Predicting complex traits and diseases from genetic data

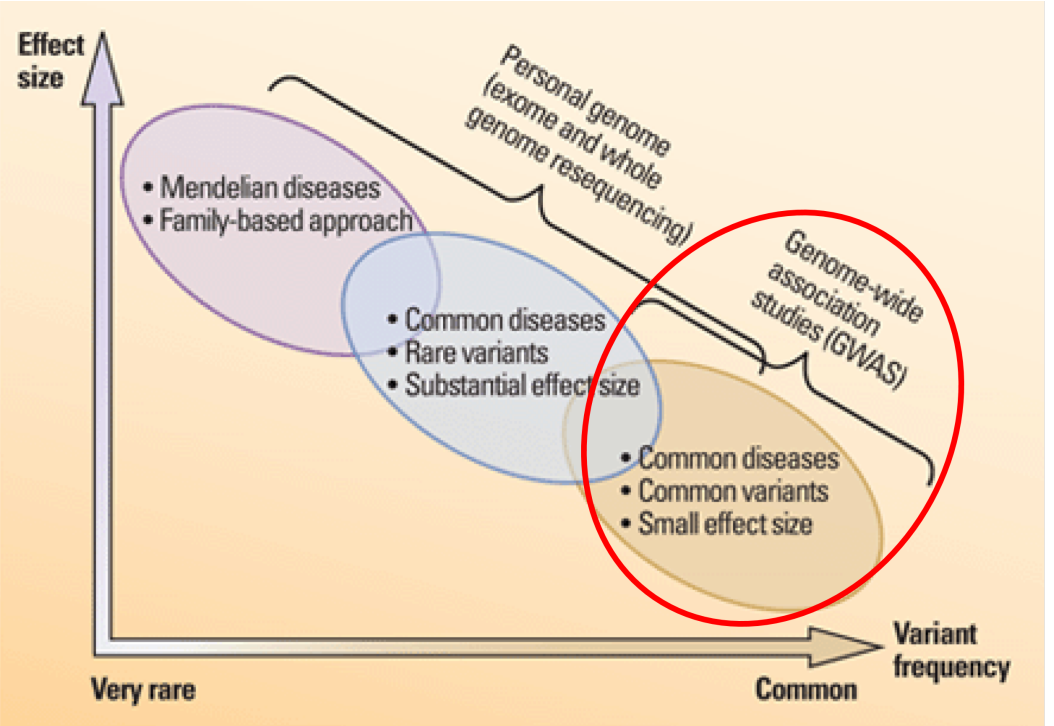
SMPGD 2022

Florian Privé

Senior Researcher, Aarhus University (DK)

Introduction

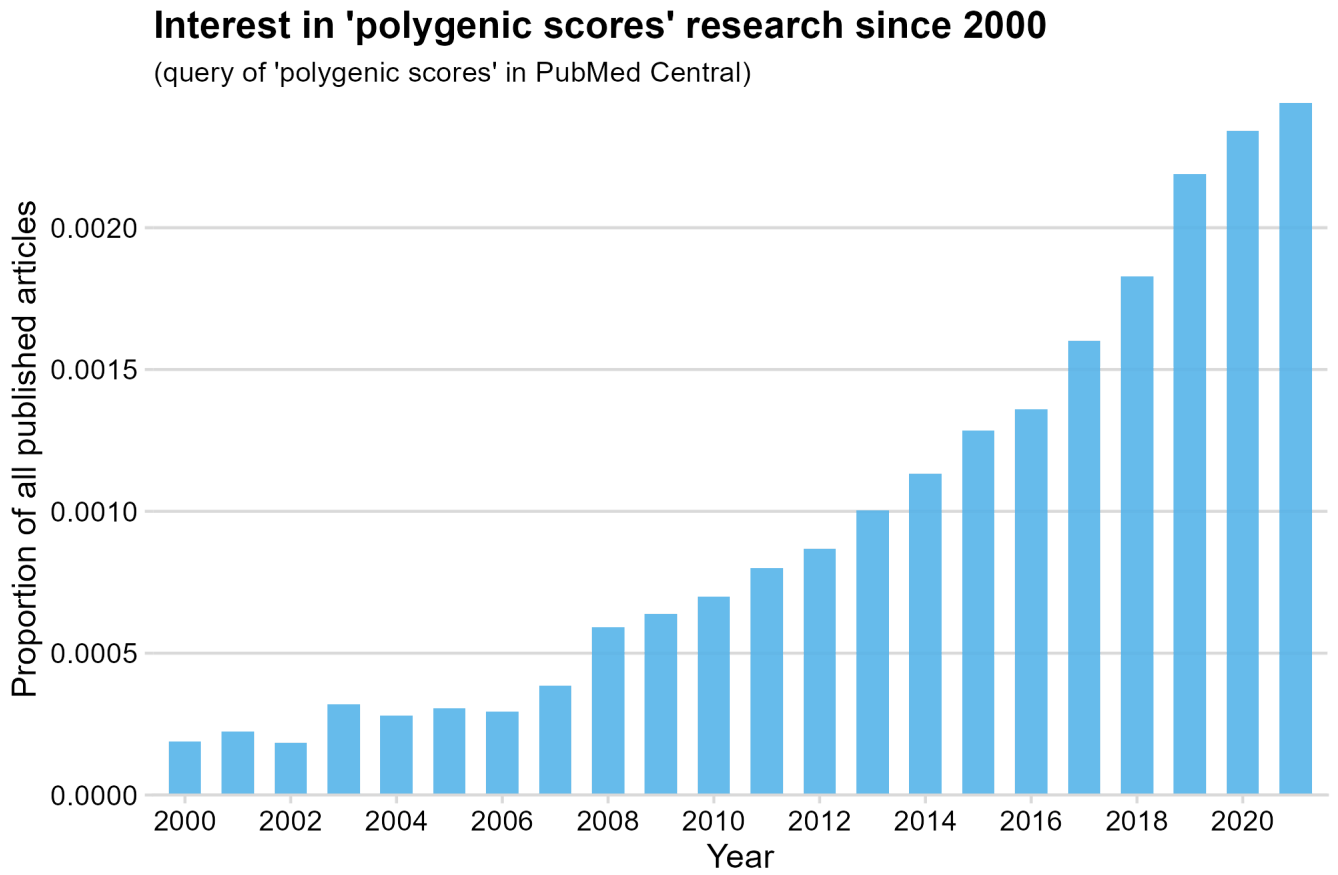
Disease architecture



Many genetic variants contribute to the risk of getting a common disease $\Longrightarrow$ build a predictive score that combines many genetic variants (polygenic risk score)

Source: 10.1126/science.338.6110.1016

Interest in Polygenic Scores (PGS)



How to predict from genetic data?

