Use and Interpretation of LD Score Regression

Brendan Bulik-Sullivan

bulik@broadinstitute.org

PGC Stat Analysis Call

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Outline of Talk

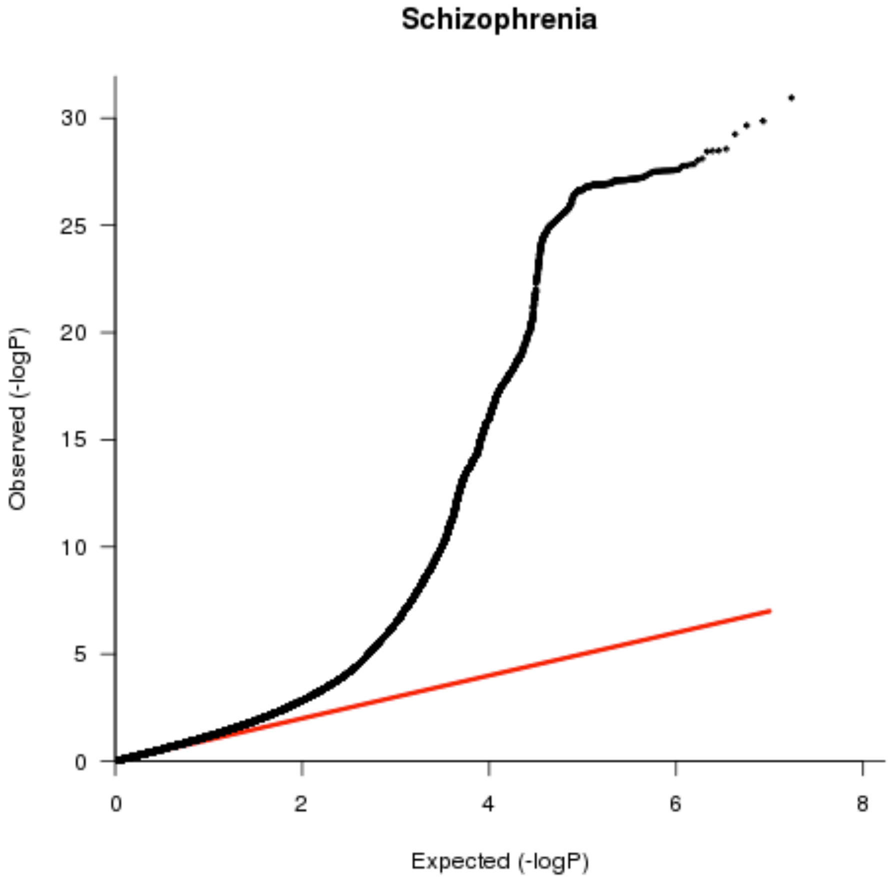
- Intuition, Theory, Results
  - LD Score regression intercept: distinguishing polygenicity from population stratification
  - Genetic correlation from summary statistics
- What can LD Score Regression do for *you*?
  - Practical advice on using LD Score in day-to-day GWAS analysis
- Useful links at the end

LD Score Regression Intercept

Distinguishing Polygenicity from Population Stratification

Test Statistic Inflation

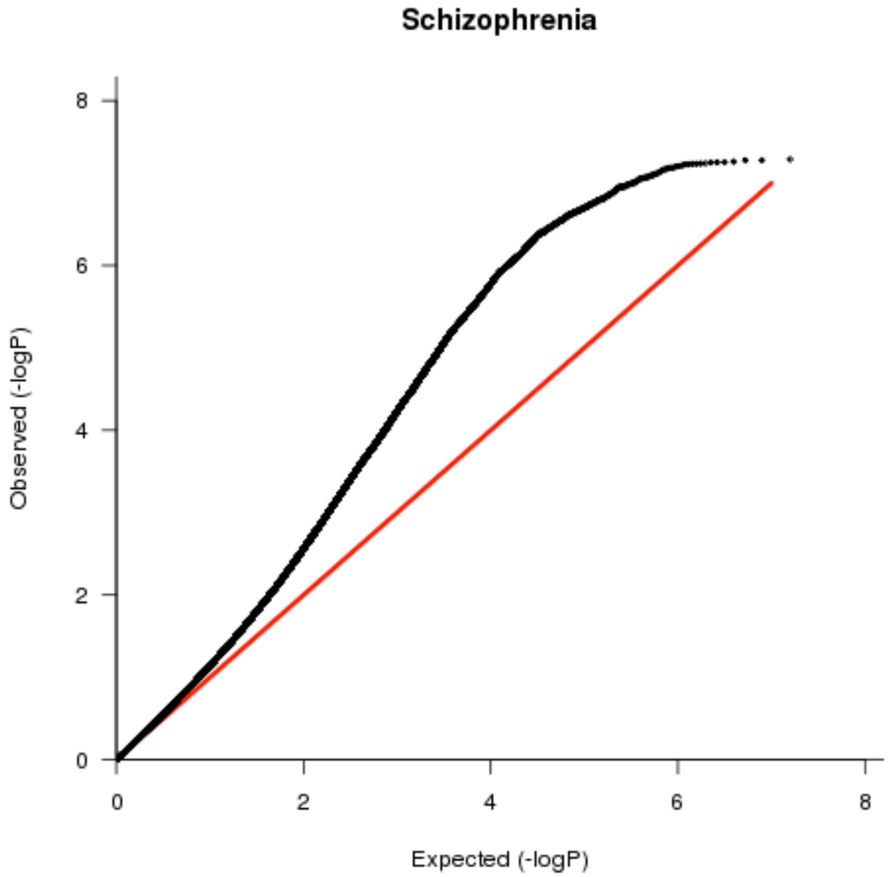
Genome-wide distribution of test statistics from large GWAS deviate strongly from the null



PGC SCZ, Nature, 2014

Test Statistic Inflation

Even when all gwas loci (+/- 1 MB, 10MB for MHC) removed



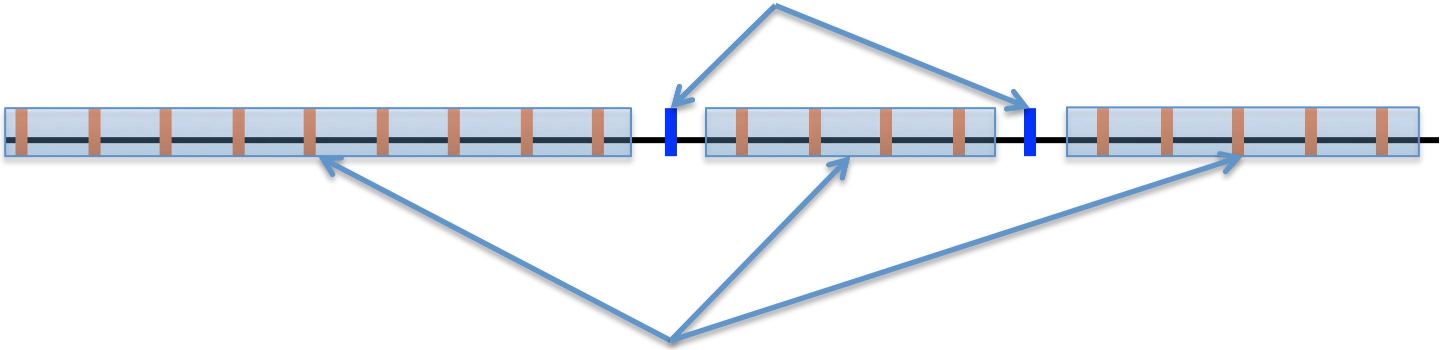
PGC SCZ, Nature, 2014

Toy Illustration of Genome

🟦 LD Block

▌ Lonely SNP

Lonely SNPs [no LD]

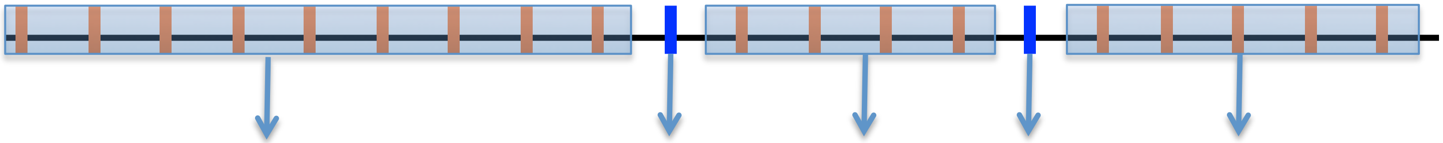


LD blocks

What happens under genetic drift?

