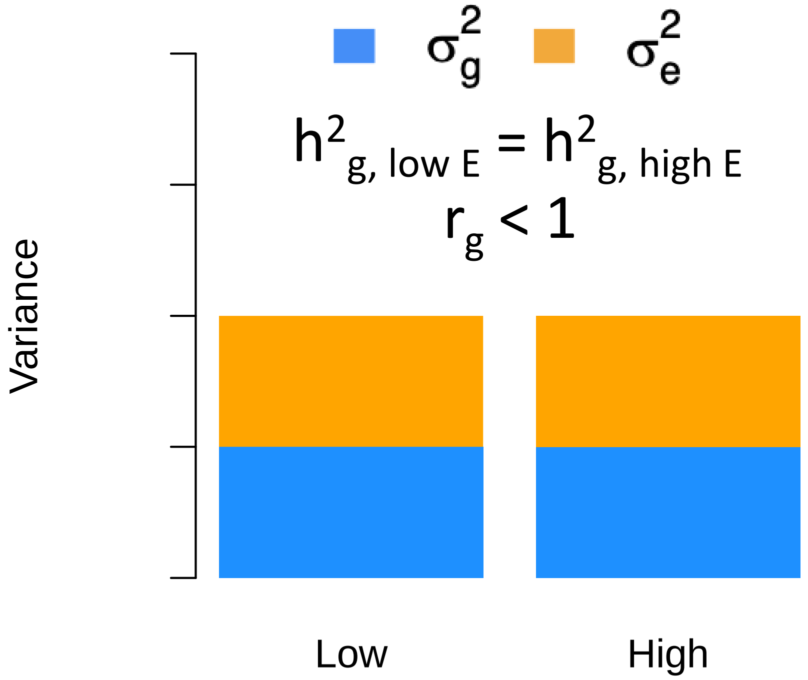

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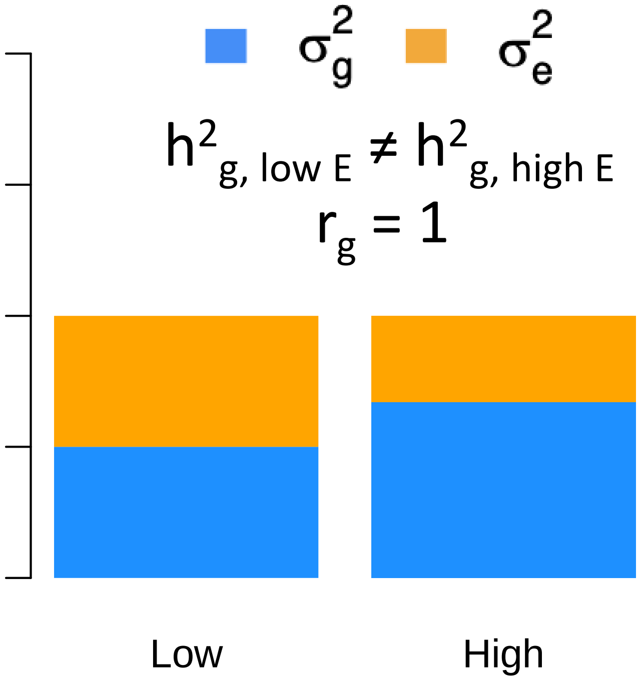
Varying genetic variance



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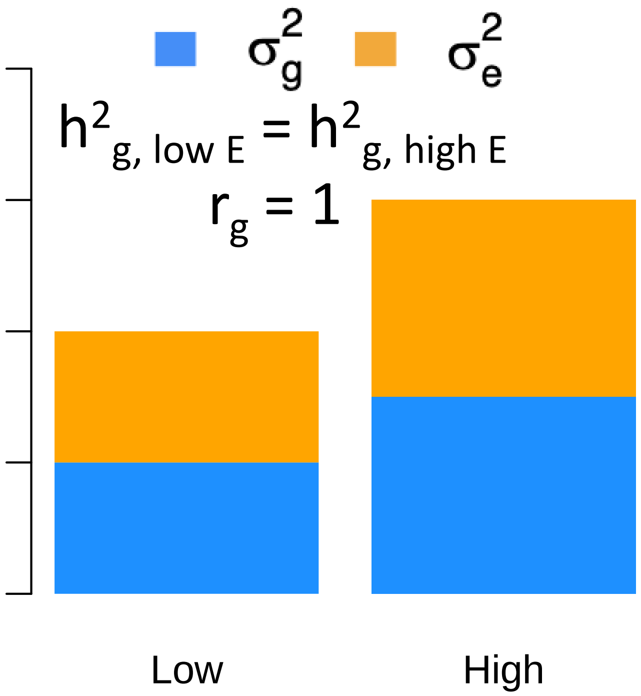

$h^2_{g,\text{ low E}} = h^2_{g,\text{ high E}}$

$r_g = 1$

Non-locus dependent GxE:
Effect sizes or phenotypic variance multiplied by a constant factor across all SNPs

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We can distinguish between polygenic GxE scenarios with three metrics

Scenarios / Metrics	Imperfect genetic correlation	Varying genetic variance	Proportional amplification
Genetic correlation	✓	✗	✗

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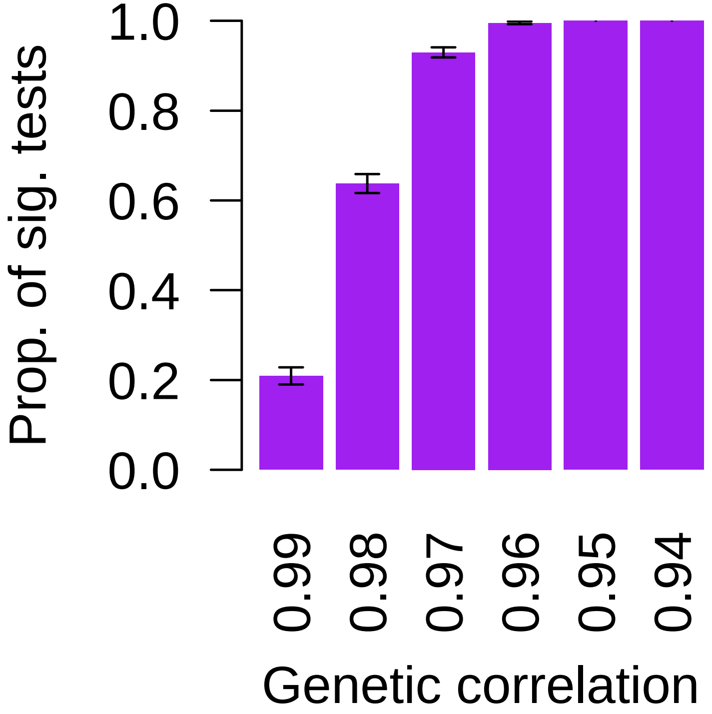
Genetic correlation	✓	✗	✗
PRS x E regression	✗	✓	✓

