Polygenic Risk Scores based on statistical learning

Thesis follow-up n°2

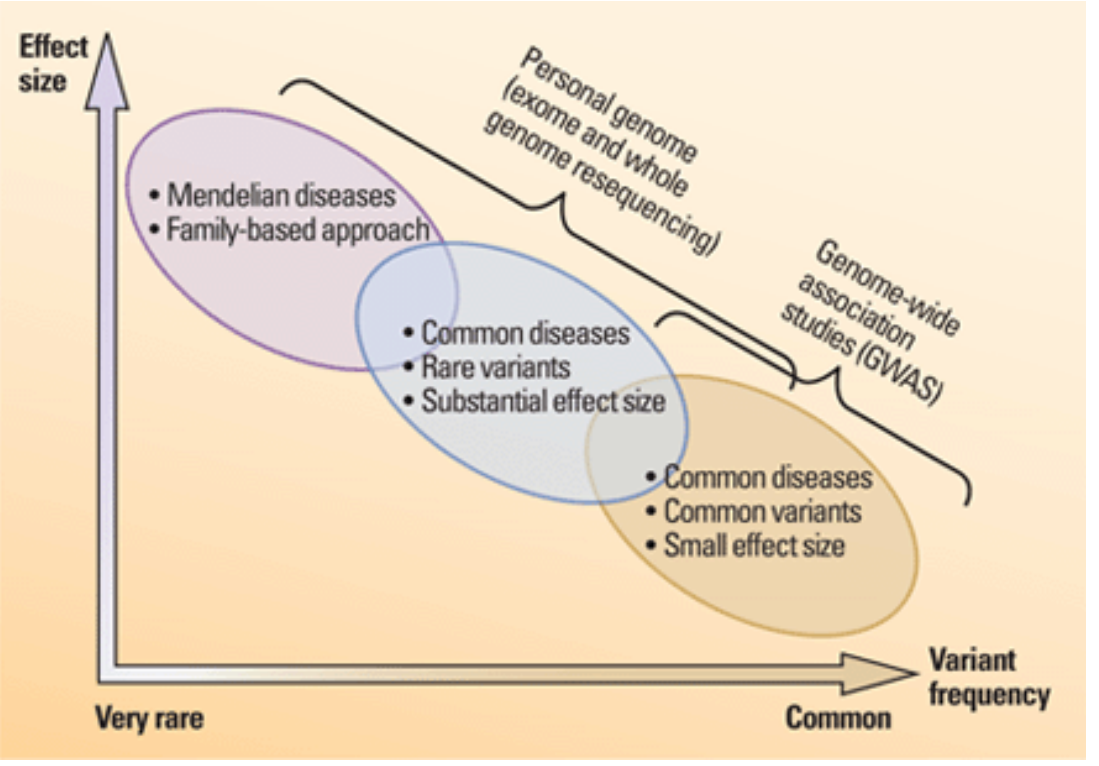
Florian Privé

October 1, 2018

Outline

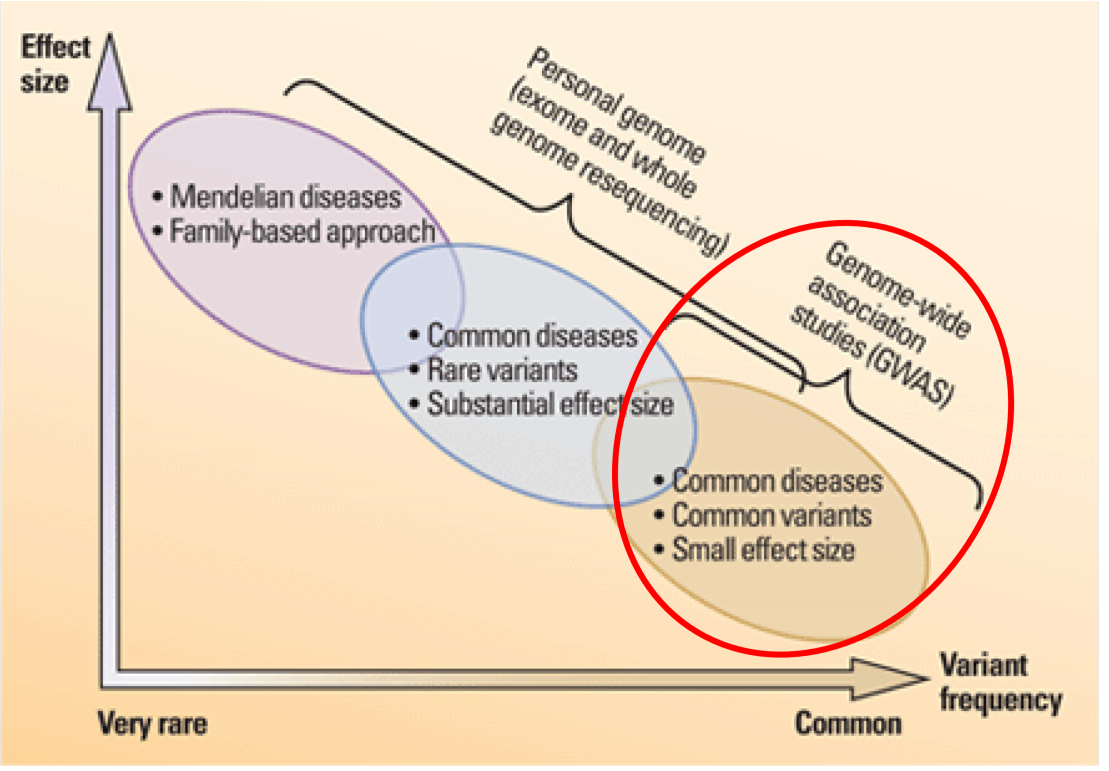
Introduction

Disease architectures



Source: 10.1126/science.338.6110.1016

Disease architectures



How to derive a genetic risk score for common diseases based on common variants with small effects?

Interest in prediction: polygenic risk scores (PRS)

- Wray, Naomi R., Michael E. Goddard, and Peter M. Visscher. "**Prediction of individual genetic risk** to disease from genome-wide association studies." Genome research 17.10 (**2007**): 1520-1528.
- Wray, Naomi R., et al. "Pitfalls of **predicting complex traits** from SNPs." Nature Reviews Genetics 14.7 (**2013**): 507.
- Dudbridge, Frank. "Power and **predictive accuracy of polygenic risk scores**." PLoS genetics 9.3 (**2013**): e1003348.
- Chatterjee, Nilanjan, Jianxin Shi, and Montserrat García-Closas. "Developing and evaluating **polygenic risk prediction** models for stratified disease prevention." Nature Reviews Genetics 17.7 (**2016**): 392.
- Martin, Alicia R., et al. "Human demographic history impacts **genetic risk prediction** across diverse populations." The American Journal of Human Genetics 100.4 (**2017**): 635-649.

Still a gap between current predictions and clinical utility.
Need more optimal predictions + larger sample sizes.

