Polygenic Risk Scores for SSNS, SRNS

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Overview

- Include CureGN's SSNS/SRNS (allows base data to be for both SSNS-SRNS and SSNS-Ctrl, as with old setup)
- Obsoleted previous evals that split Bristol into two (error bars were so large it was all useless data)
- Under the hood
  - Now always use base's LD data (instead of training data's; slightly better, theoretically the right choice)
  - Painful code updates

How PRS works

Score is generally a linear model:

$$\text{PRS}_j = \sum_i \beta_i x_{ij}.$$

- i: variant index
- j: individual index
- β_i: coefficient of variant i
- x_{ij}: genotype (0,1,2) at variant i, individual j

Challenge is about picking β_i:

- Not all variants are in all datasets
- If starting from GWAS, need to decorrelate (LD or clumping), shrink (p-value threshold or fancier models)

Basics of PRS construction and evaluation

- PRS construction and validation requires 3 disjoint datasets:
  - Base set: Used to fit "GWAS summary statistics": variant coefficients (betas), standard errors, p-values
  - Training set: Used to fit PRS parameters: p-value threshold, or heritability and sparsity
    - Modifies betas, usually by shrinking them to zero and reducing correlation due to LD
  - Testing set: Data where nothing was trained, reveals true performance (correlation to trait)

Testing setups

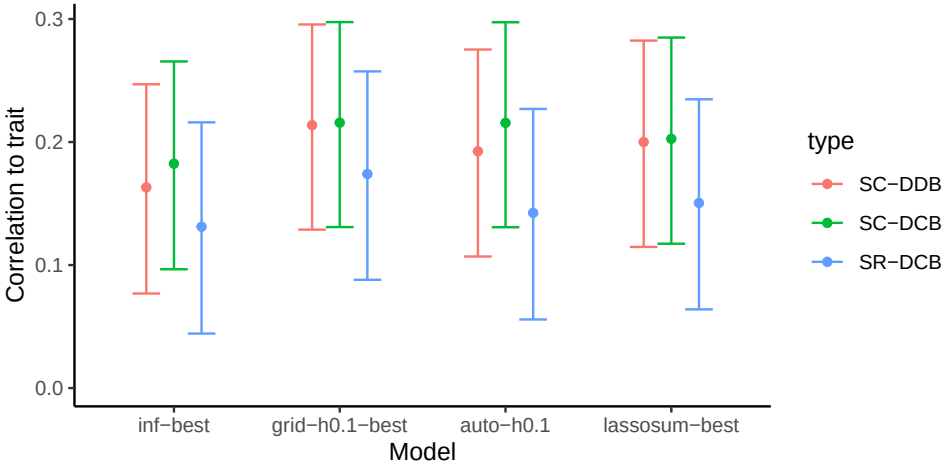
Name	Base	Train	Test
SC-DDB	D SC (532/3553)	D SR (193/193)	B SR (365/149)
SC-DCB	D SC (725/3553)	C SR (250/170)	B SR (365/149)
SR-DCB	D SR (725/193)	C SR (250/170)	B SR (365/149)

SR=SSNS-SRNS; SC=SSNS-Ctrl

D=Discovery; B=Bristol; C=CureGN, based on these rules:

- SSNS: MCD and age ≤ 21
- SRNS: FSGS and age ≤ 21

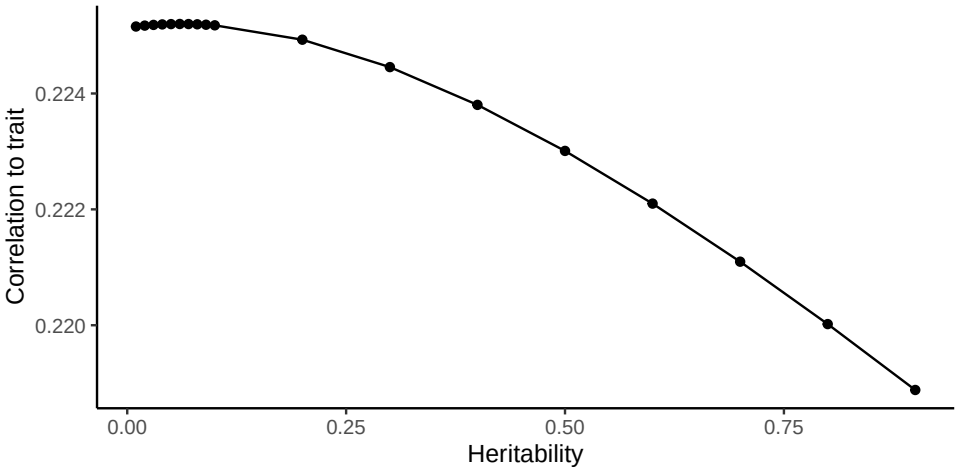
Test results: SSNS-Ctrl base with CureGN best, SSNS-SRNS base worst



Next steps

- Rerun with SAIGE data (direct coefficient estimates; right now we're using GMMAT score stats, transforming those to estimate coefficients, which may be suboptimal but also somewhat inflated)
- Include clump and threshold method
- Use HLA haplotypes!
- Vary SNP set filters
  - Due to LD runtime, only using array SNPs right now
  - Could enrich for more significant ones or higher severity variants
- Try Barry et al., 2023 base data

Train results: SC-DDB ldpred2-inf



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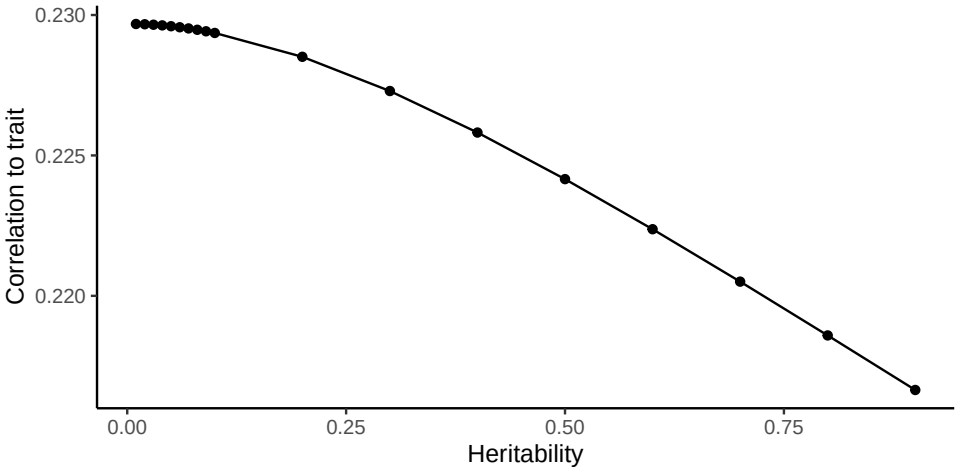