We can distinguish between polygenic GxE scenarios with three metrics

Scenarios / Metrics	<u>Imperfect genetic correlation</u>	<u>Varying genetic variance</u>	<u>Proportional amplification</u>
Genetic correlation	✅	❌	❌
PRS x E regression	❌	✅	✅
h^2 by E	❌	✅	❌

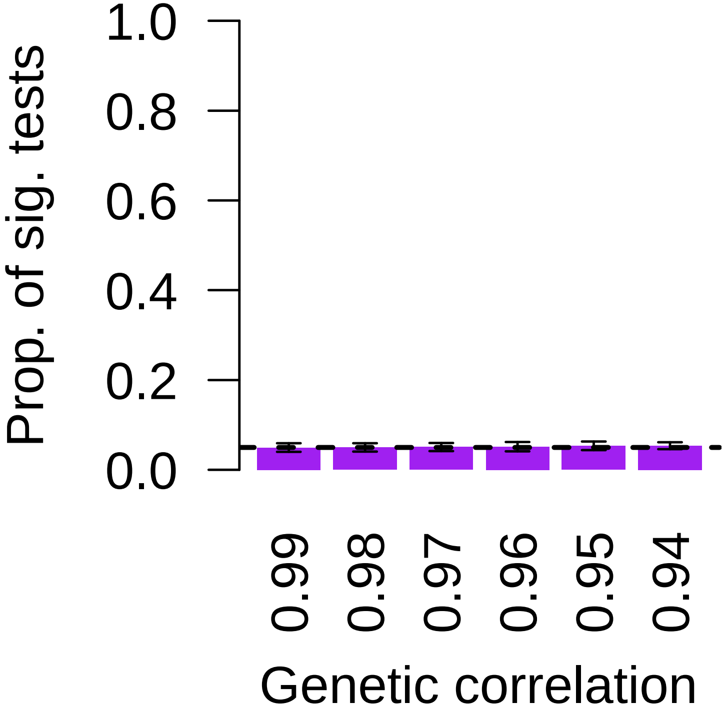
LDSC genetic correlation is well-powered to detect $r_g < 97\%$ across E bins in Scenario 1

Genetic correlation across E bins



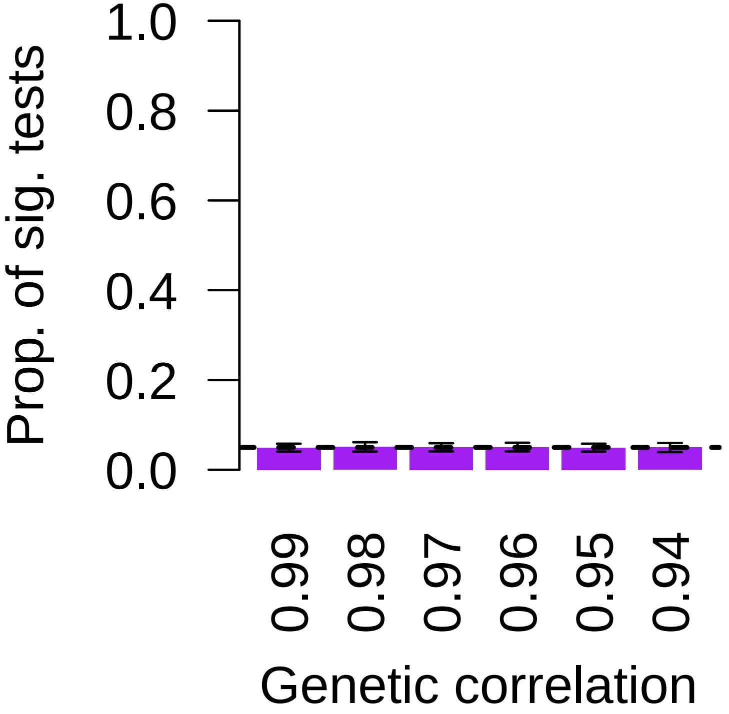
N=67K per bin

PRSxE regression



N=337K training
N=47K test

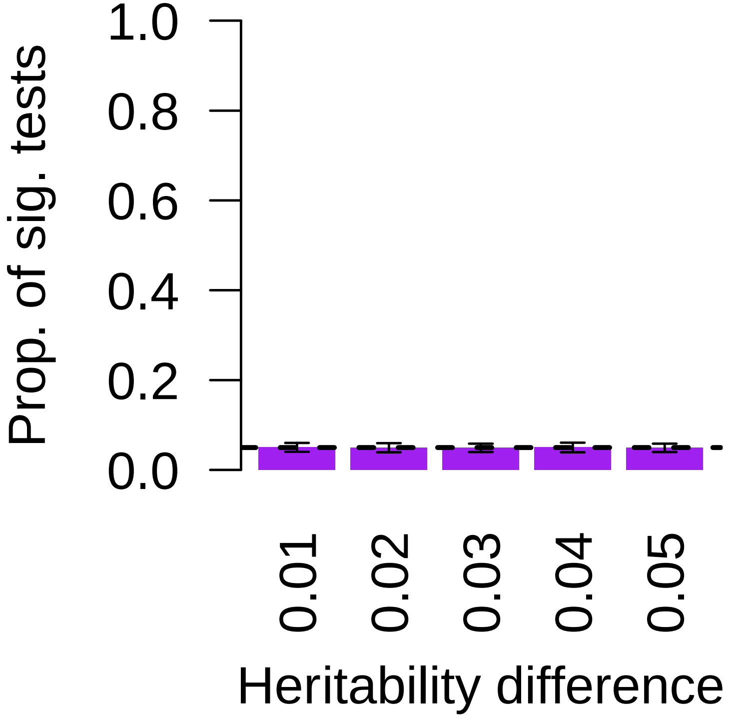
SNP-heritability across E bins



N=67K per bin

h^2 estimation across E bins and PRSxE regression are well-powered to detect heritability differences between E bins > 2% in Scenario 2