1) using individual-level data

Data: very large genotype matrices

Matrices of genetic variants (DNA mutations)

counting the number of alternative alleles (**0, 1, or 2**)
or imputed dosages (between 0 and 2)

for each individual (row) and each genome position (column)

Data I typically work with:

- UK Biobank genotyped data: 500K x 800K (~3TB)
- UK Biobank imputed data (common variants): 500K x 11M

Penalized Linear/Logistic Regression (PLR)

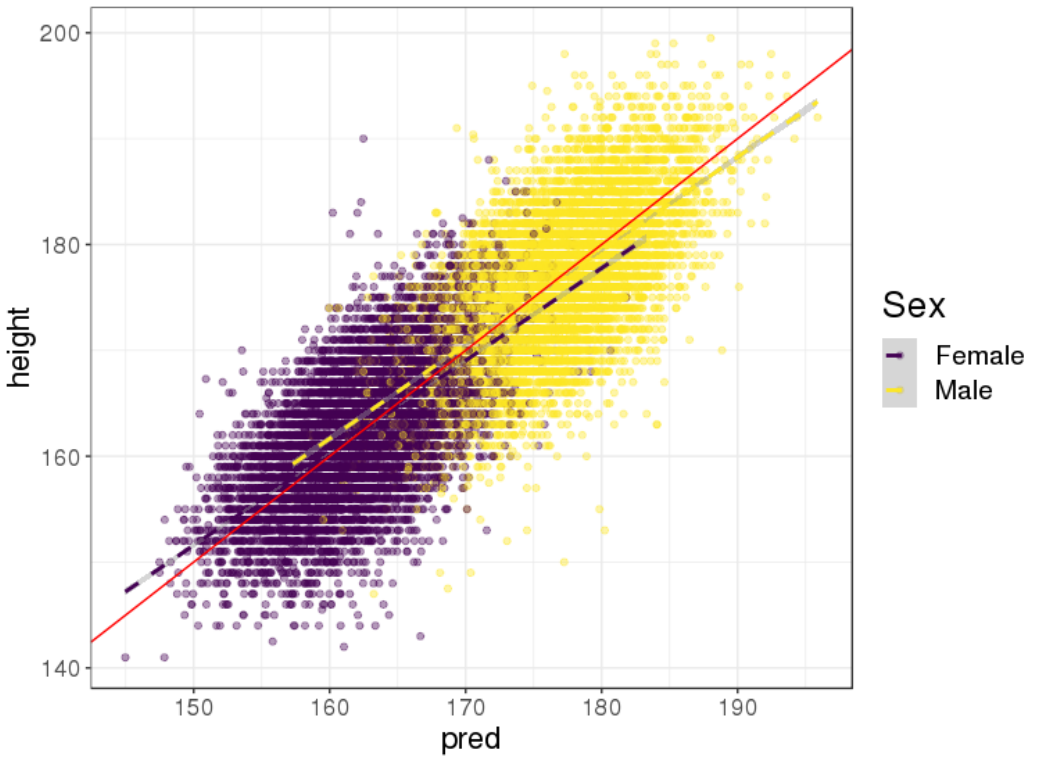
$$\underset{\beta_0,\,\beta}{\operatorname{argmin}}(\lambda, \alpha) \left\{ \underbrace{\sum_{i=1}^{n} \left(y_i - (\beta_0 + x_i^T \beta)\right)^2}_{\text{Loss function (linear reg)}} + \underbrace{\lambda \left((1-\alpha)\frac{1}{2}\|\beta\|_2^2 + \alpha\|\beta\|_1 \right)}_{\text{Penalization}} \right\}$$

- x is the **genotypes** and covariates (e.g. sex and principal components),
- y is the trait / disease status we want to predict,
- λ is a regularization parameter that needs to be determined and
- α determines relative parts of the regularization $0 \leq \alpha \leq 1$.

In R package {bigstatsr}, very fast implementation with automatic choice of λ and α [bit.ly/plr-bigstatsr]

PLR for predicting height from genotypes

- 350K individuals x 656K variants in less than one day
- Within each both males and females, 65.5% of correlation between predicted and true height