🟦 LD Block

▮ Lonely SNP



Rate of drift $1/N_{eff}$ $1/N_{eff}$ $1/N_{eff}$ $1/N_{eff}$ $1/N_{eff}$

Under pure drift, LD is uncorrelated to magnitude of allele frequency differences between populations

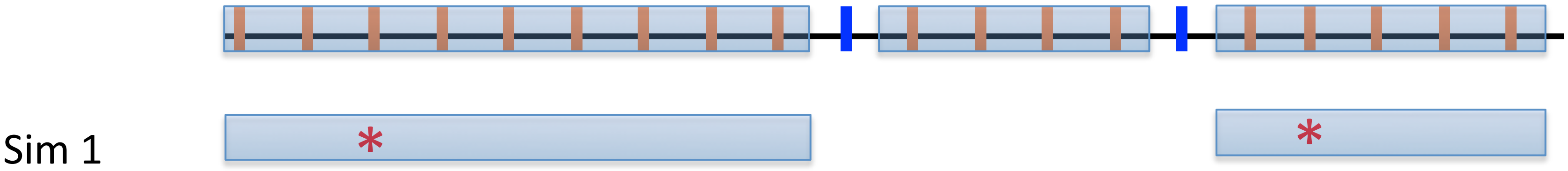
Simulation of a genetic signal in polygenic architecture

▭ LD Block

▮ Lonely SNP

* Causal SNP

All SNPs in LD blocks w/ causal SNP have high chi-square



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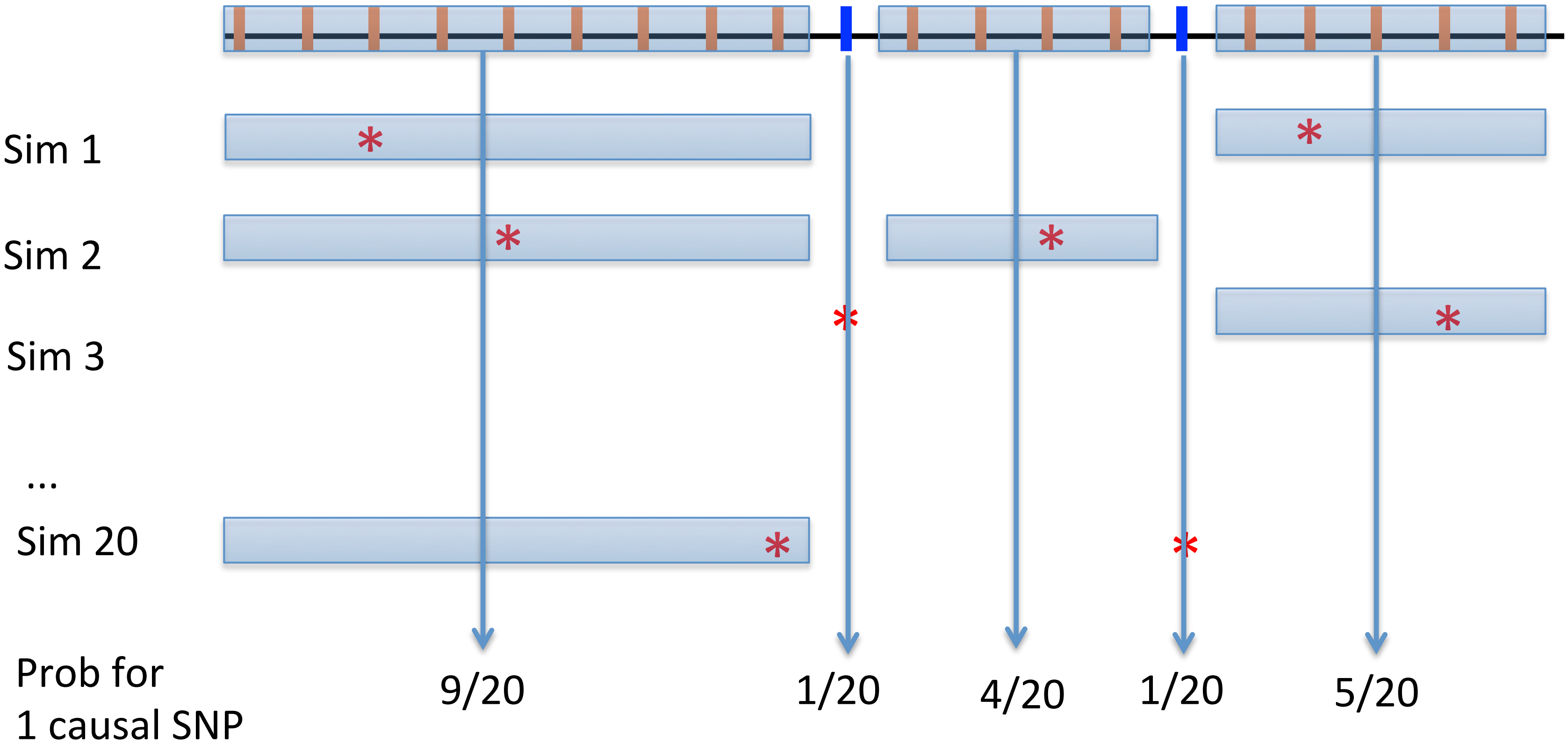

Sim 1

Sim 2

Sim 3

...

Sim 20

Prob for
1 causal SNP

9/20 1/20 4/20 1/20 5/20

Simulation of a genetic signal in polygenic architecture

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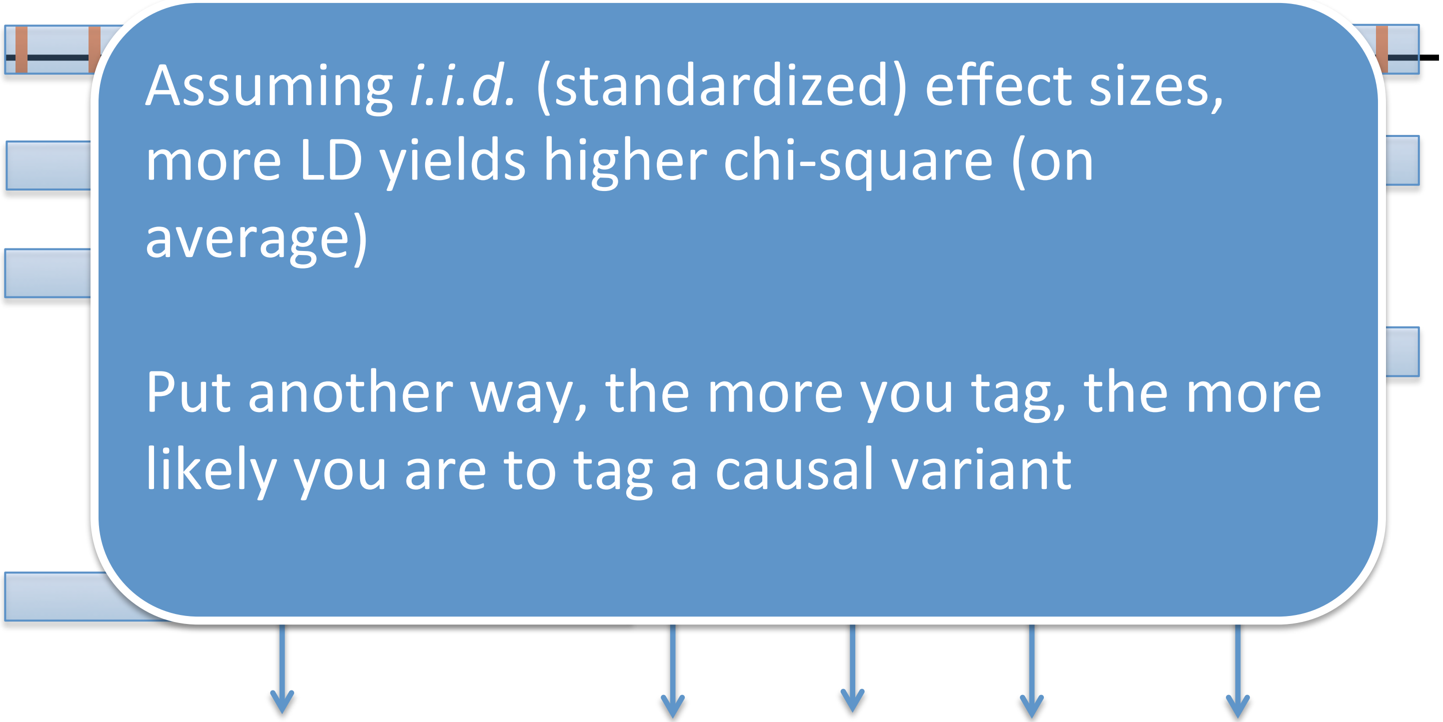


Assuming *i.i.d.* (standardized) effect sizes, more LD yields higher chi-square (on average)

Put another way, the more you tag, the more likely you are to tag a causal variant

Sim 1

Sim 2

Sim 3

...