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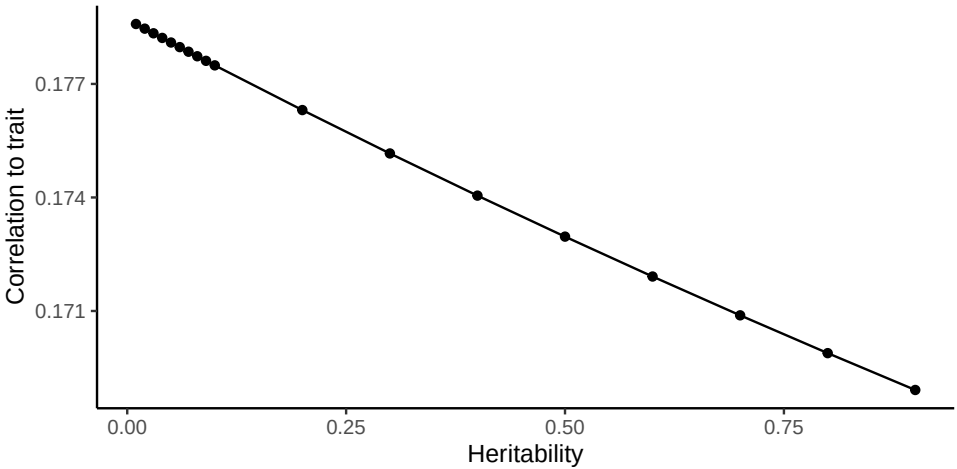
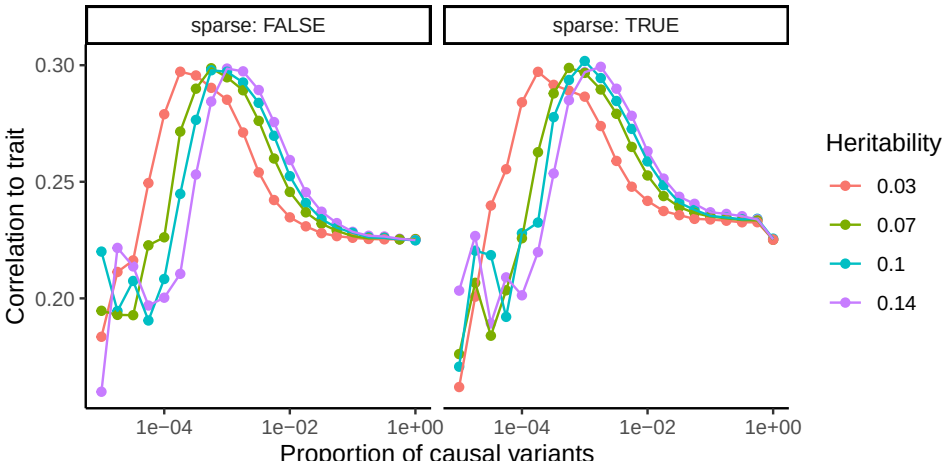


Train results: SC-DDB ldpred2-grid-h0.1



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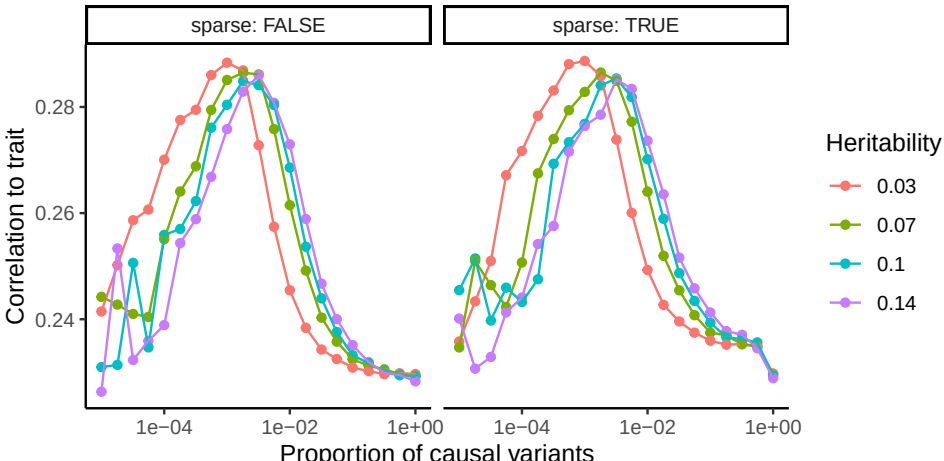