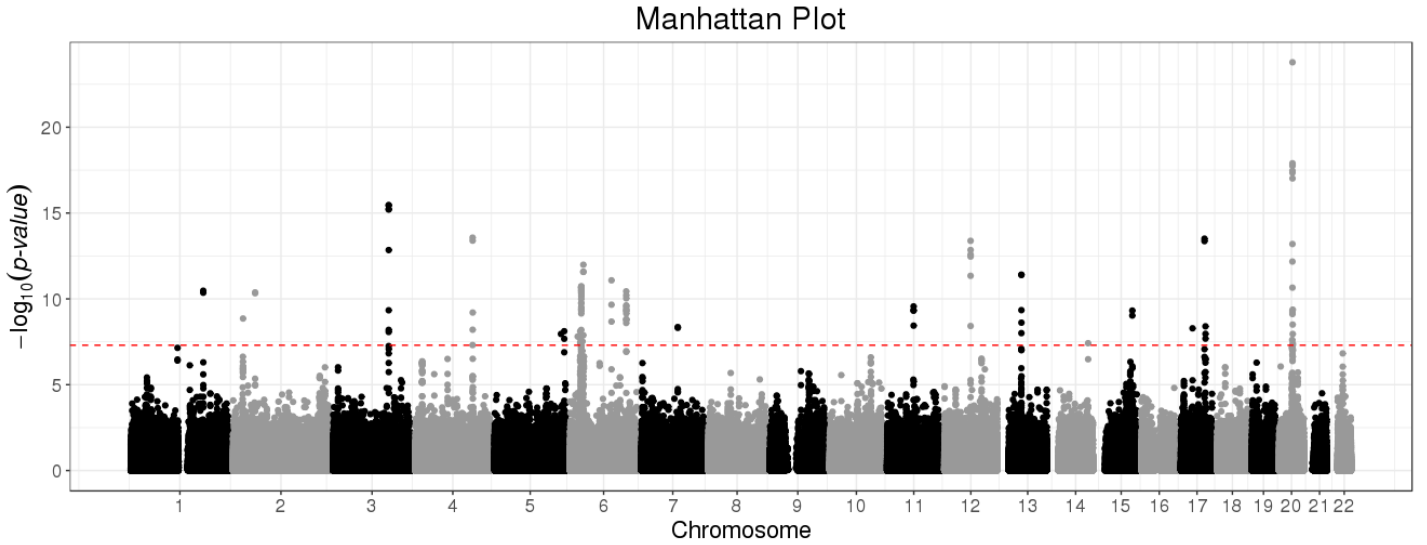
How to predict from genetic data?

2) using GWAS summary statistics

Standard PRS - part 1: estimating effects

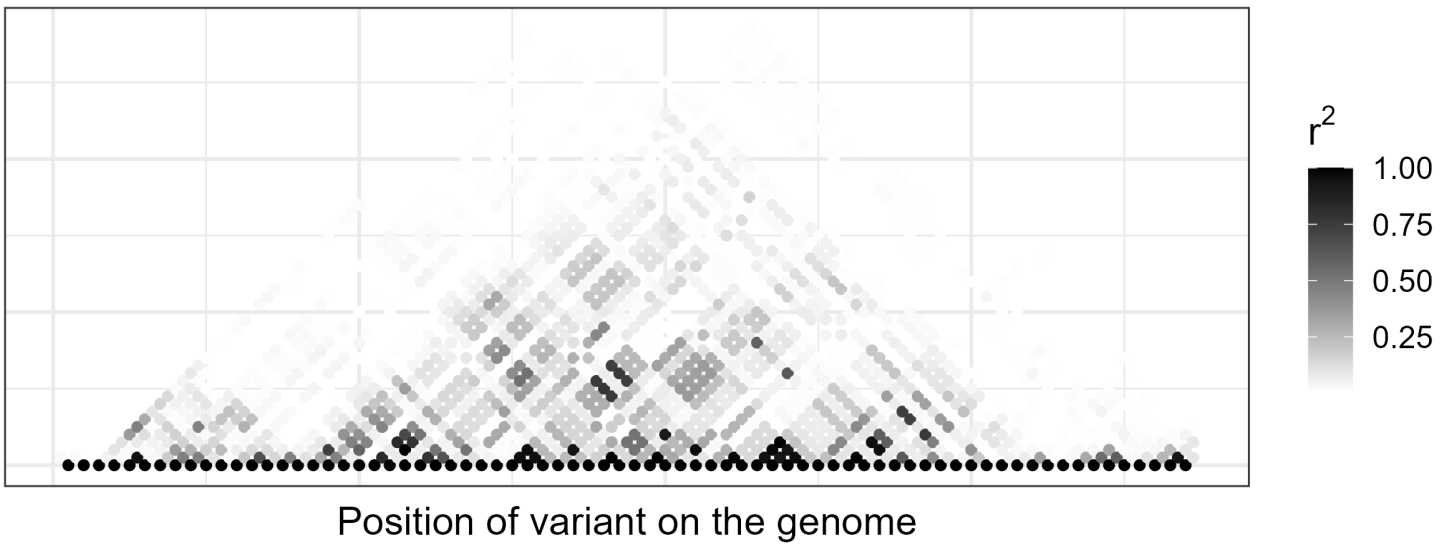
Genome-wide association studies (GWAS)

In a GWAS, each genetic variant is tested **independently**, resulting in one **effect size** $\hat{\beta}$ and one **p-value** p for each variant.



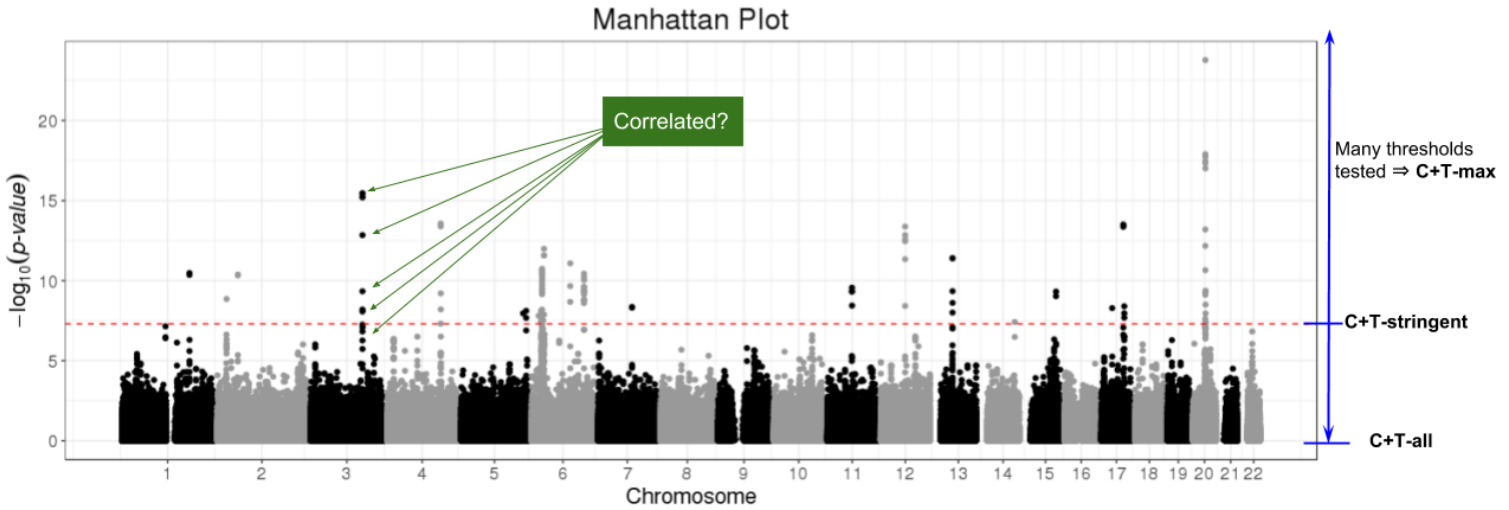
Easy combining: $PRS_i = \sum_j \hat{\beta}_j \cdot G_{i,j}$