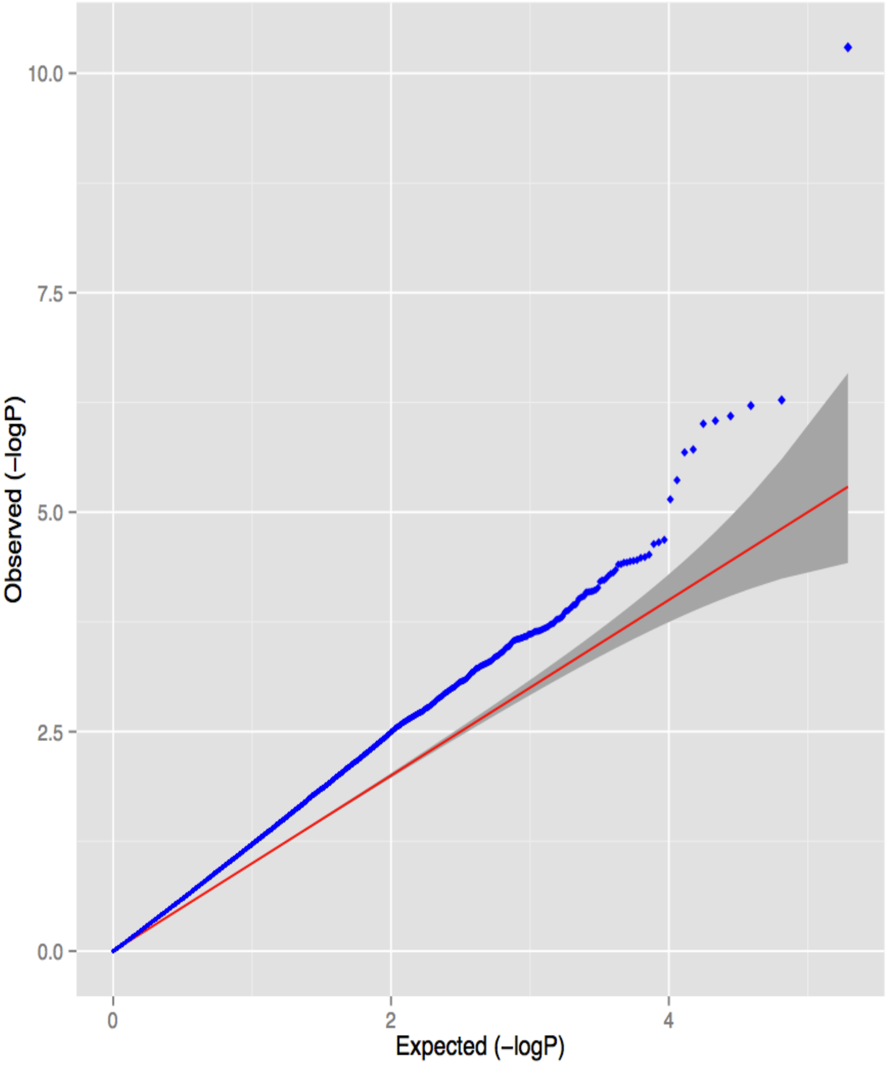
Sim 20

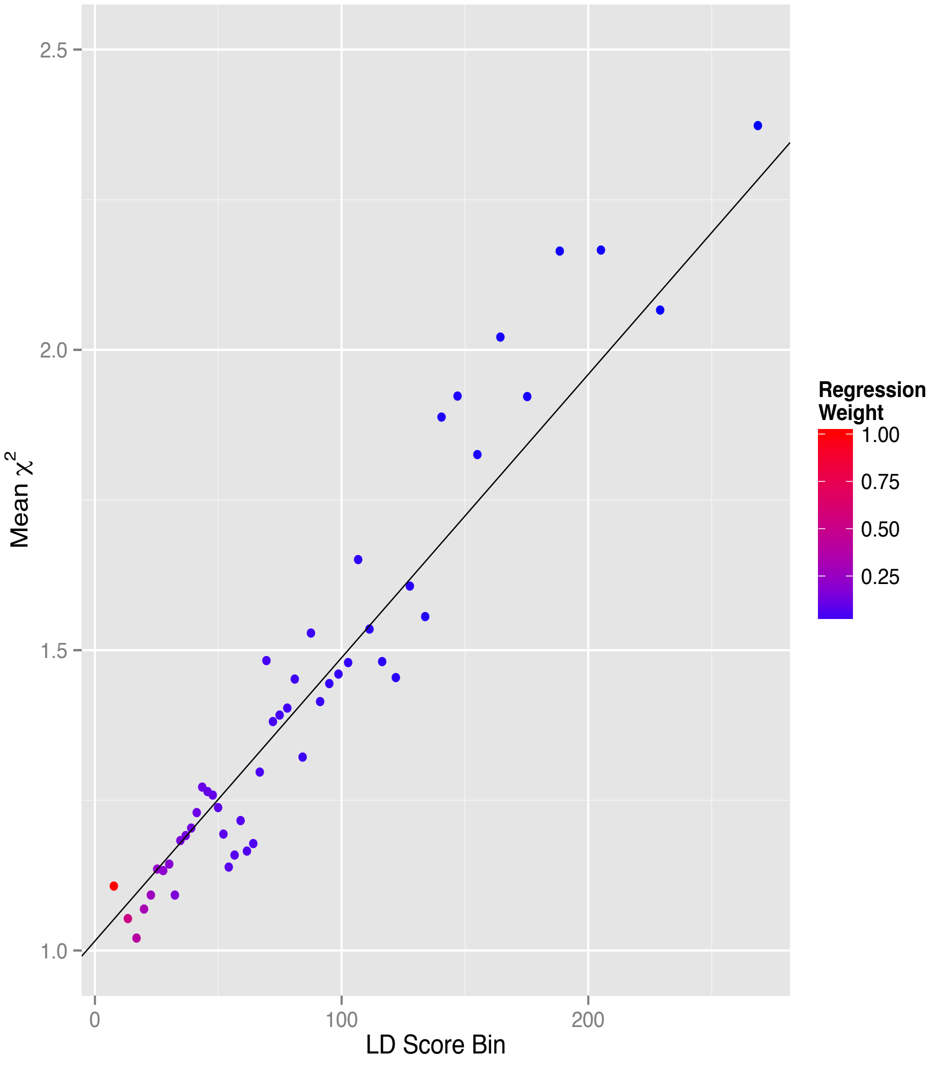
Prob for 1 causal SNP

9/20 1/20 4/20 1/20 5/20

Simulated Polygenicity

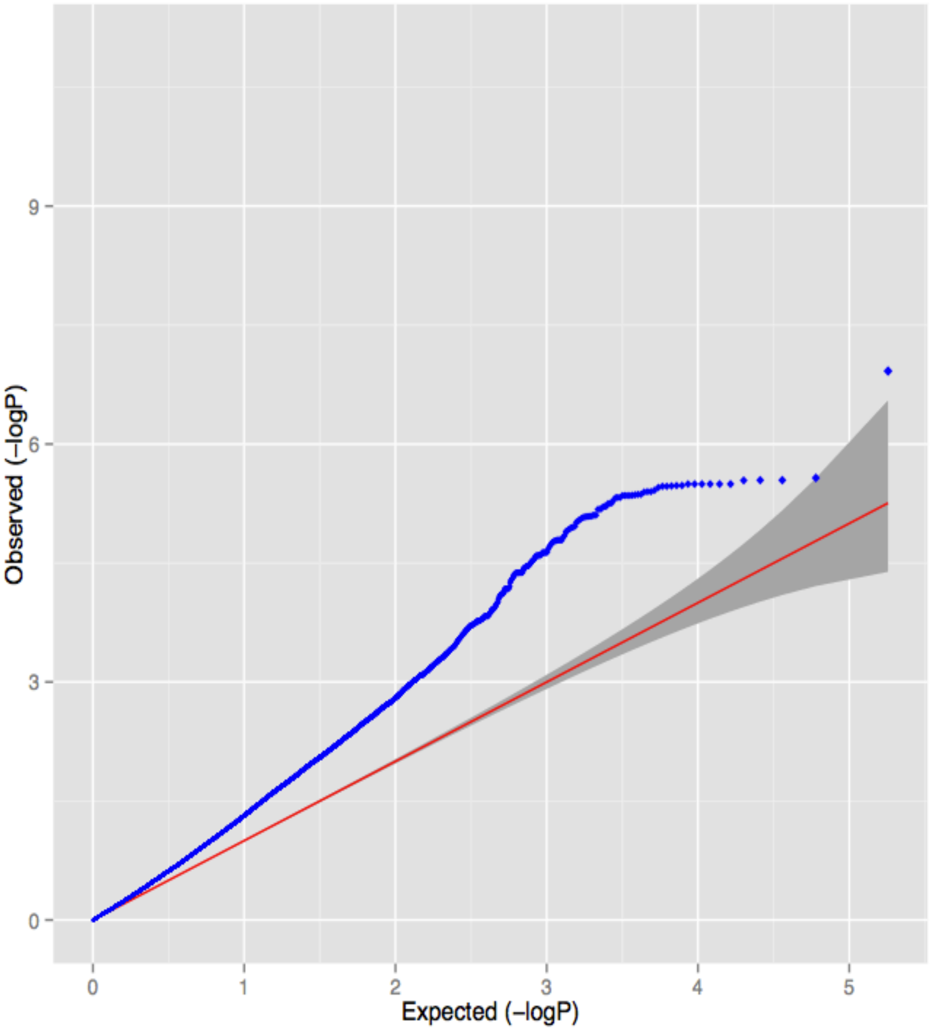
- λ_{GC} = 1.30; LD Score Regression intercept = 1.02