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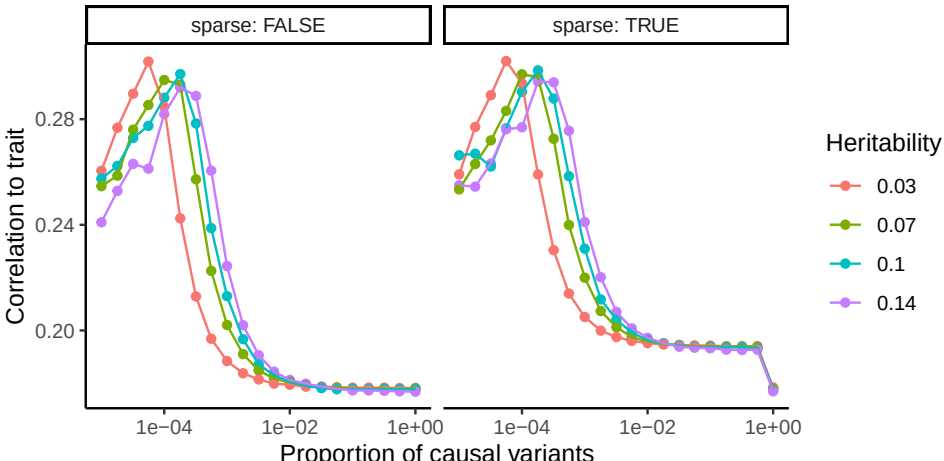
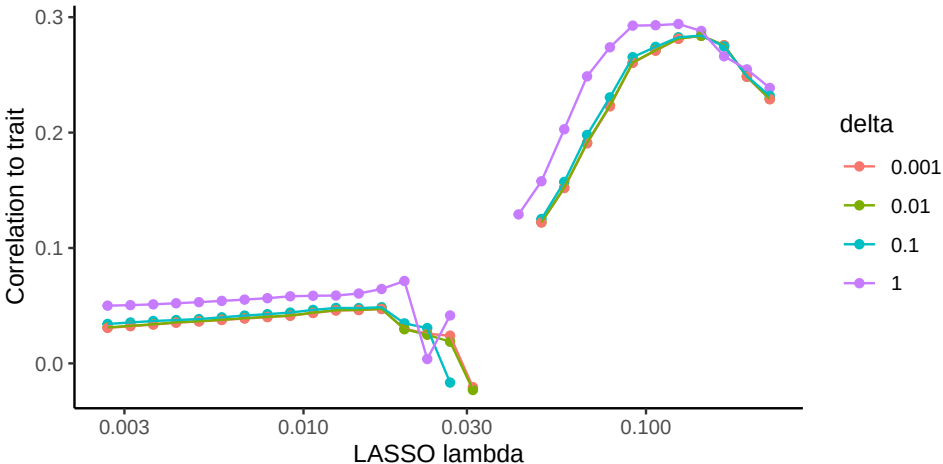
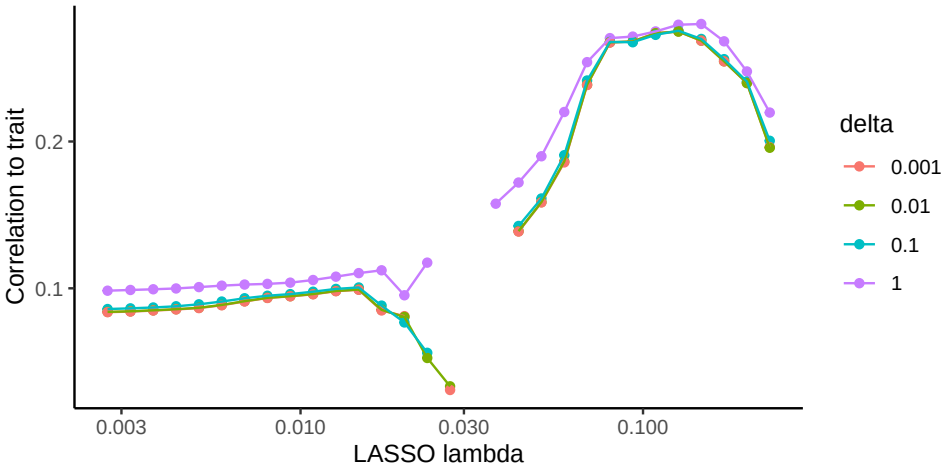


Train results: SC-DDB ldpred2-lassosum



Train results: SC-DCB ldpred2-lassosum



Train results: SR-DCB ldpred2-lassosum