Local correlation between variants causes redundant GWAS signals

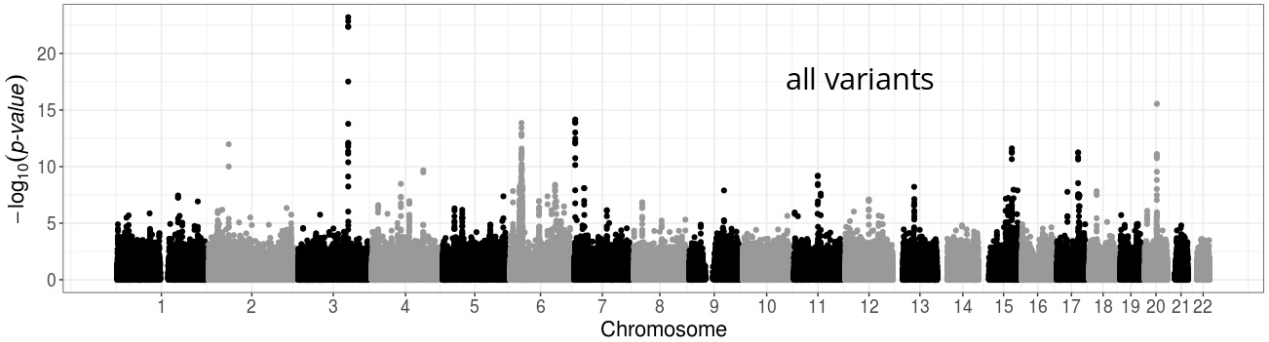


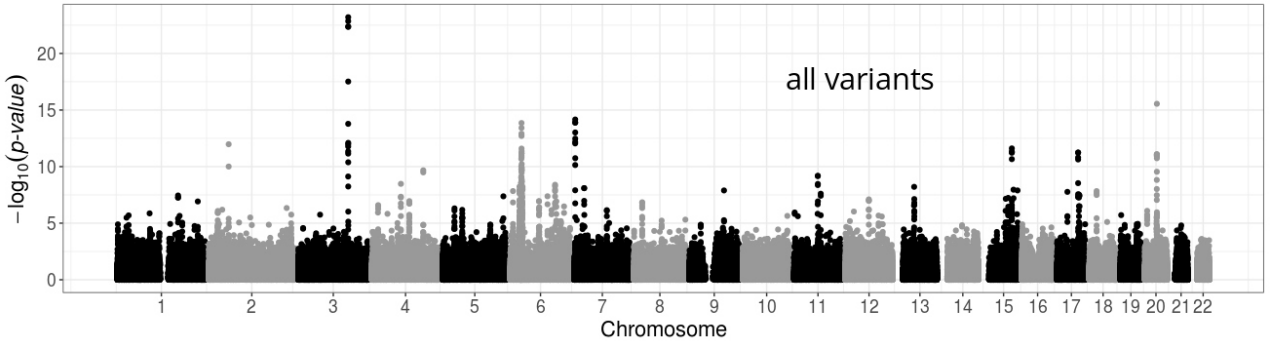
Standard PRS - part 2: restricting predictors

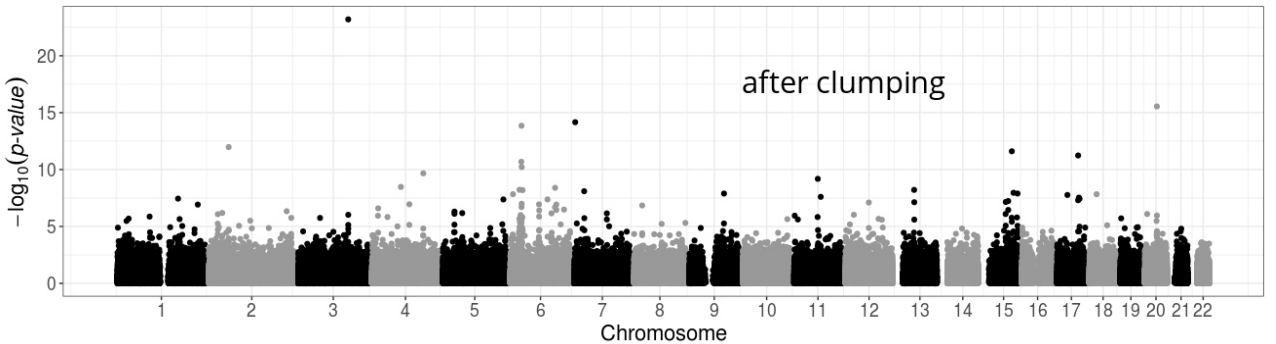
Clumping + Thresholding (C+T, or P+T)