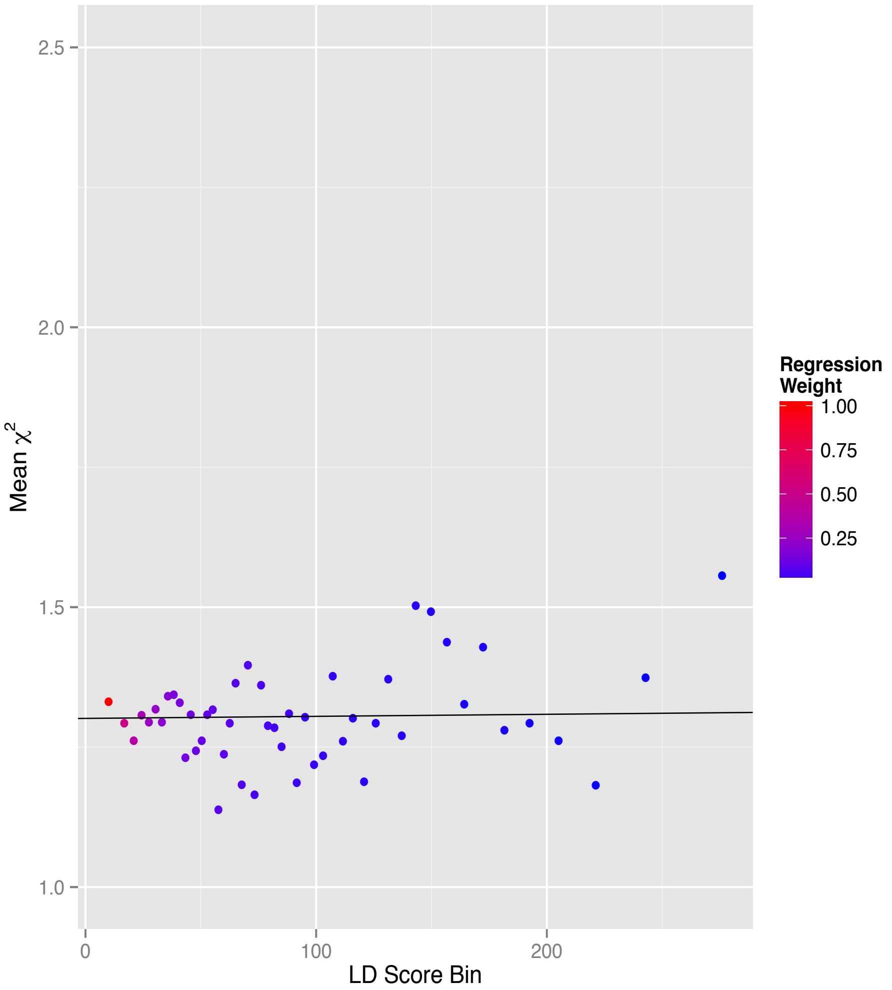




Simulated Pop Strat (Sweden vs UK)

- λ_{GC} = 1.30; LD Score Regression intercept = 1.32

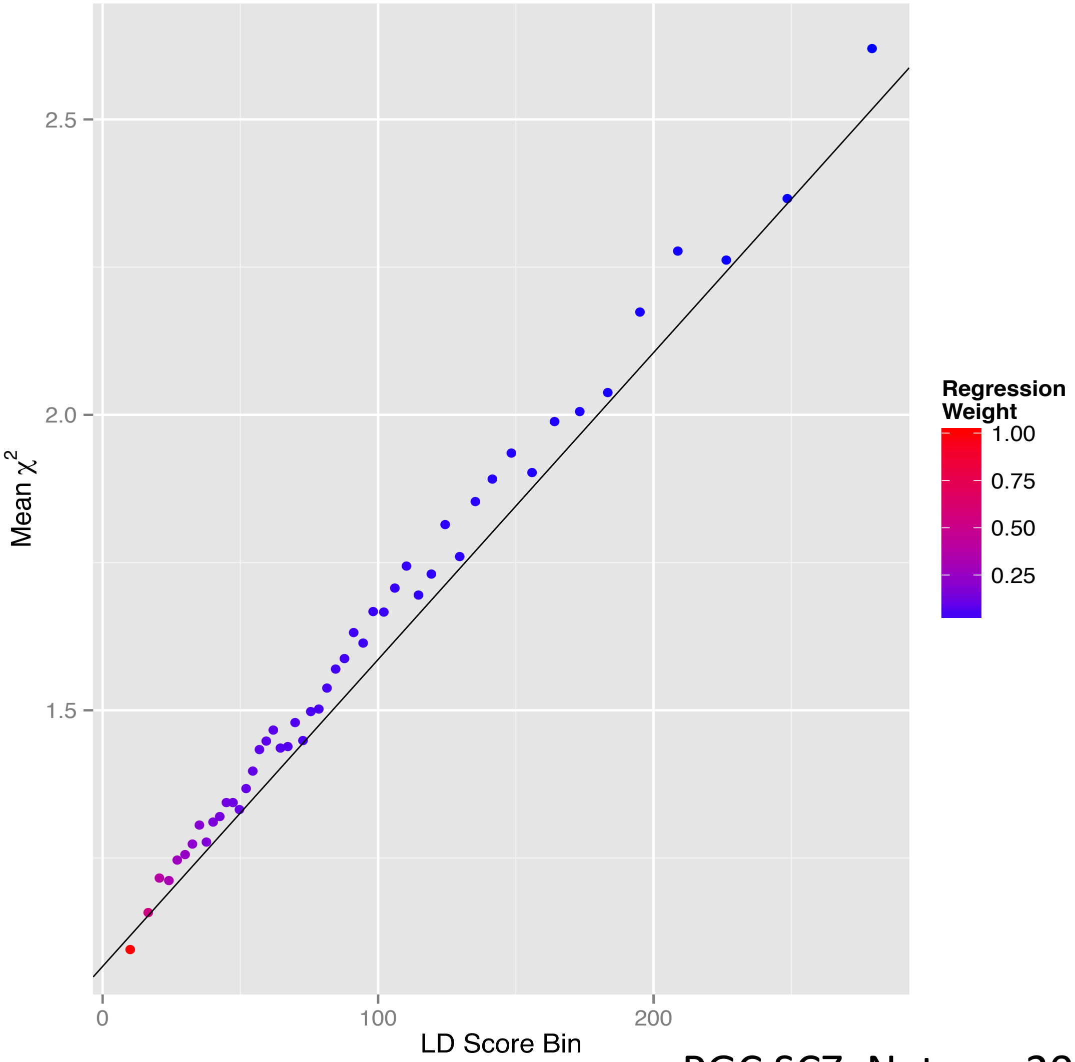




PGC Schizophrenia

- $\lambda_{GC} = 1.48$
- Intercept = 1.06
- *p*-value < 10^{-300}

Overwhelming majority of inflation is consistent with polygenic architecture



Bulik-Sullivan et al., Nat Genet, 2015

PGC SCZ, Nature, 2014

LD Score Regression

- Regress χ2 statistics against LD Score

$$E[\chi^2 \mid \ell_j] = Nh^2 \ell_j / M + Na + 1$$

  - LD Score (L_j) is a property of SNP j, defined as sum r^2, estimated as sum r^2 w/ all other SNPs a 1cM window.
  - N is sample size.
  - M is # SNPs.
  - h^2 is SNP-heritability.
  - a is inflation from pop strat/cryptic relatedness.