Genetic correlation
across E bins



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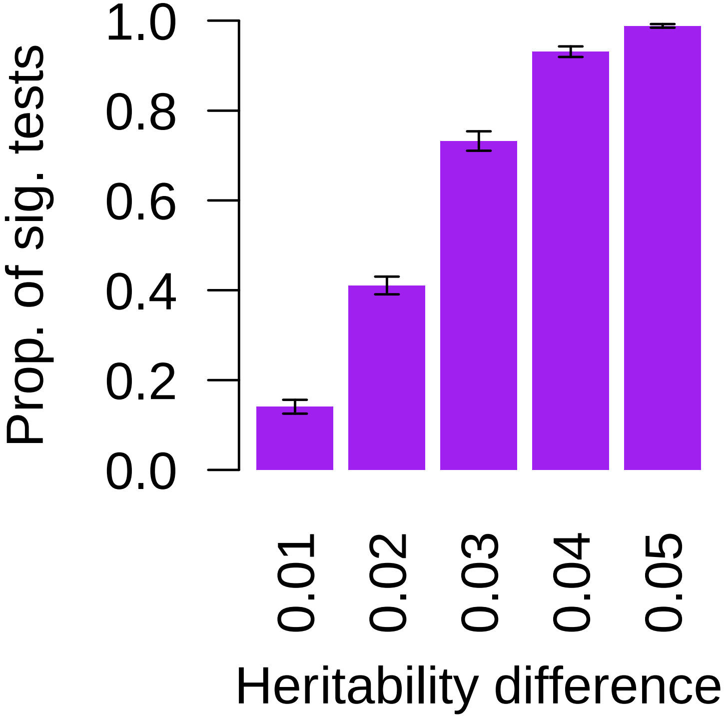
PRSxE
regression



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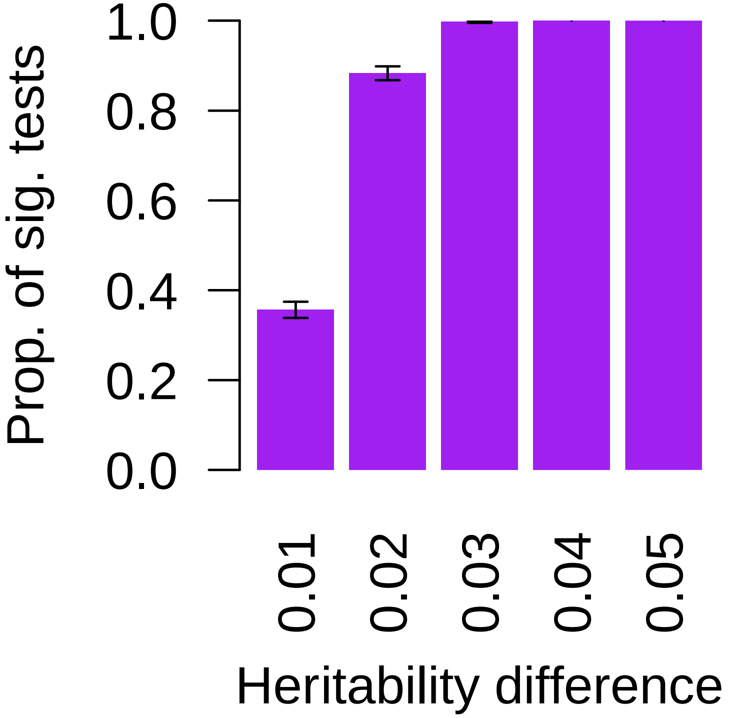
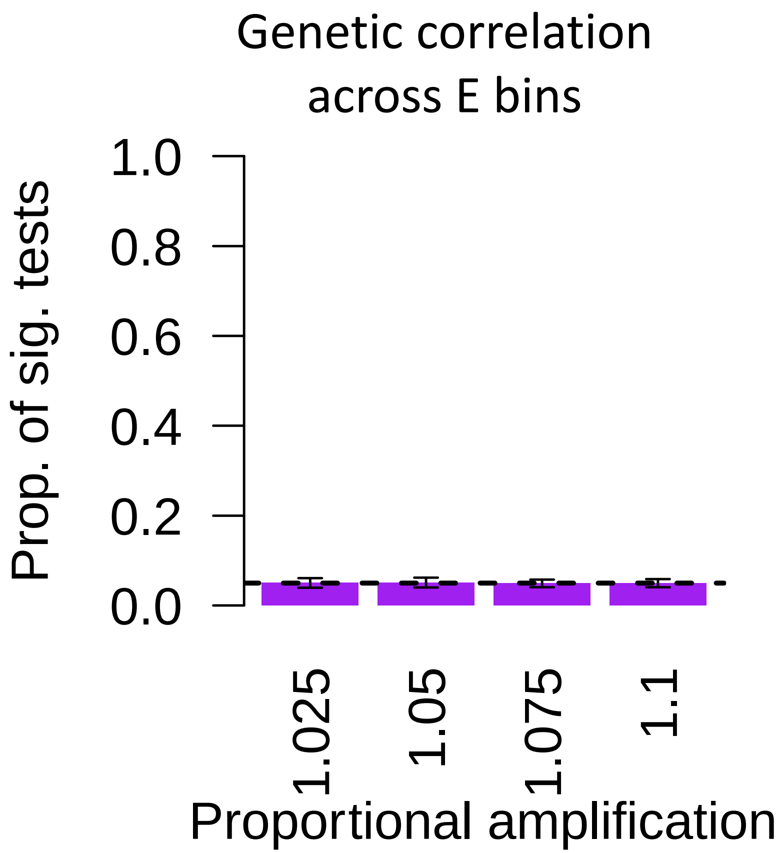