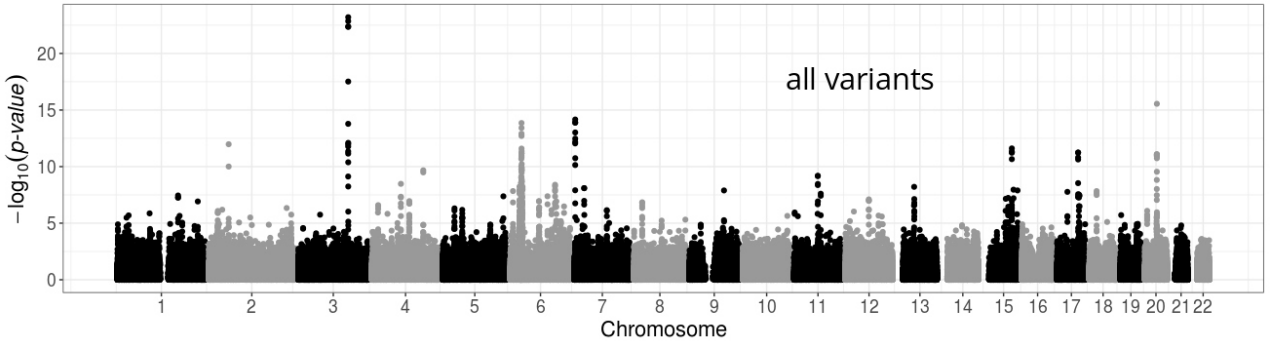


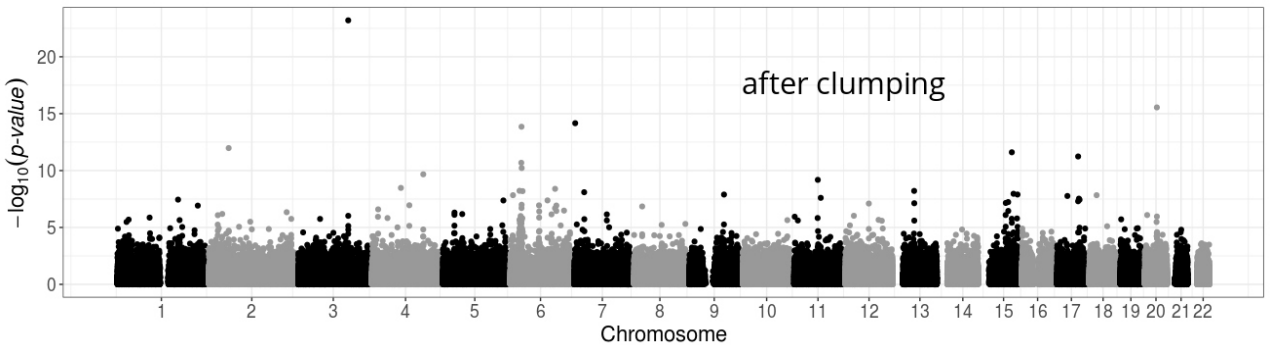
$$PRS_i = \sum_{\substack{j \in S_{\text{clumping}} \\ p_j < p_T}} \hat{\beta}_j \cdot G_{i,j}$$

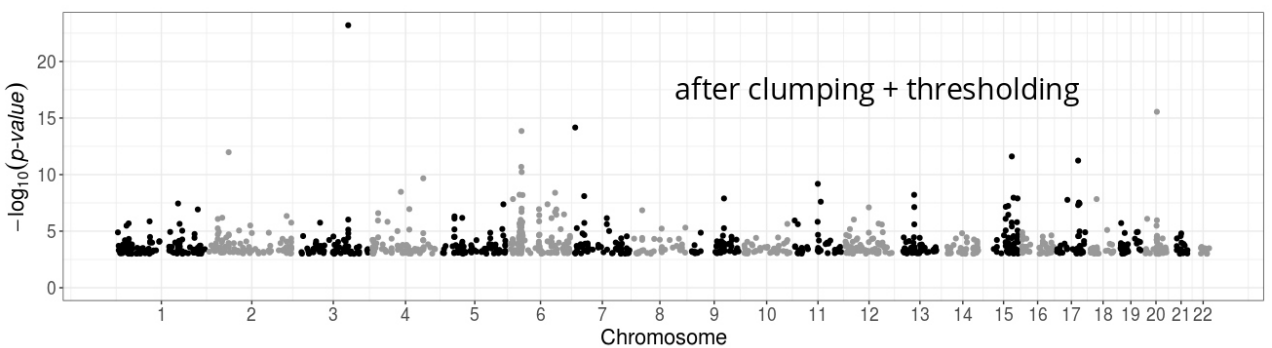

all variants
$-\log_{10}(p\text{-}value)$
20
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome


all variants
$-\log_{10}(p\text{-value})$
0
5
10
15
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


after clumping
$-\log_{10}(p\text{-value})$
0
5
10
15
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


all variants
$-\log_{10}(p\text{-value})$
0
5
10
15
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


after clumping
$-\log_{10}(p\text{-value})$
0
5
10
15
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome


after clumping + thresholding
$-\log_{10}(p\text{-value})$
0
5
10
15
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome

Making the most of C+T

Hyper-parameters in C+T

- threshold on squared correlation of clumping (e.g. $r_c^2 > 0.2$) and window size for LD computation (e.g. $w_c = 500kb$)
- p-value threshold (p_T between 1 and 10^{-8} and choose the best one)
- other parameters such as the threshold of imputation quality score (e.g. $INFO > 0.3$) or minor allele frequency (e.g. $MAF > 0.01$)

$\Longrightarrow$ *stdCT* (standard C+T)