Recall of 1st year

Developing tools to help

researchers (me!) in their analysis

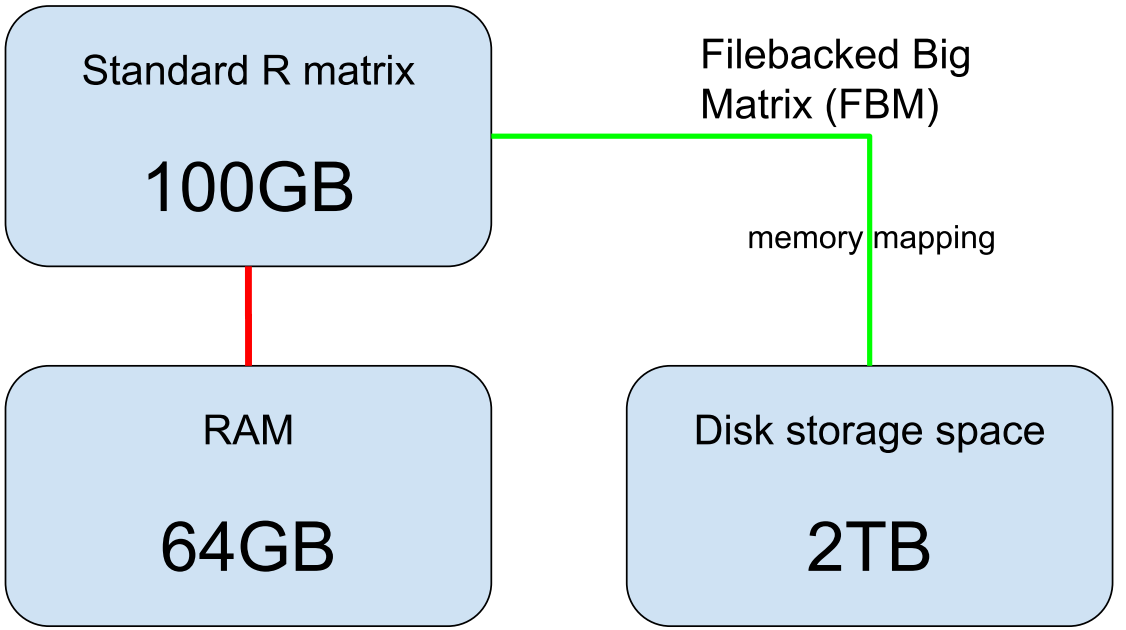
What I want to be able to do

Data analysis on large-scale genotype matrices!

- Be fast to test many ideas quickly
  - code should be fast
  - I shouldn't have to make many conversions between formats
  - easily combine multiple functions
- Not be restricted in my analysis
  - Basically use all I already know in R
- Work on my computer (interactively)
  - I have 64 GB of RAM and 12 cores
  - Working on a server is not as easy as on my computer

Smooth and fast analysis!

Memory solution when working in R



My first paper

Efficient analysis of large-scale genome-wide data with two R packages: bigstatsr and bigsnpr

Florian Privé ✉, Hugues Aschard, Andrey Ziyatdinov, Michael G B Blum ✉

Bioinformatics, bty185, https://doi.org/10.1093/bioinformatics/bty185

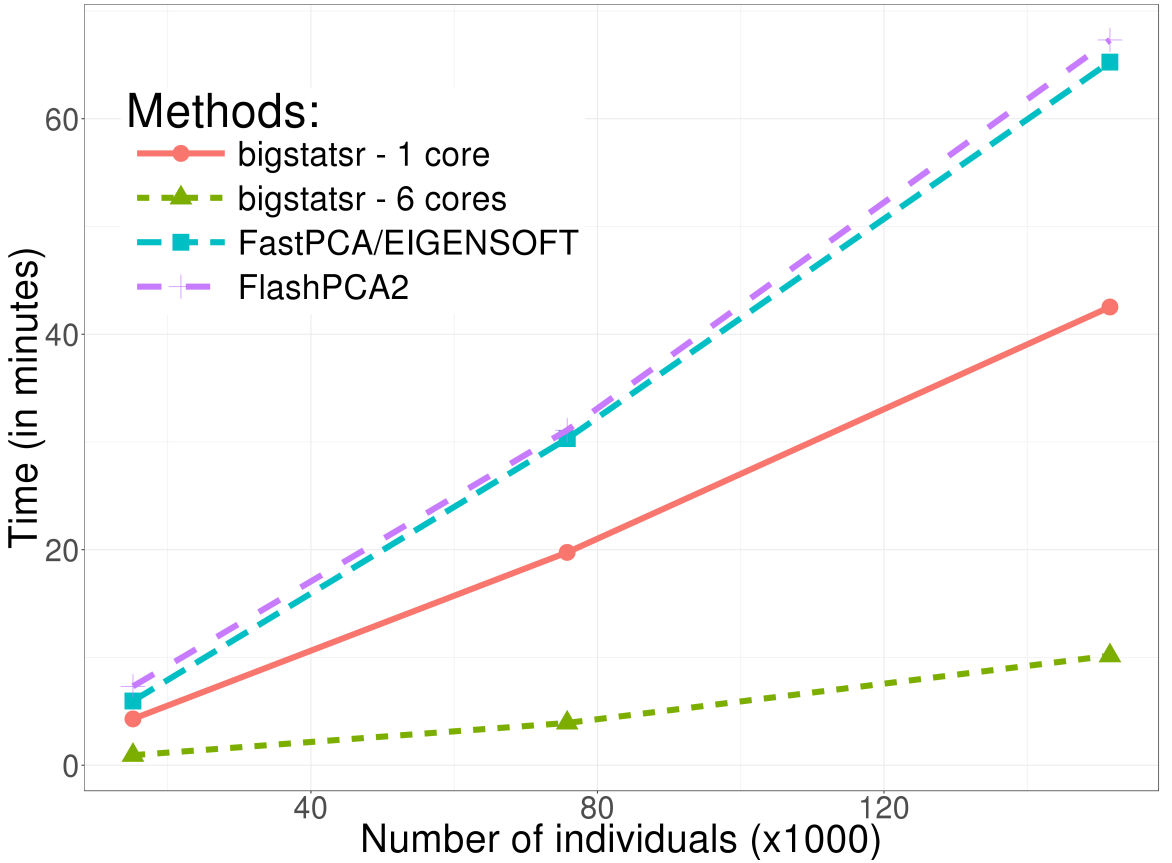
Two R packages: {bigstatsr} and {bigsnpr}