N=67K per bin

PRSxE regression is well-powered to detect proportional phenotype amplification >5% in Scenario 3



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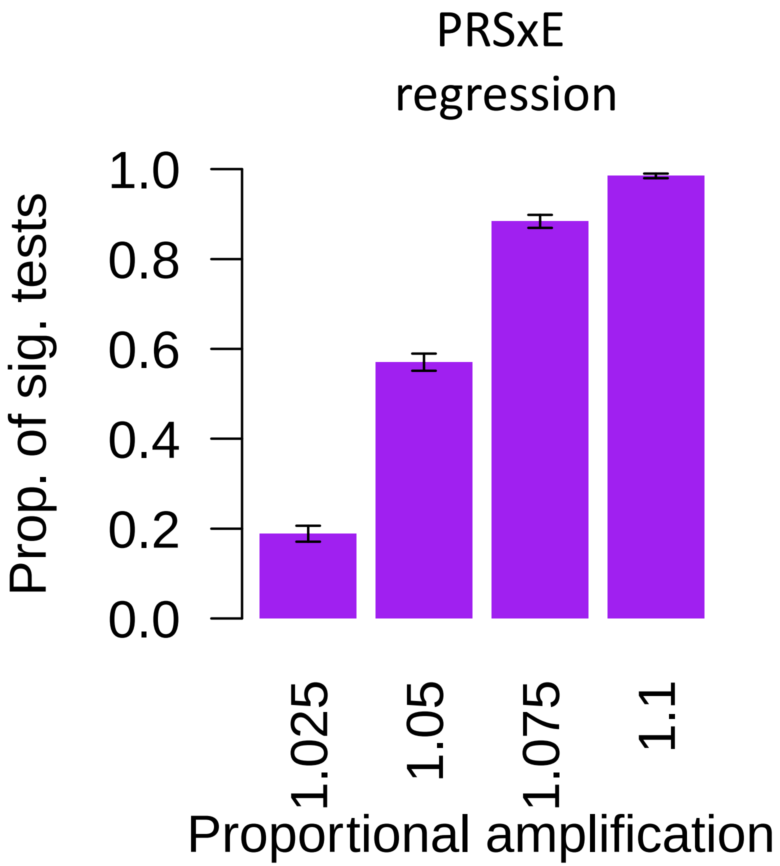

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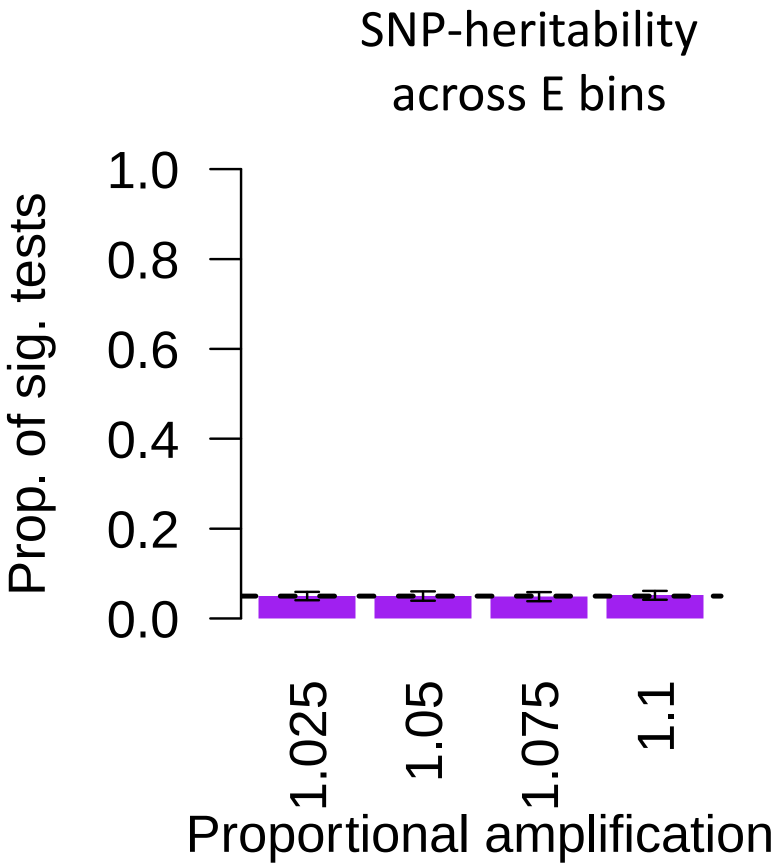

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Inferring the contribution of GxE in UKBiobank data

1. We analyzed 33 complex diseases and traits across 10 E variables

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    - Diet
    - Sleep
    - Alcohol
    - Smoking
    - Physical activity
    - Sex

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Average E variable h^2 = 6%
Max = 15% (Smoking)

Inferring the contribution of GxE in UKBiobank data

1. We analyzed 33 complex diseases and traits across 10 E variables
    - Diet
    - Sleep
    - Alcohol
    - Smoking
    - Physical activity
    - Sex

2. For h^2 and r_g we binned individuals into 5 bins (or 2 bins for binary E variables) according to their E variables:
    - r_g and h^2 : N=67K per bin
    - PRSxE: N=47K (PRS trained on 337K)