Making the most of C+T

Hyper-parameters in C+T

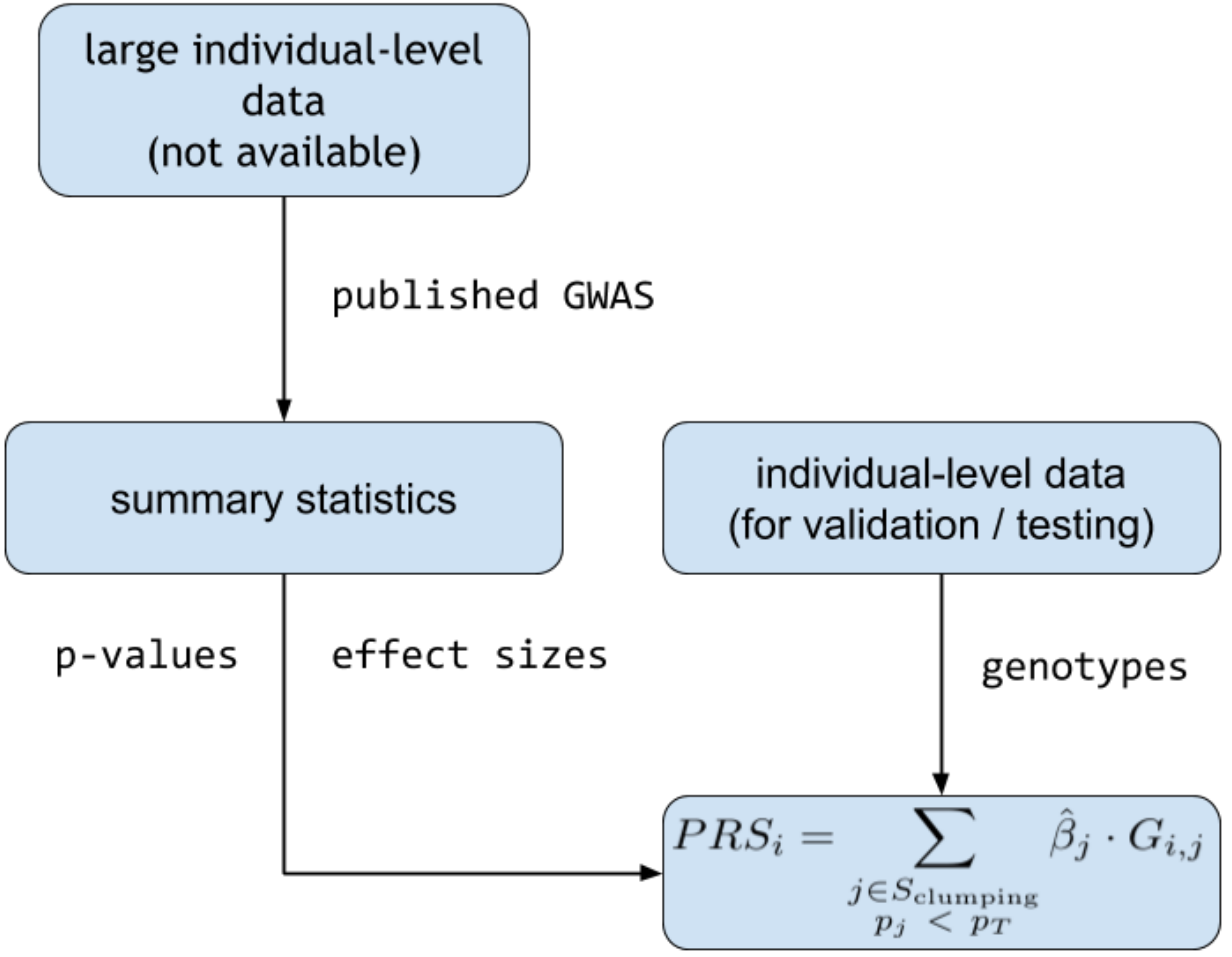
- threshold on squared correlation of clumping (e.g. $r_c^2 > 0.2$) and window size for LD computation (e.g. $w_c = 500kb$)
- p-value threshold (p_T between 1 and 10^{-8} and choose the best one)
- other parameters such as the threshold of imputation quality score (e.g. $INFO > 0.3$) or minor allele frequency (e.g. $MAF > 0.01$)

$\Longrightarrow$ *stdCT* (standard C+T)

Our contribution [bit.ly/sct-paper]

- an efficient implementation to compute thousands of C+T scores corresponding to different sets of hyper-parameters
  $\Longrightarrow$ *maxCT* (maximized C+T)
- going further by **stacking** with a linear combination of all C+T models (instead of just choosing the best model)
  $\Longrightarrow$ *SCT* (Stacked C+T)

Using summary statistics from large GWAS



Alternative: approximating a penalized regression

A linear model with elastic-net regularization using coordinate descent by iteratively updating:

$$\beta_j^{(t+1)} = \begin{cases} \operatorname{sign}\left(u_j^{(t)}\right)\left(\left|u_j^{(t)}\right| - \lambda_1\right) / \left(1 + \lambda_2\right) & \text{if } \left|u_j^{(t)}\right| > \lambda_1 \ , \\ 0 & \text{otherwise.} \end{cases}$$

where

$$u_j^{(t)} = \sum_i \left[G_{i,j} \left(y_i - \sum_{k \neq j} G_{i,k} \beta_k^{(t)} \right) \right] = \sum_i G_{i,j} y_i - \sum_{k \neq j} \left(\sum_i G_{i,j} G_{i,k} \right) \beta_k^{(t)} \ .$$

Alternative: approximating a penalized regression

A linear model with elastic-net regularization using coordinate descent by iteratively updating:

$$\beta_j^{(t+1)} = \begin{cases} \text{sign}\left(u_j^{(t)}\right)\left(\left|u_j^{(t)}\right| - \lambda_1\right) / \left(1 + \lambda_2\right) & \text{if } \left|u_j^{(t)}\right| > \lambda_1 \ , \\ 0 & \text{otherwise.} \end{cases}$$

where

$$u_j^{(t)} = \sum_i \left[G_{i,j} \left(y_i - \sum_{k \neq j} G_{i,k} \beta_k^{(t)} \right) \right] = \sum_i G_{i,j} y_i - \sum_{k \neq j} \left(\sum_i G_{i,j} G_{i,k} \right) \beta_k^{(t)} \ .$$

- $\sum_i G_{i,j} y_i$ can be obtained from GWAS summary statistics
- $\sum_i G_{i,j} G_{i,k}$ can be estimated from another dataset

$\Longrightarrow$ we can use summary statistics only (no individual-level data).