- {bigstatsr} for many types of matrix, to be used by any field of research
- {bigsnpr} for functions which are specific to the analysis of SNP arrays

I've presented {bigstatsr} at 3 R conferences.

Comparative performance

Computing partial SVD



Results of 2nd year

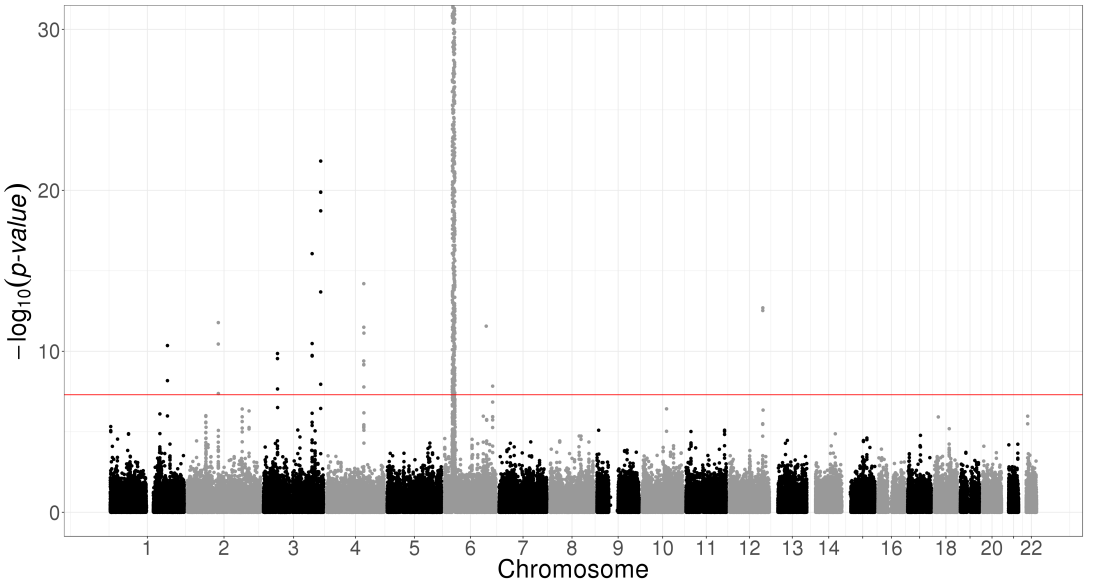
Comparing models for computing

Polygenic Risk Scores (PRS)

Standard PRS - part 1: estimating effects

Genome-wide association studies (GWAS)