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3. Simulations
4. **Results**
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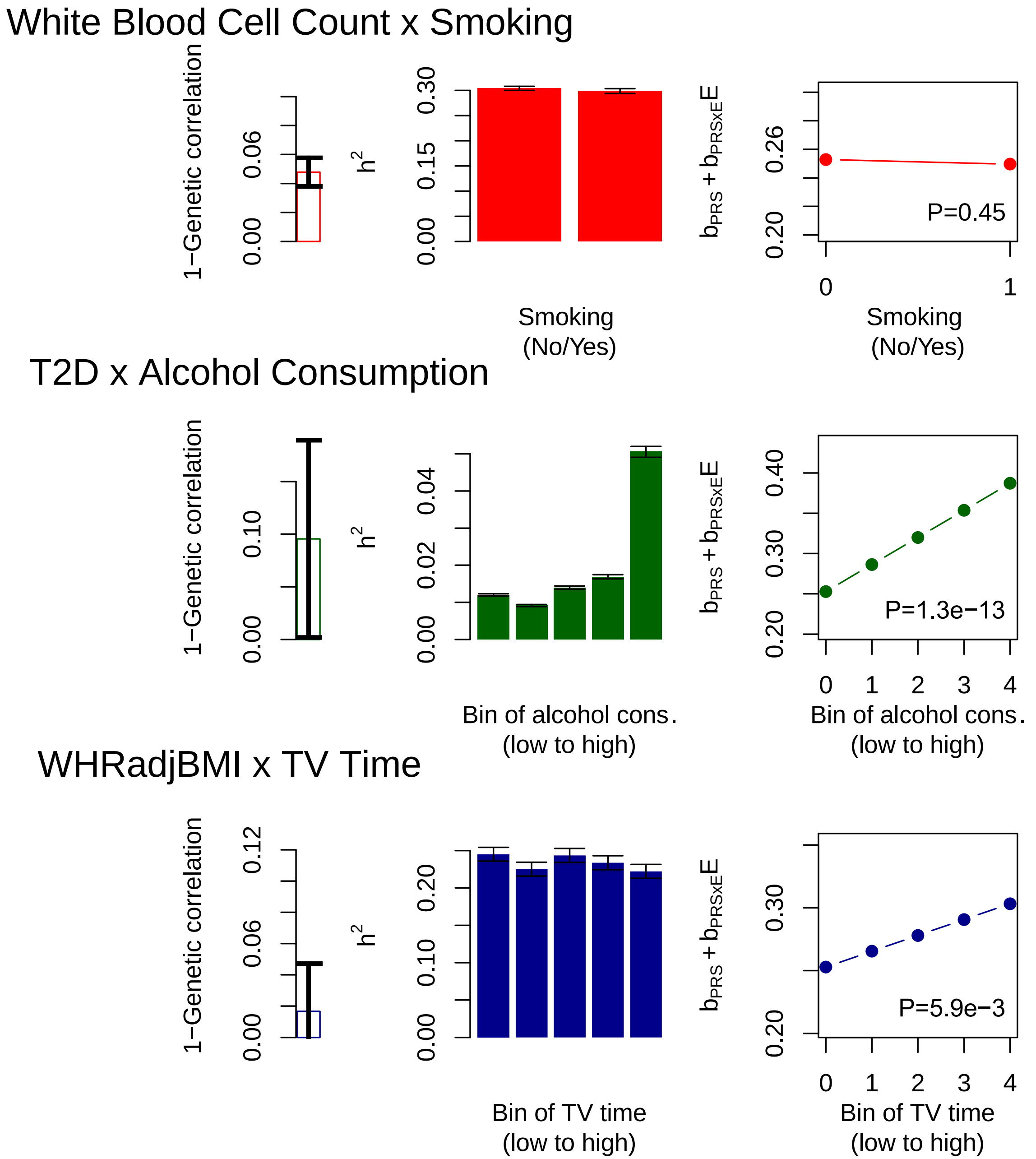
We find examples of all three Scenarios of GxE