Bulik-Sullivan et al., Nat Genet, 2015

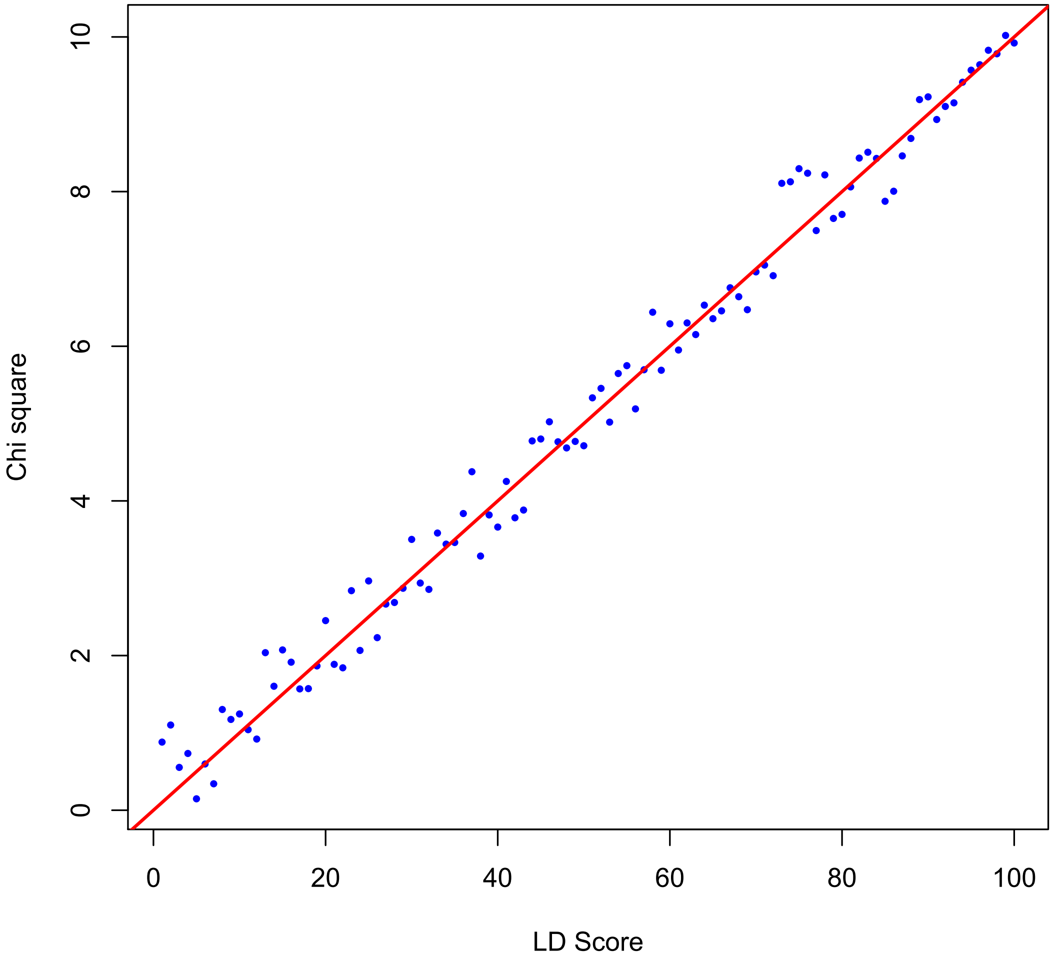
LD Score Results

- Applied to > 20 GWAS
  - Almost all inflation due to polygenicity.
  - LD Score intercept < λ_{GC} in all studies.
- Conclusions:
  - PCA / mixed models mostly appear to work.
  - Genomic control (dividing all $\chi 2$ statistics by λ_{GC}) is unnecessarily conservative.

Bulik-Sullivan et al., Nat Genet, 2015

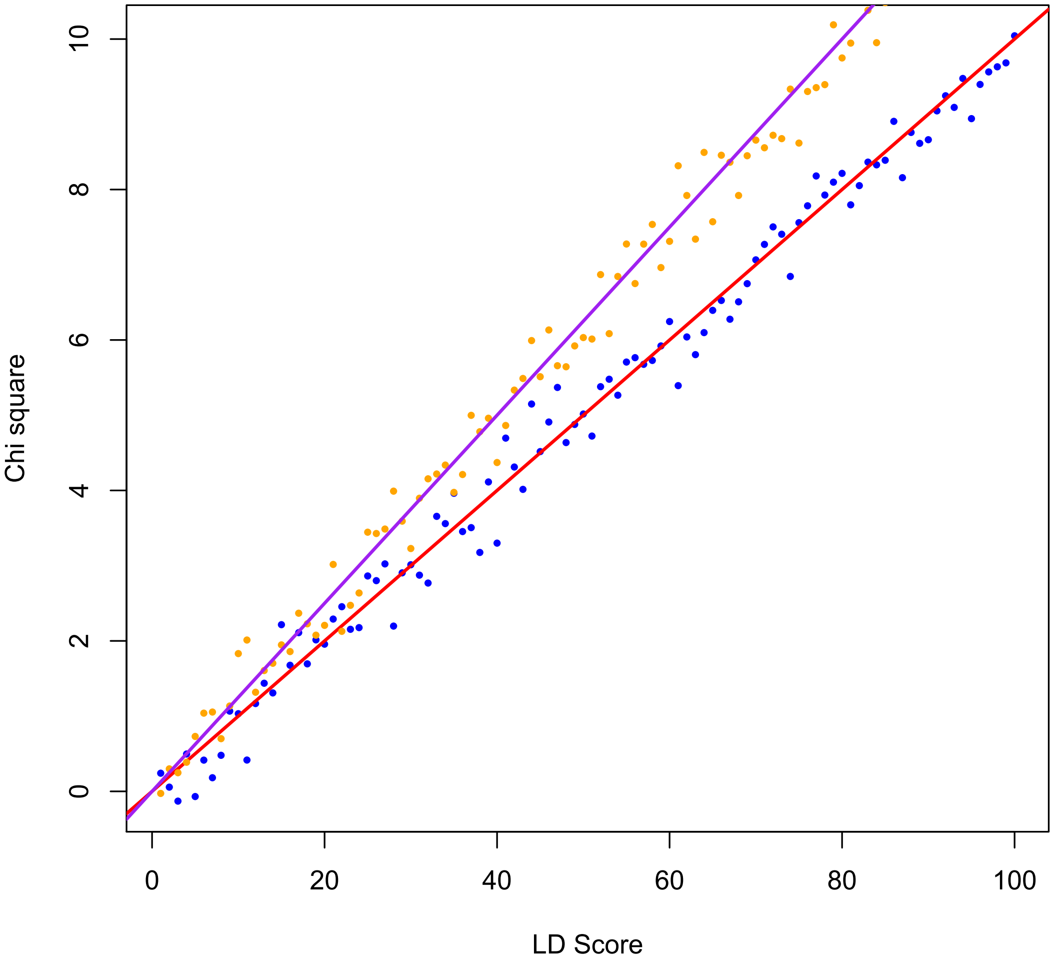
Genetic correlation

Reminder - univariate:

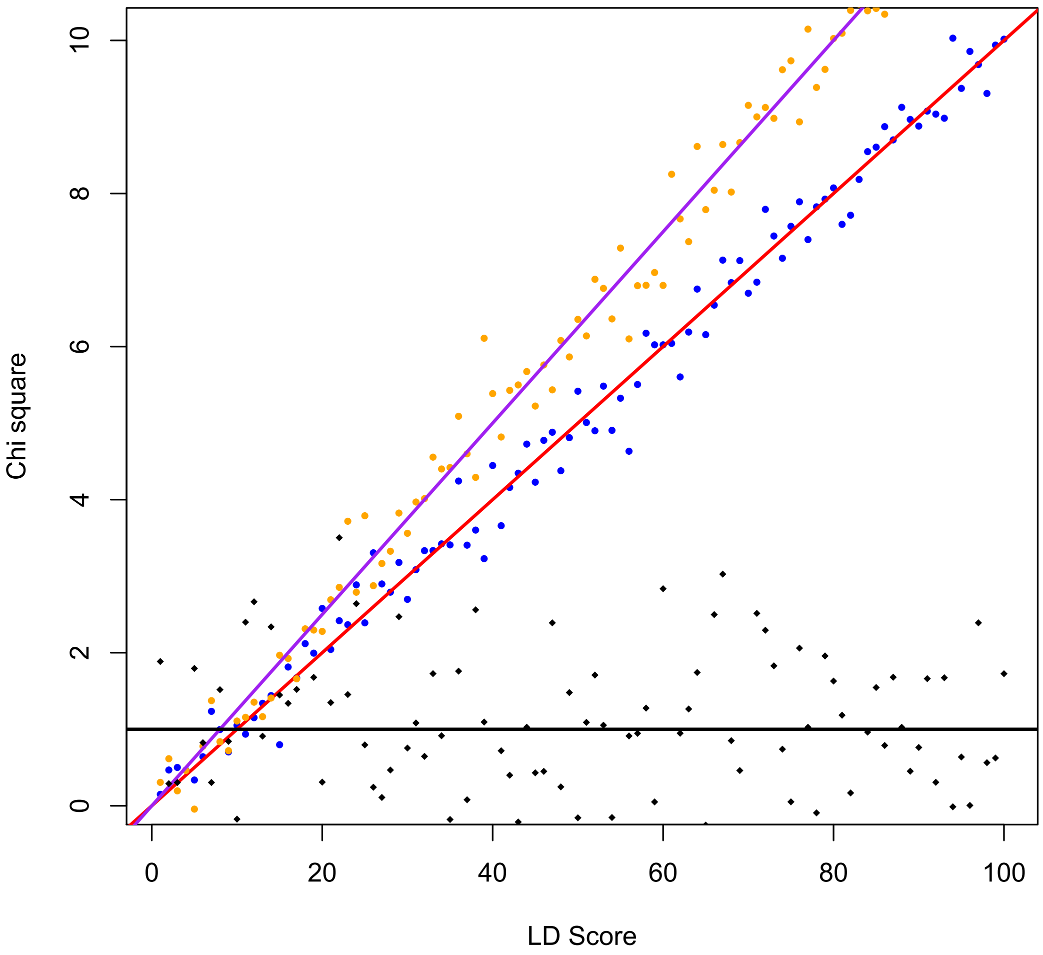


The slope of this regression line is an estimator of heritability

Add a second trait:

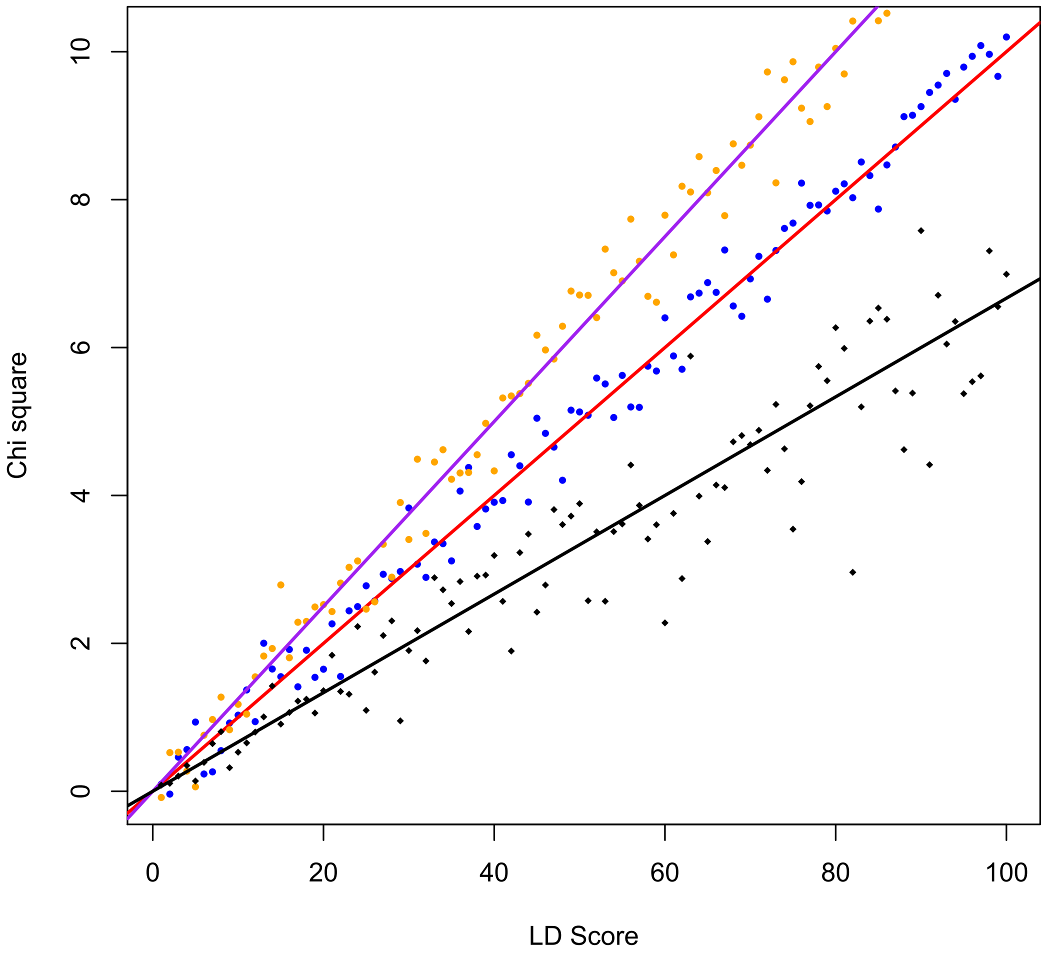


Genetic correlation = 0



Recall that $\chi 2 = Z^2$;
to estimate $r_{g,}$ replace
$\chi 2$ with Z_1Z_2.

Genetic correlation of ~0.5



The signed positive slope shows that genetic effects tend to be shared genome-wide

Formally

$$\mathbb{E}[z_{1j}z_{2j}] = \frac{\sqrt{N_1 N_2}\rho_g}{M}\ell_j + \frac{\rho N_s}{\sqrt{N_1 N_2}}$$

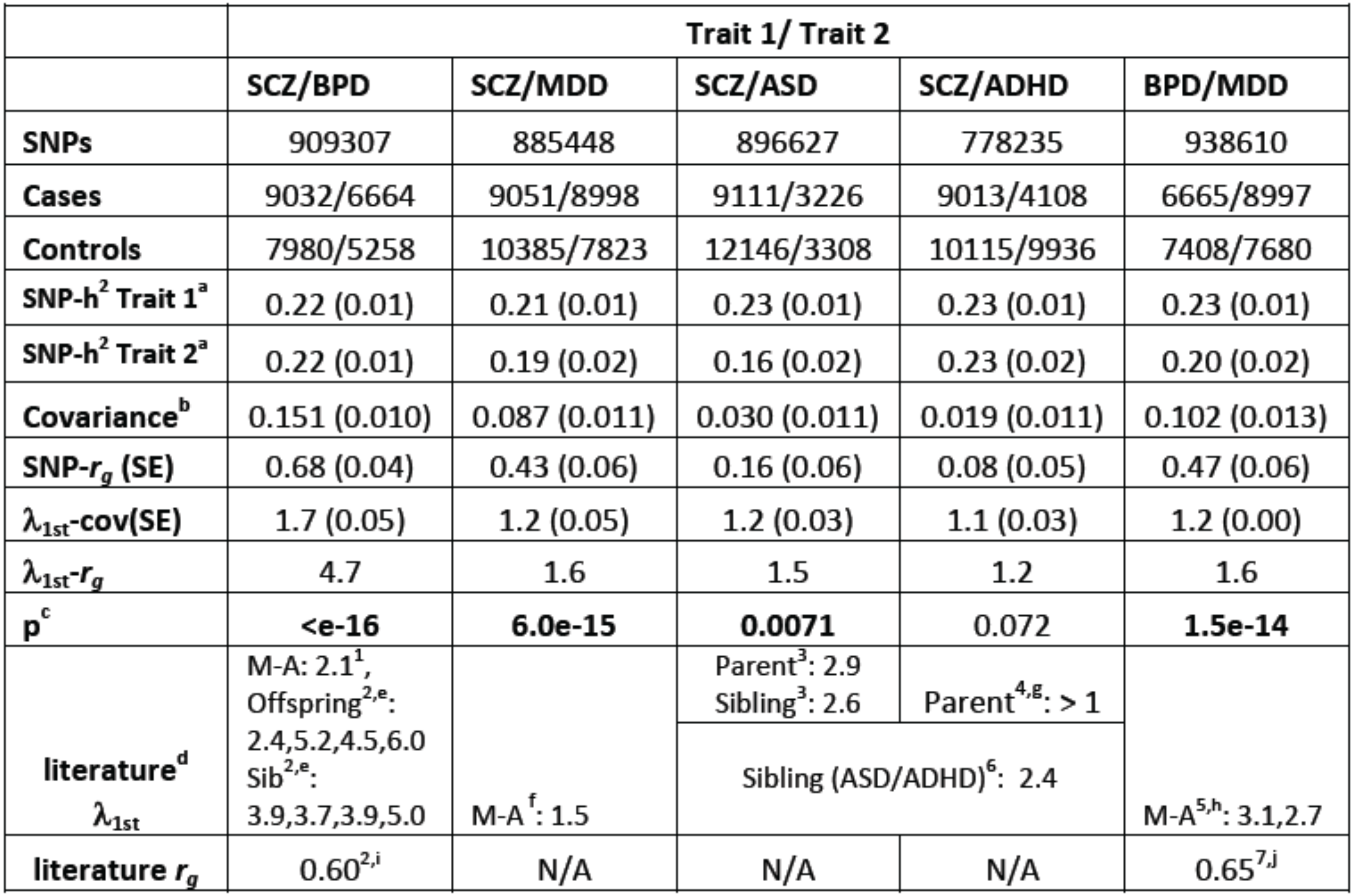
where N_1 and N_2 are the sample sizes for the two studies
p_g is the genetic correlation
l_j is the LD score
M is the total number of markers
p is the phenotypic correlation
N_s is the number of overlapping samples