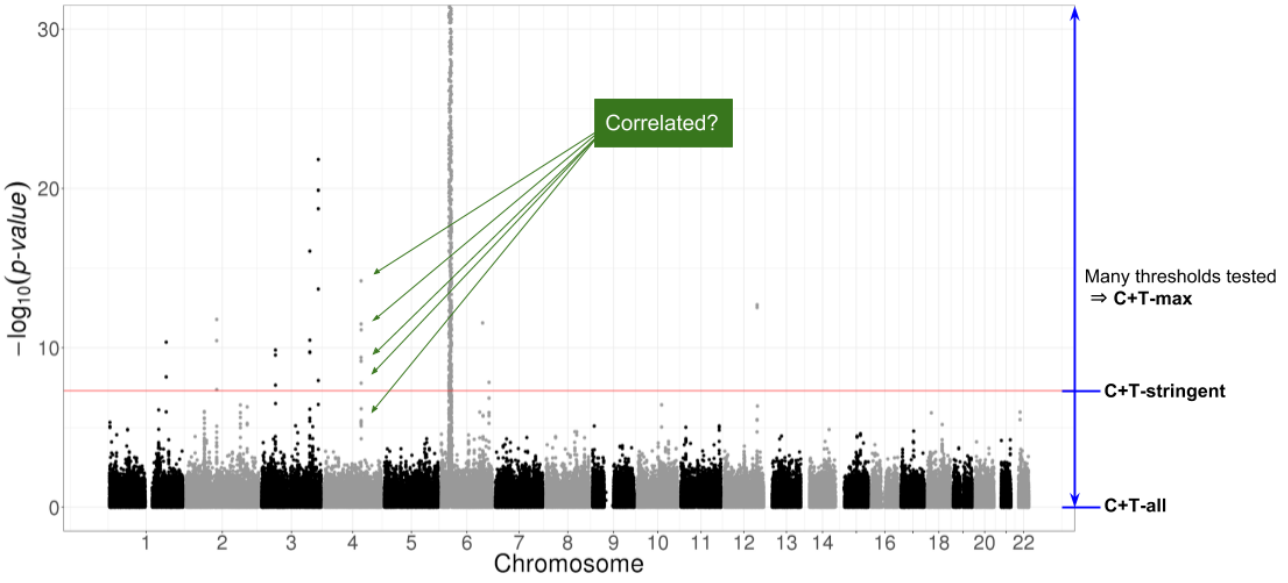
In a GWAS, each single-nucleotide polymorphism (SNP) is tested **independently**, resulting in one **effect size** $\hat{\beta}$ and one **p-value** p for each SNP.



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

Standard PRS - part 2: restricting predictors

Clumping + Thresholding (C+T)



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

A more optimal approach to computing PRS?

In C+T: weights learned independently and heuristics for correlation and regularization.

Statistical learning

- joint models of all SNPs at once
- use regularization to account for correlated and null effects
- already proved useful in the litterature (Abraham et al. 2013; Okser et al. 2014; Spiliopoulou et al. 2015)

Our contribution

- a memory- and computation-efficient implementation to be used for biobank-scale data
- an automatic choice of the regularization hyper-parameter
- a comprehensive comparison for different disease architectures

Methods

Penalized Logistic Regression (PLR)

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

- $p_i = 1/\left(1+\exp\left(-(\beta_0 + x_i^T\beta)\right)\right)$
- x is denoting the genotypes and covariables (e.g. principal components),
- y is the disease status we want to predict,
- λ is a regularization parameter that needs to be determined and
- α determines relative parts of the regularization $0 \leq \alpha \leq 1$.

Efficient algorithm

- sequential strong rules for discarding predictors in lasso-type problems (Tibshirani et al. 2012; Zeng et al. 2017)
- implemented in our R package {bigstatsr}

Efficient analysis of large-scale genome-wide data with two R packages: bigstatsr and bigsnpr