Scenario 1:
Imperfect Genetic correlation

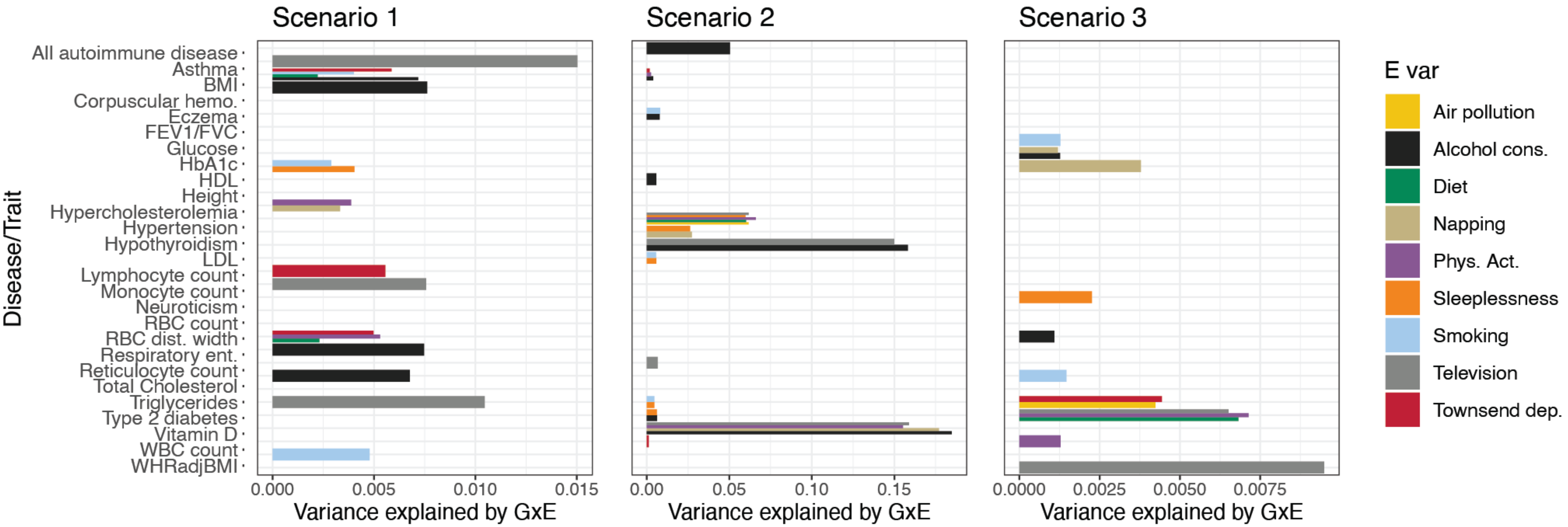
Scenario 2:
Varying Genetic variance

Scenario 3:
Proportional amplification

Genetic correlation | Heritability by E | PRSxE regression



GxE explains 3% of trait variance on average across traits



We find examples of all three Scenarios of GxSex

Genetic correlation

Heritability by E

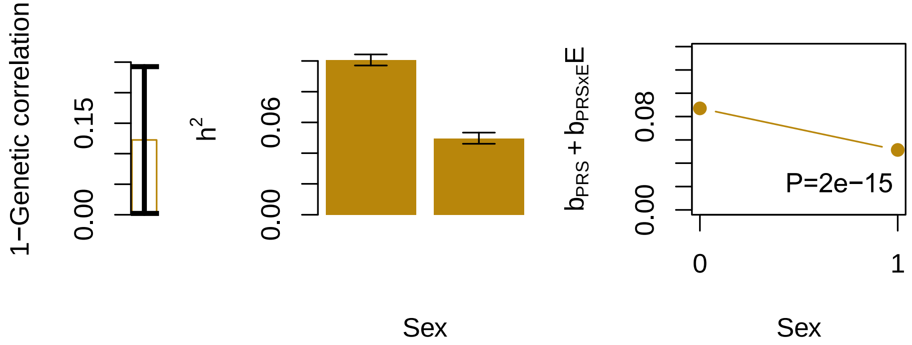
PRSxE regression

Scenario 1:
Imperfect Genetic correlation

A. Neuroticism x Sex

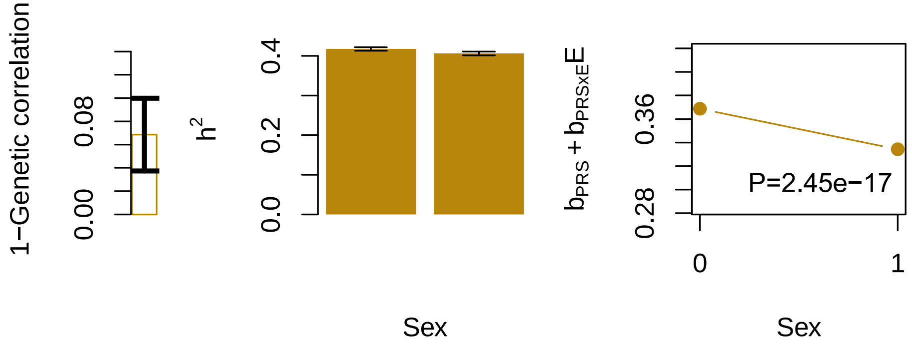
Scenario 2:
Varying Genetic variance

B. Autoimmune Disease x Sex

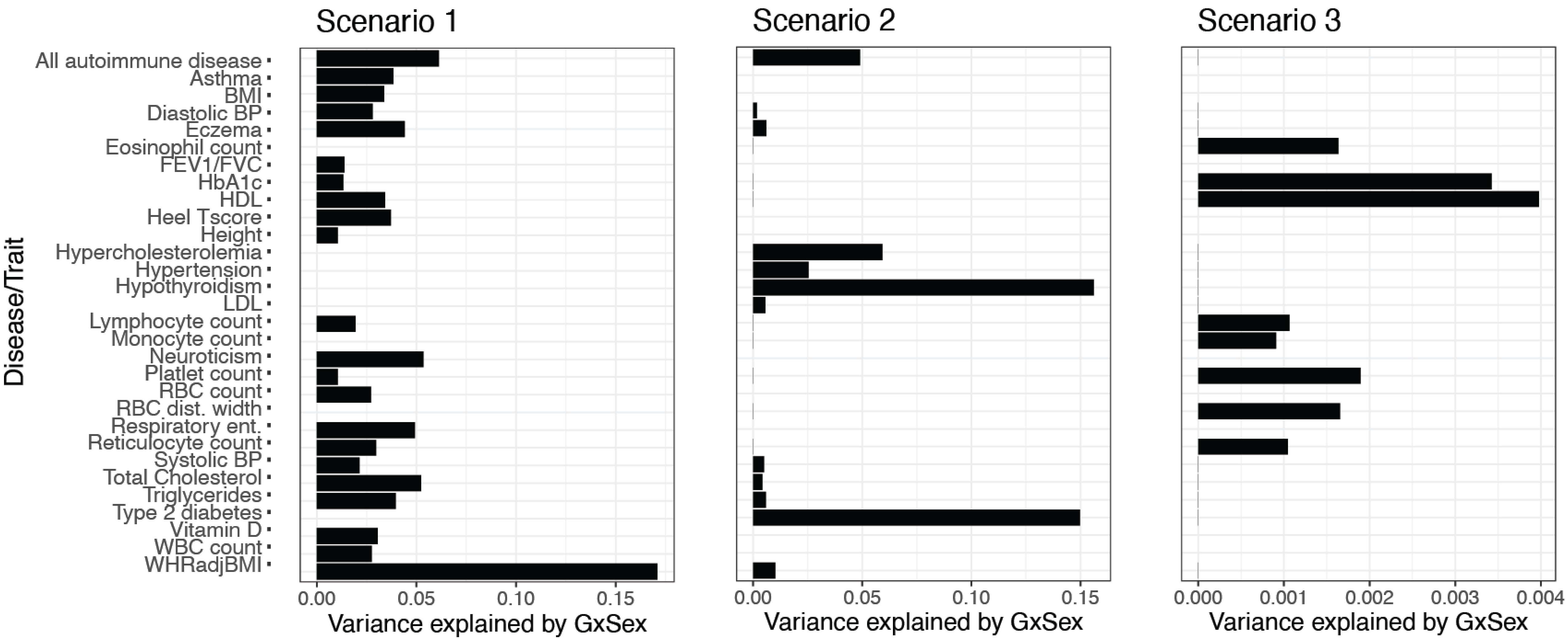