This idea is used in lassosum (TSH Mak et al. "Polygenic scores via penalized regression on summary statistics." Genetic epidemiology (2017))

Computational considerations

- correlation between genetic variants is local ($\sum_i G_{i,j} G_{i,k}$, when G is appropriately scaled)
- the correlation matrix $G^T G$ is very sparse (banded)
- $\Rightarrow$ we can use e.g. 1M variants without too much difficulty

Computational considerations

- correlation between genetic variants is local ($\sum_i G_{i,j}G_{i,k}$, when G is appropriately scaled)
- the correlation matrix G^TG is very sparse (banded)
- $\Rightarrow$ we can use e.g. 1M variants without too much difficulty

---

Other methods for polygenic prediction from summary statistics

Many other methods have been developed, lots being Bayesian.

They all use the same idea of approximating the linear regression model using GWAS summary statistics and an external reference for the correlation between variants.

For example, we have developed LDpred2 [bit.ly/ldpred2-paper].

What influences predictive power of polygenic scores

What influences predictive power?

- Predictive power r^2 is bounded by the heritability h^2 captured by the set of variants used.
- r^2 increases with sample size N (of course)
- r^2 decreases with polygenicity (proportion of causal variants), because there are more small effects, harder to detect and estimate.
  Let's denote M_c the number of causal variants.

What influences predictive power?

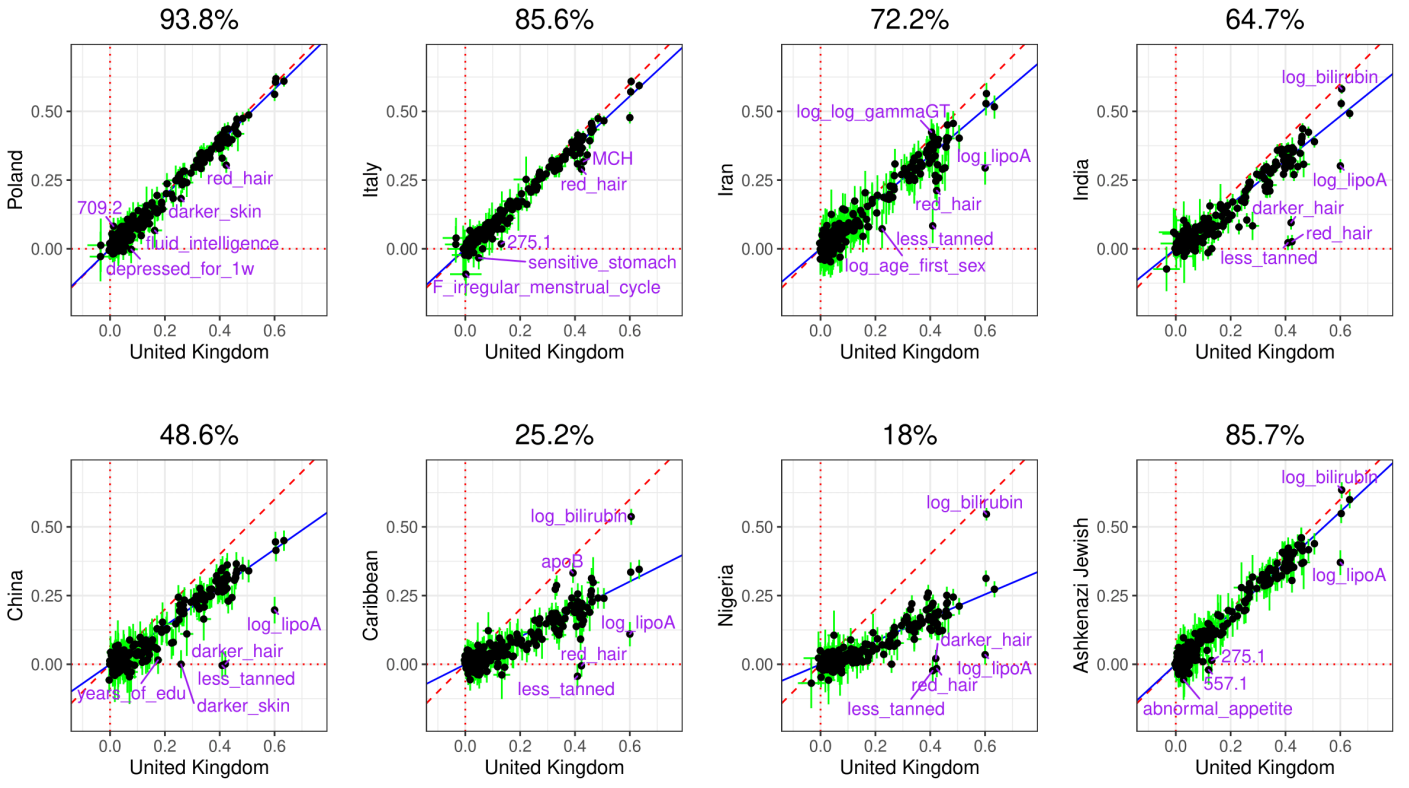
- Predictive power r^2 is bounded by the heritability h^2 captured by the set of variants used.
- r^2 increases with sample size N (of course)
- r^2 decreases with polygenicity (proportion of causal variants), because there are more small effects, harder to detect and estimate.
  Let's denote M_c the number of causal variants.