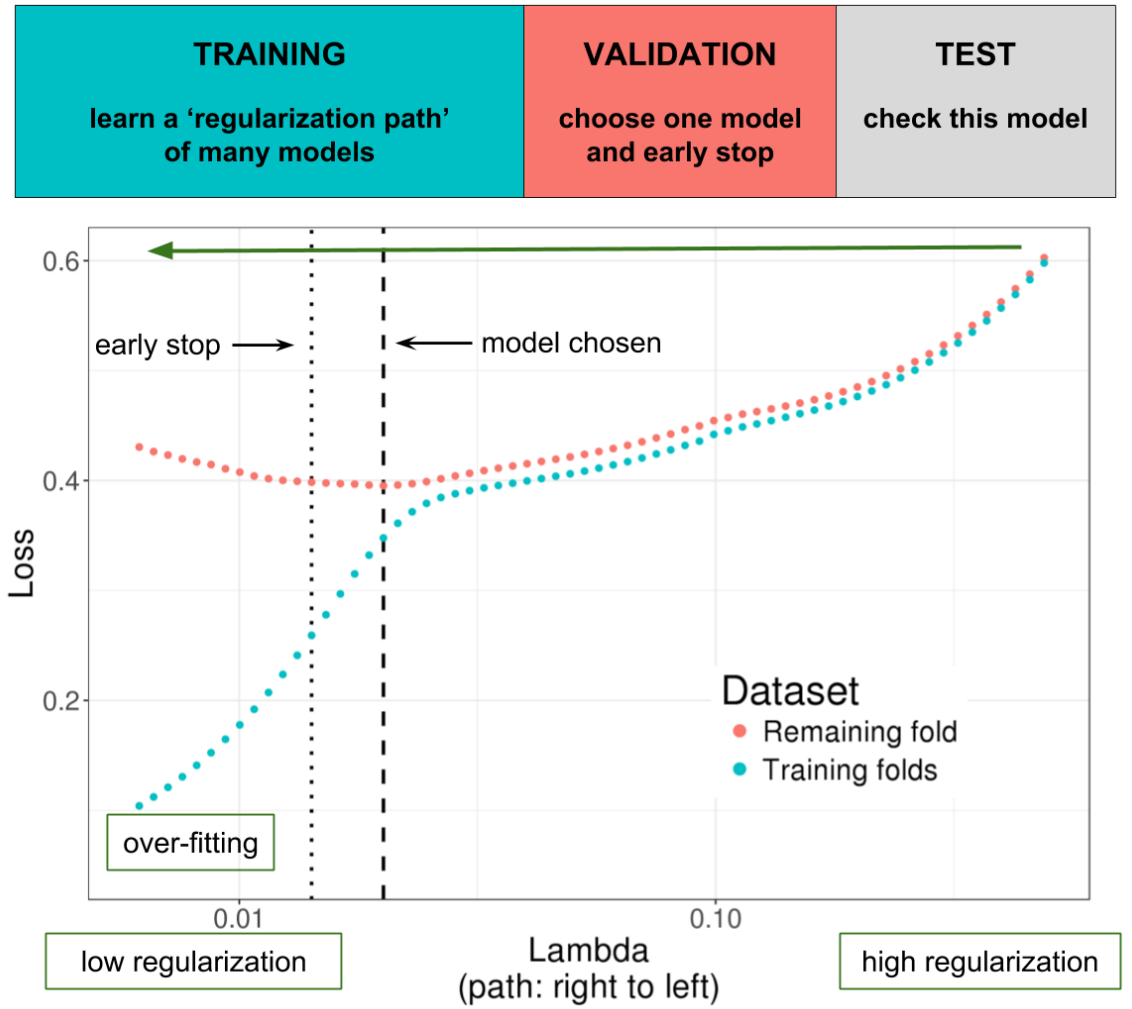
Florian Privé, Hugues Aschard, Andrey Ziyatdinov, Michael G B Blum

Bioinformatics, bty185, https://doi.org/10.1093/bioinformatics/bty185

Our implementation

- uses memory-mapping to matrices stored on disk
- functioning choice of the hyper-parameter λ + embedded grid-search for α
- early stopping criterion to fasten the overall procedure

Choice of the hyper-parameter λ



Comprehensive simulations: varying many parameters

Simulation models

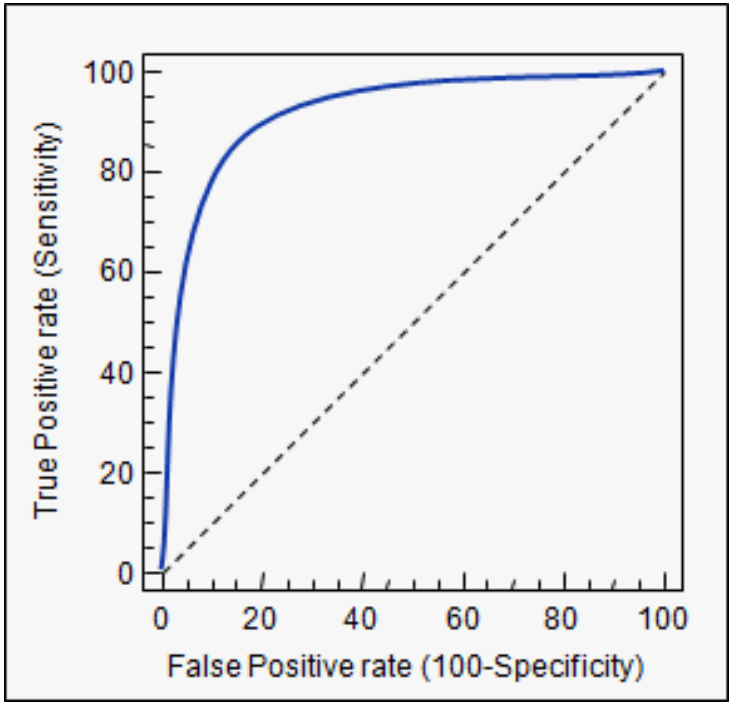
Numero of scenario	Dataset	Size of training set	Causal SNPs (number and location)	Distribution of effects	Heritability	Simulation model	Methods
1	All 22 chromosomes	6000	30 in HLA 30 in all 300 in all 3000 in all	Gaussian Laplace	0.5 0.8	ADD COMP	C+T PLR PLR3 (T-Trees)
2	Chromosome 6 only	-	-	-	-	ADD	C+T PLR
3	All 22 chromosomes	1000 2000 3000 4000 5000	300 in all	-	-	-	-