Scenario 3:
Proportional amplification

C. HDL Cholesterol x Sex



GxSex explains 4% of trait variance on average across traits



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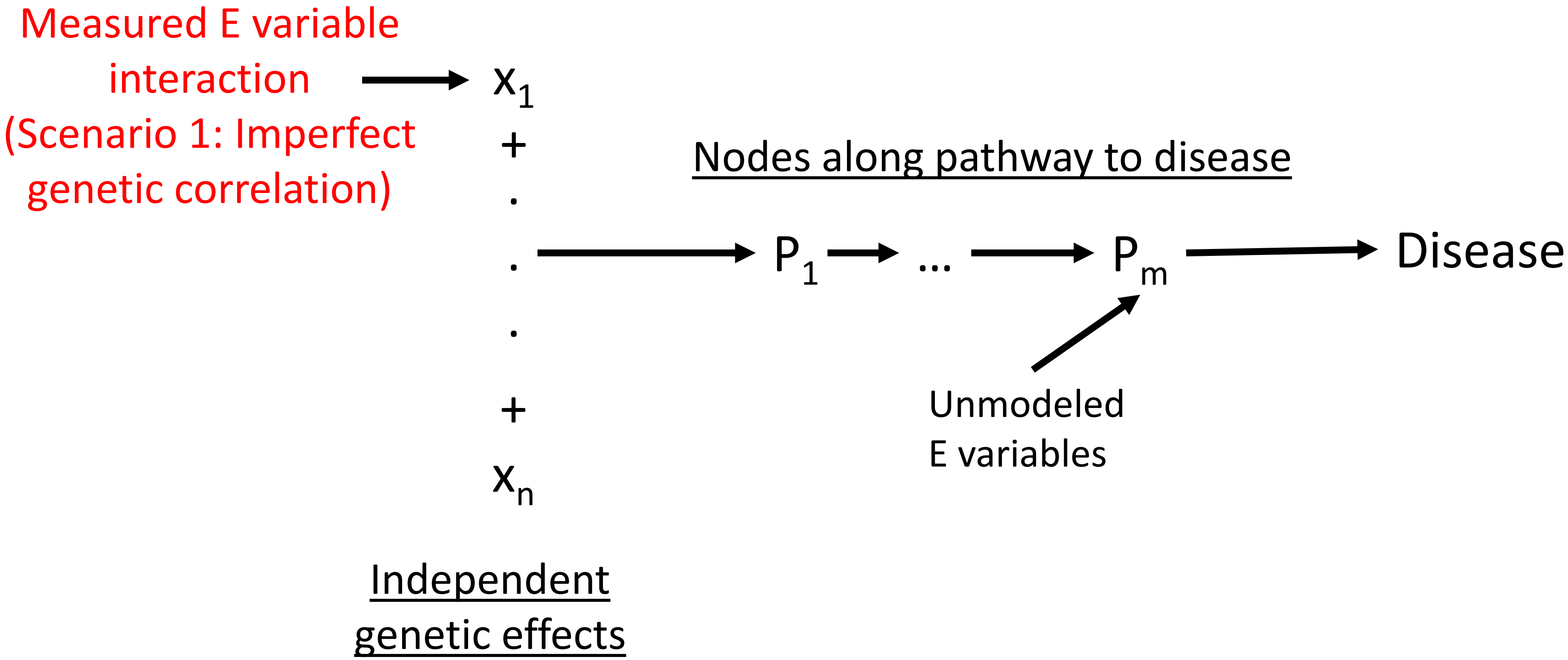
Our results point to a model where E variables interact with genetics at several levels



Measured E variable interaction (Scenario 1: Imperfect genetic correlation)

x_1
+
.
.
.
+
x_n

Independent genetic effects

Nodes along pathway to disease

P_1 … P_m

Disease

Unmodeled
E variables

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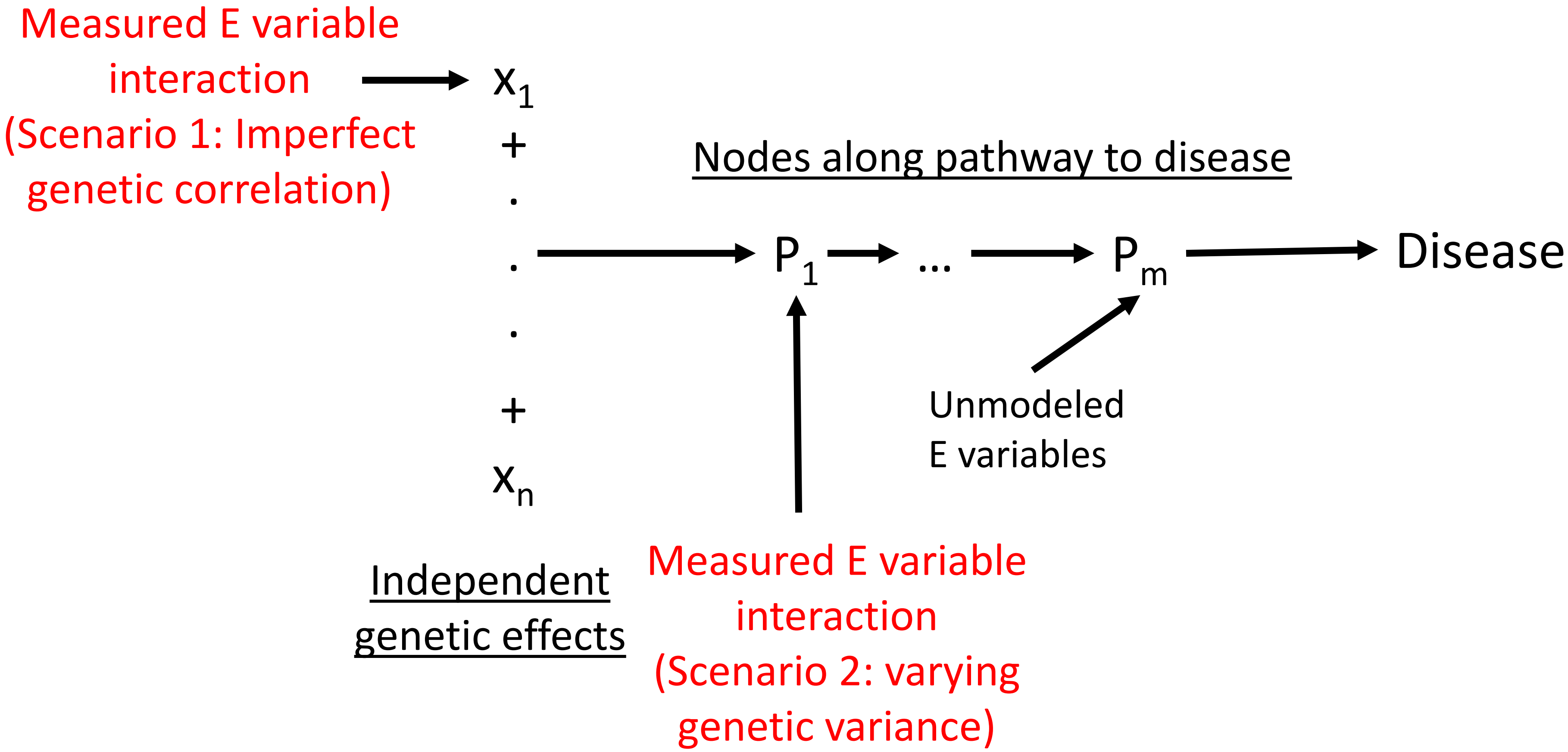