$$r^2_{\max} = \frac{h^2}{1 + (1 - r^2_{\max})\frac{M_c}{Nh^2}}$$

Source: 10.1371/journal.pone.0003395

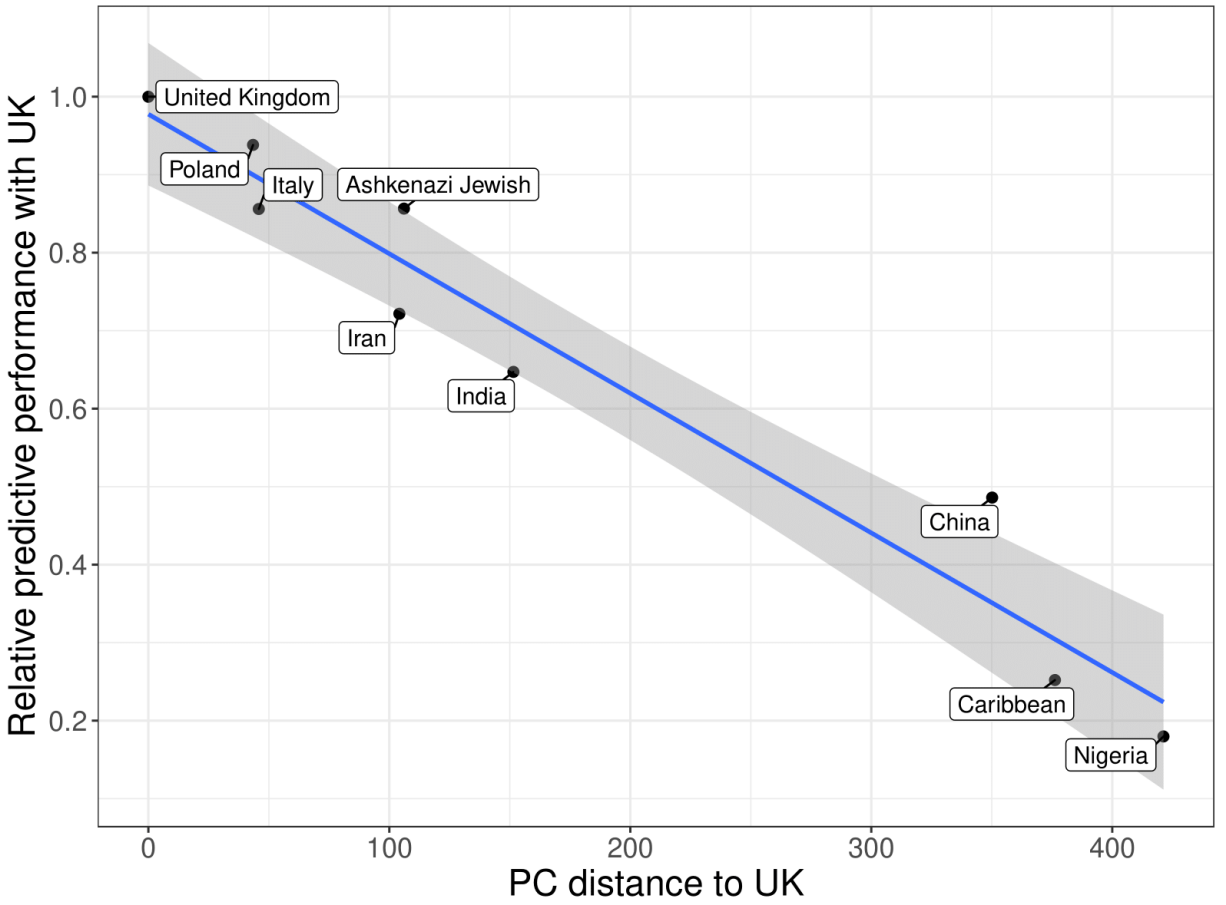
A major limitation of polygenic scores: their poor portability across ancestries

Portability across 245 phenotypes and 9 ancestry groups

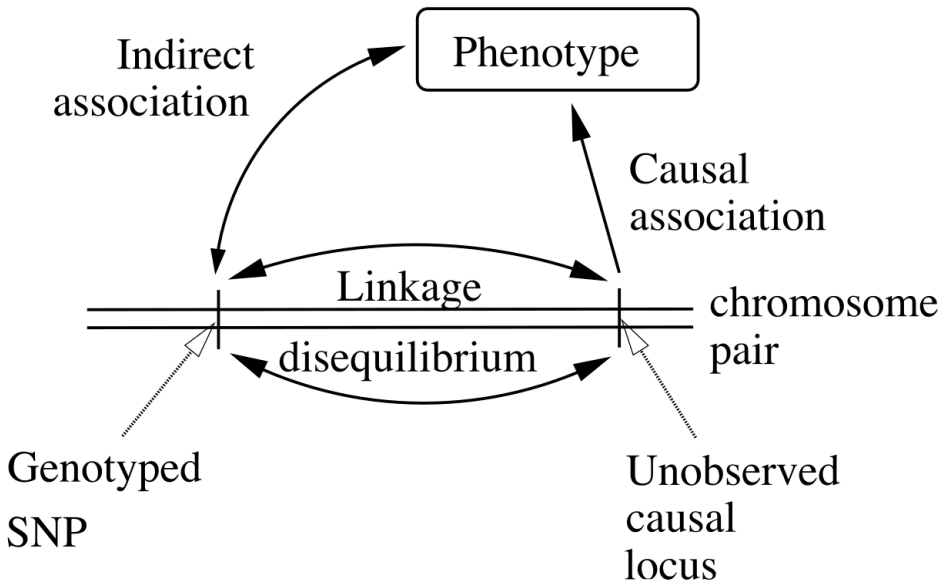


Percentage in figure title = squared slope (in blue) -- Source: [bit.ly/portability-paper]

Predictive performance drops with genetic distance



One possible explanation: different tagging



Linkage disequilibrium = correlation between genetic variants
(can be different across populations)

Source: 10.1214/09-STS307

Conclusion

Take-home messages

- We can predict traits and diseases from genetic data (up to the heritability)
- One can use supervised learning methods when individual-level data is available (but, beware scalability)
- Many methods using summary statistics only have been developed (because we can easily obtain larger sample sizes through meta-analysis)
- For some traits, we have large sample sizes (e.g. 5M for height), but we still need larger sample sizes for most complex traits and diseases
- We still need to address the concern of providing PGS that work well in ALL ancestries
  This could be achieved by recruiting more people from non-European ancestries, and developing new methods for multi-ancestry training

Thanks!

Presentation available at
https://privefl.github.io/thesis-docs/smpgd22.html

privefl privefl F. Privé

Slides created via the R package **xaringan**.