Key point: *not biased by sample overlap*

Bulik-Sullivan et al, bioRxiv

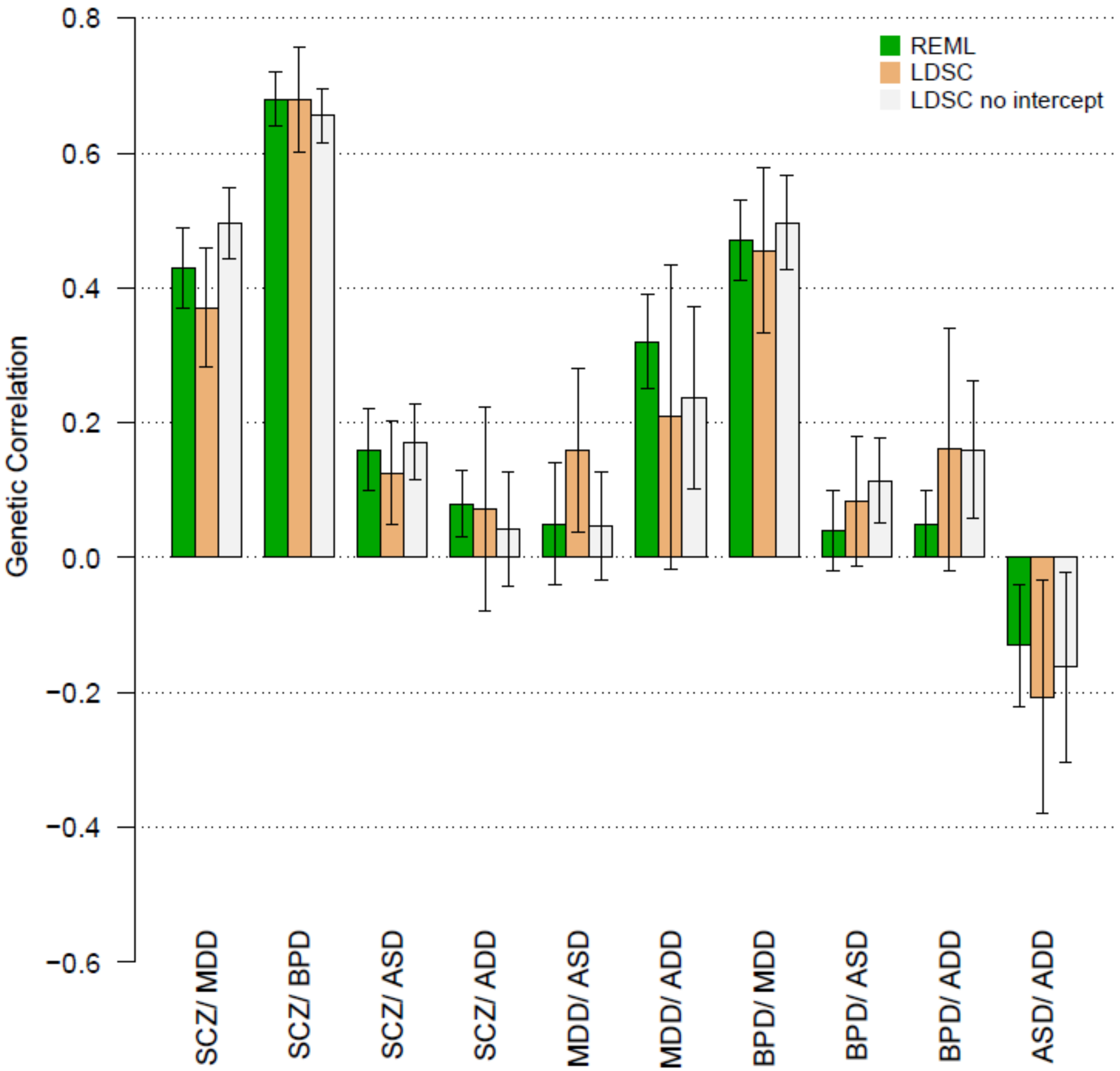
Proof of concept

Supplementary Table 1. Bivariate analyses

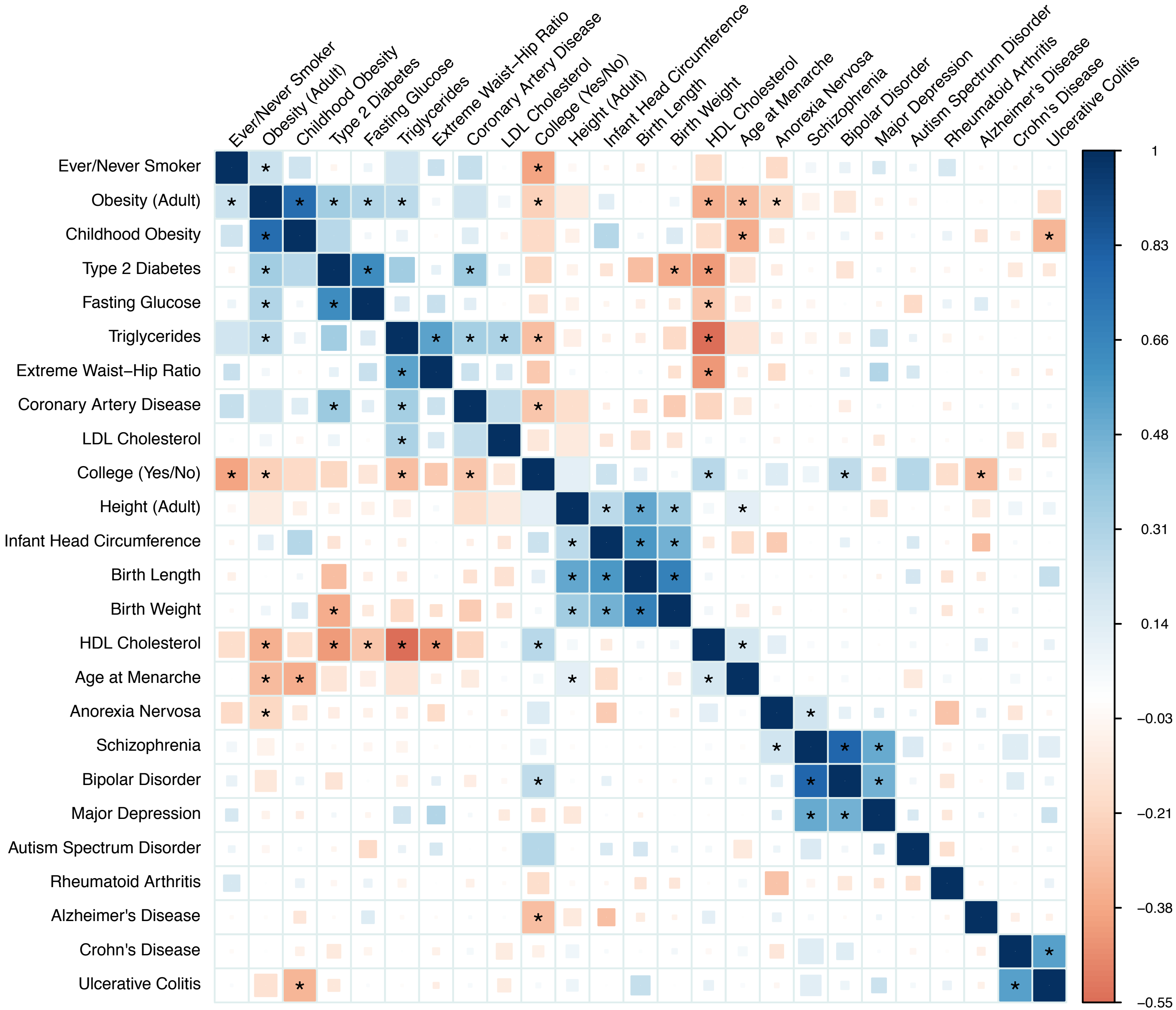


	Trait 1/ Trait 2				
	SCZ/BPD	**SCZ/MDD**	**SCZ/ASD**	**SCZ/ADHD**	**BPD/MDD**
SNPs	909307	885448	896627	778235	938610
Cases	9032/6664	9051/8998	9111/3226	9013/4108	6665/8997
Controls	7980/5258	10385/7823	12146/3308	10115/9936	7408/7680
SNP-h^2 Trait 1[a]	0.22 (0.01)	0.21 (0.01)	0.23 (0.01)	0.23 (0.01)	0.23 (0.01)
SNP-h^2 Trait 2[a]	0.22 (0.01)	0.19 (0.02)	0.16 (0.02)	0.23 (0.02)	0.20 (0.02)
Covariance[b]	0.151 (0.010)	0.087 (0.011)	0.030 (0.011)	0.019 (0.011)	0.102 (0.013)
SNP-r_g (SE)	0.68 (0.04)	0.43 (0.06)	0.16 (0.06)	0.08 (0.05)	0.47 (0.06)
λ_{1st}-cov(SE)	1.7 (0.05)	1.2 (0.05)	1.2 (0.03)	1.1 (0.03)	1.2 (0.00)
λ_{1st}-r_g	4.7	1.6	1.5	1.2	1.6
p[c]	**<e-16**	**6.0e-15**	**0.0071**	0.072	**1.5e-14**
literature[d] λ_{1st}	M-A: 2.1[1], Offspring[2,e]: 2.4,5.2,4.5,6.0 Sib[2,e]: 3.9,3.7,3.9,5.0	M-A[f]: 1.5	Parent[3]: 2.9 Sibling[3]: 2.6	Parent[4,g]: > 1	M-A[5,h]: 3.1,2.7
			Sibling (ASD/ADHD)[6]: 2.4		
literature r_g	0.60[2,i]	N/A	N/A	N/A	0.65[7,j]