Measured E variable interaction (Scenario 1: Imperfect genetic correlation)

x_1 + . . . + x_n

Independent genetic effects

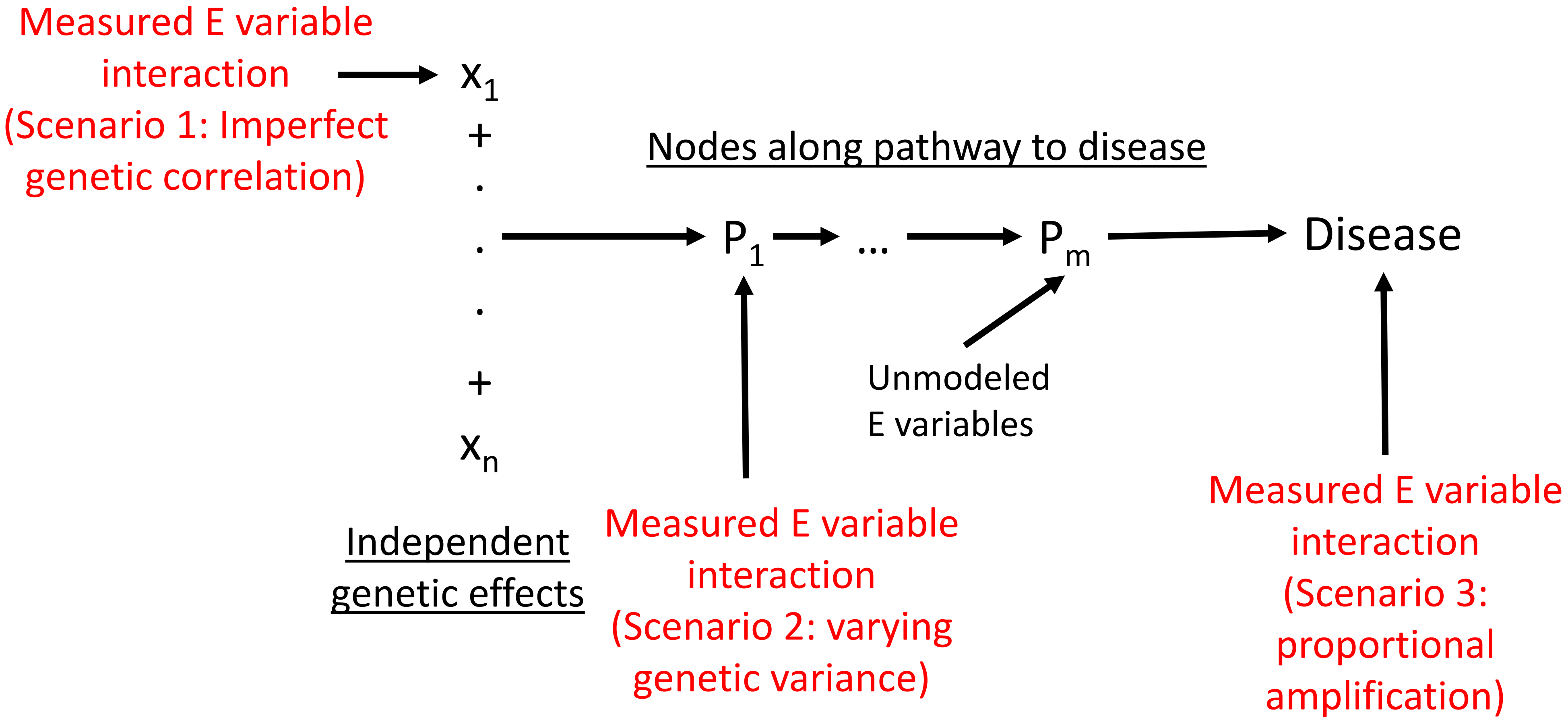
Nodes along pathway to disease

P_1 → … → P_m → Disease

Unmodeled E variables

Measured E variable interaction (Scenario 2: varying genetic variance)

Our results point to a model where E variables interact with genetics at several levels



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Independent genetic effects

Nodes along pathway to disease

P_1 → … → P_m → Disease

Unmodeled E variables

Measured E variable interaction (Scenario 2: varying genetic variance)

Measured E variable interaction (Scenario 3: proportional amplification)

Summary and conclusions

- For many diseases, the genetic effects are context-dependent

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- We find evidence for polygenic GxE arising from locus dependent interactions

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- For many diseases, the genetic effects are context-dependent
- We find evidence for polygenic GxE arising from locus dependent interactions
- We also find evidence for polygenic GxE arising from non-locus dependent interactions

Acknowledgements

- UKBiobank participants
  - Application #16549
- Alkes Price
- Xilin Jiang
- Ben Strober
- Martin Zhang
- Price Lab

The Durvasula Lab @ USC is hiring

- We are hiring postdoctoral researchers and graduate students
- We have projects related to gene-environment interactions, statistical genetics, and complex trait evolution
- Get in touch if you are interested!

Email: durvasul@usc.edu
Website: sites.usc.edu/durvasula

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