Lee et al, 2013 Nat Gen

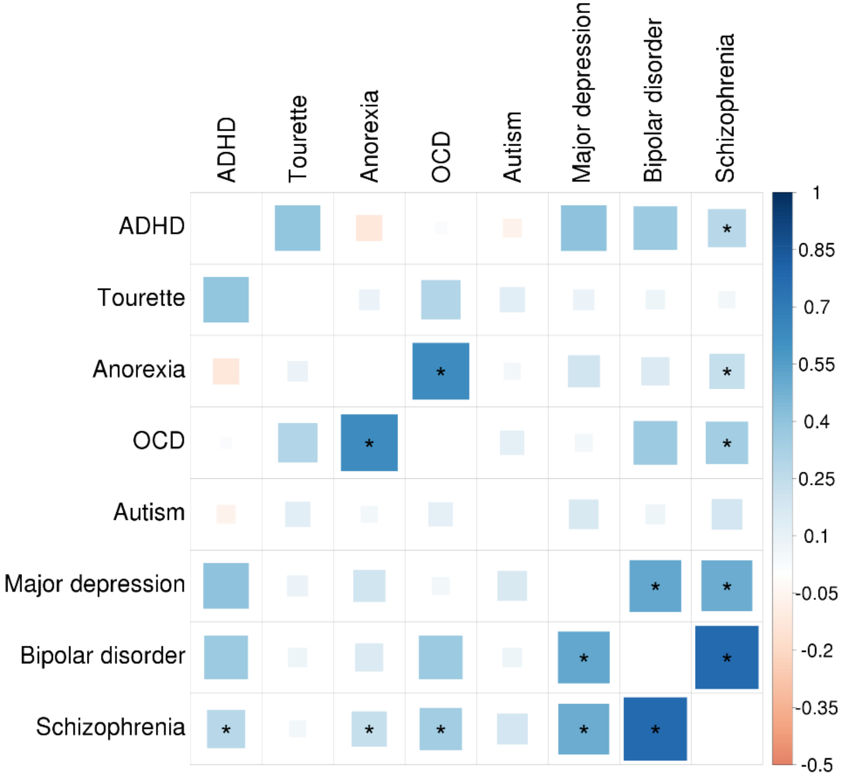


Bulik-Sullivan et al, bioRxiv



Bulik-Sullivan et al, bioRxiv

New Psychiatric r_g



In addition:
+20% rg between AN and BMI

V. Anttila, Brainstorm Project

Pause for questions …

What can LD Score do for *you?*

Practical advice on using LD Score in day-to-day GWAS analysis

Software

- LD Score regression implemented in free + open-source python command-line tool ldsc:
  - github.com/bulik/ldsc
- Tutorials & FAQ here:
  - github.com/bulik/ldsc/wiki
- Ask me questions on the google group!

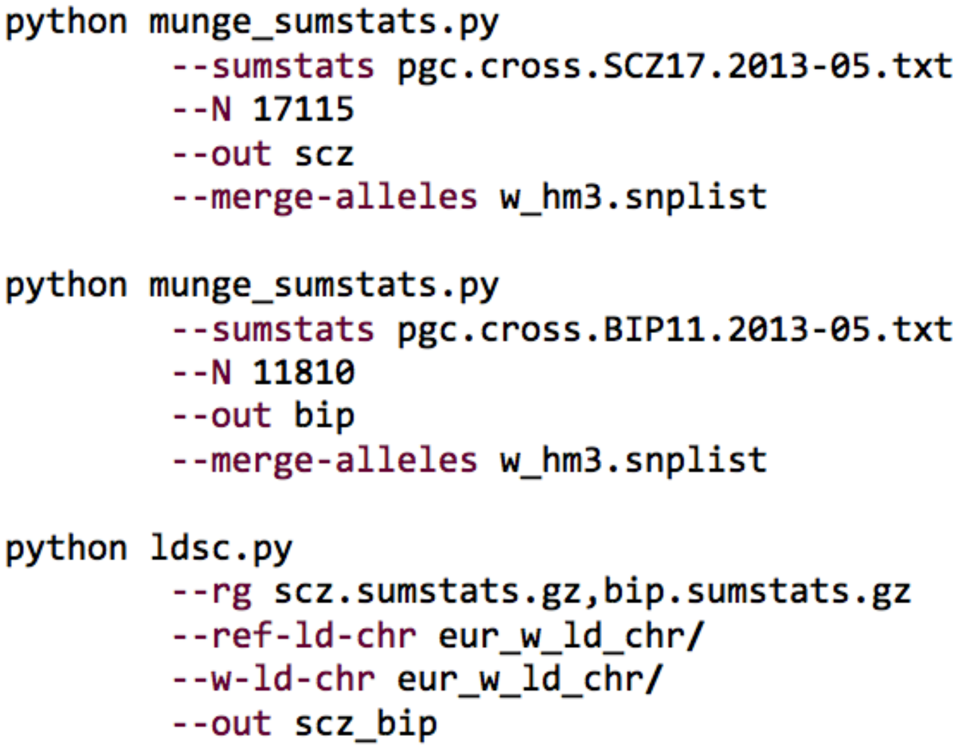
LD Score is Fast and Easy

- Trivial run-time & memory (~15s, ~1GB for h^2).
- Automated data re-formatting and QC.
  - munge_sumstats.py included w/ ldsc.
  - No need for one-off perl scripts.
- Download pre-computed LD Scores.
  - broadinstitute.org/~bulik/eur_ldscores/
  - (European-only, for now)

Example: Estimating r_g(BIP, SCZ)

Automatically applies same MAF/INFO etc filters used in our papers + various sanity checks (e.g., log odds in OR column?)

Automatically aligns strand + ref allele + filters out strand ambiguous SNPs



```
python munge_sumstats.py
        --sumstats pgc.cross.SCZ17.2013-05.txt
        --N 17115
        --out scz
        --merge-alleles w_hm3.snplist

python munge_sumstats.py
        --sumstats pgc.cross.BIP11.2013-05.txt
        --N 11810
        --out bip
        --merge-alleles w_hm3.snplist

python ldsc.py
        --rg scz.sumstats.gz,bip.sumstats.gz
        --ref-ld-chr eur_w_ld_chr/
        --w-ld-chr eur_w_ld_chr/
        --out scz_bip
```

45 seconds on my MacBook Air

Basic QC with LD Score intercept

- QC Question: *have we adequately controlled for confounding from population stratification?*
- Solution: check LD Score intercept close to 1.
  - Caveat: only sensitive to sources of genome-wide inflation; can't tell you whether 10 suspect SNPs are OK.

QC with LD Score h^2

- QC Question: *do we see more or less inflation than we would expect given N and h^2?*
- Low inflation can mean phenotype problems.
  - Non-screened controls.
  - Bad phenotype def'n.
  - Data munging error, e.g., column swap in ped file.
- Solution: compare h^2(old data), h^2(new data).
  - Big + significant differences may indicate problems.

QC with LD Score r_g

- QC Question: *does phenotype definition in new data match older data?*
  - Coordinating pheno def'n across studies is hard.
  - Data munging error, e.g., column swap in ped file.
- Solution: compute r_g(new data, old data)
  - Particularly useful for summary-statistic meta-analysis consortia.

Streamlined PRS

- Statements about prediction R^2 from PRS analysis are often equivalent to statements about h^2 or r_g:
- PRS for X predicts[1] Y ***if and only if*** $r_g(X, Y)$!= 0.
- PRS for X predicts[1] X ***if and only if*** $h^2(X) > 0$.

[1] In independent samples

Dudbridge, PLoS Gen, 2013

Streamlined PRS

- LD Score r_g/h^2 often faster/easier than PRS
  - No LD pruning.
  - No individual-level genotype data.
  - Don't have to worry about sample overlap.
  - Don't have to split sample into train/test sets.
  - Caveat: GCTA and PRS have (slightly) better power than LD Score, possibly makes a big difference for small N.

Practical Advice

- LD Score is noisy at small N.
  - Rule of thumb: use GCTA for N < 3k.
- Partitioned h^2 requires very large N.
  - Rule of thumb: not worth trying for < 5k cases.

Practical Advice

- ldsc not presently applicable to admixed data.
  - LD structure in admixed samples is more complex.
- If no pop strat / no sample overlap, constrained intercept LD Score has lower SE
  - Equivalent to Haseman-Elston regression (Bulik-Sullivan, bioRxiv, 2015)

Notes for PGC users

- munge_sumstats.py --daner flag processes Ricopili-format data (daner* files)
- ldsc.py --samp-prev and --pop-prev flags convert to liability-scale h^2

Acknowledgements

- r_g + functional h^2 + ldsc joint work w/ Hilary Finucane
- Ben Neale
- Alkes Price
- Nick Patterson
- Po-Ru Loh
- Mark Daly
- Many others …

URLs

- ldsc
  - github.com/bulik/ldsc
  - Installation instructions
  - FAQ
- Tutorials / wiki
  - github.com/bulik/ldsc/wiki
- Pre-computed European LD Scores
  - broadinstitute.org/~bulik/eur_ldscores/
- ldsc_users google group:
  - groups.google.com/forum/?hl=en#!forum/ldsc_users

LD Score Papers

- LD Score regression distinguishes confounding from polygenicity in genome-wide association studies
- Partitioning heritability by functional category using GWAS summary statistics
- An Atlas of Genetic Correlations across Human Diseases and Traits
- Relationship between LD Score and Haseman-Elston Regression