Methods

- C+T:
  - C+T-all (no p-value thresholding),
  - C+T-stringent (GWAS threshold of significance) and
  - C+T-max (best prediction for all thresholds, considered as an upper-bound)

Predictive performance measures

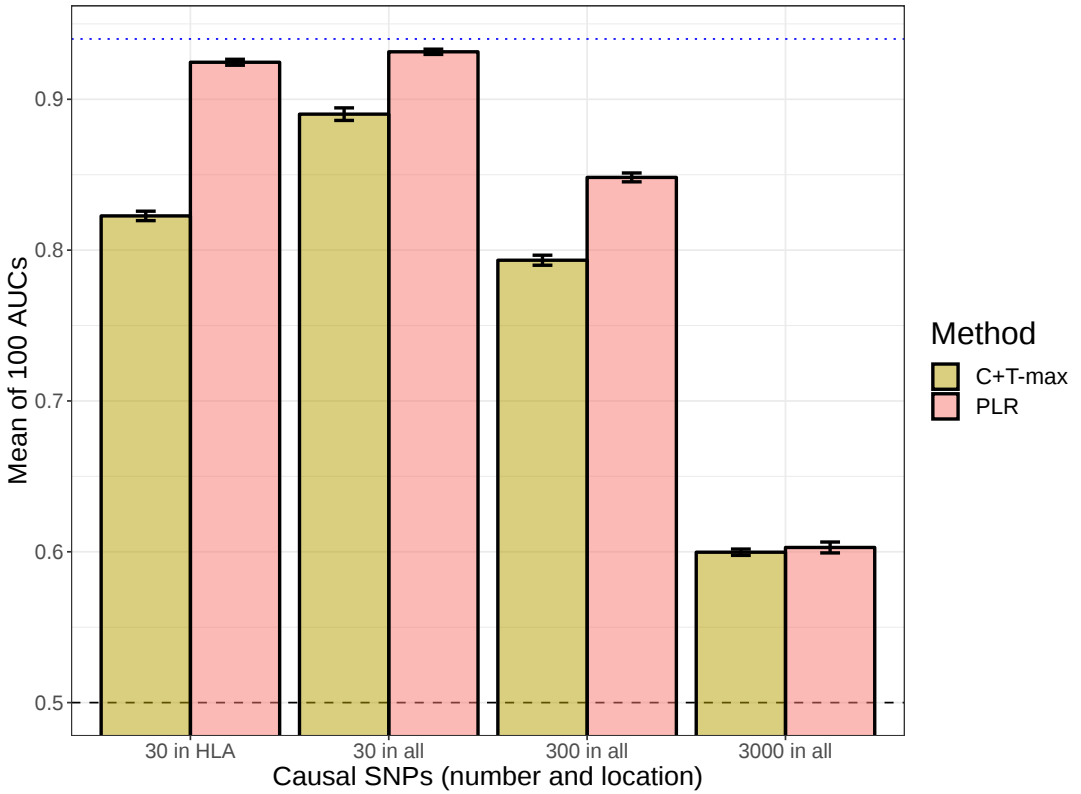
AUC (Area Under the ROC Curve) and partial AUC (FPR < 10%) are used.



$$\mathrm{AUC} = P(S_{\mathrm{case}} > S_{\mathrm{control}})$$

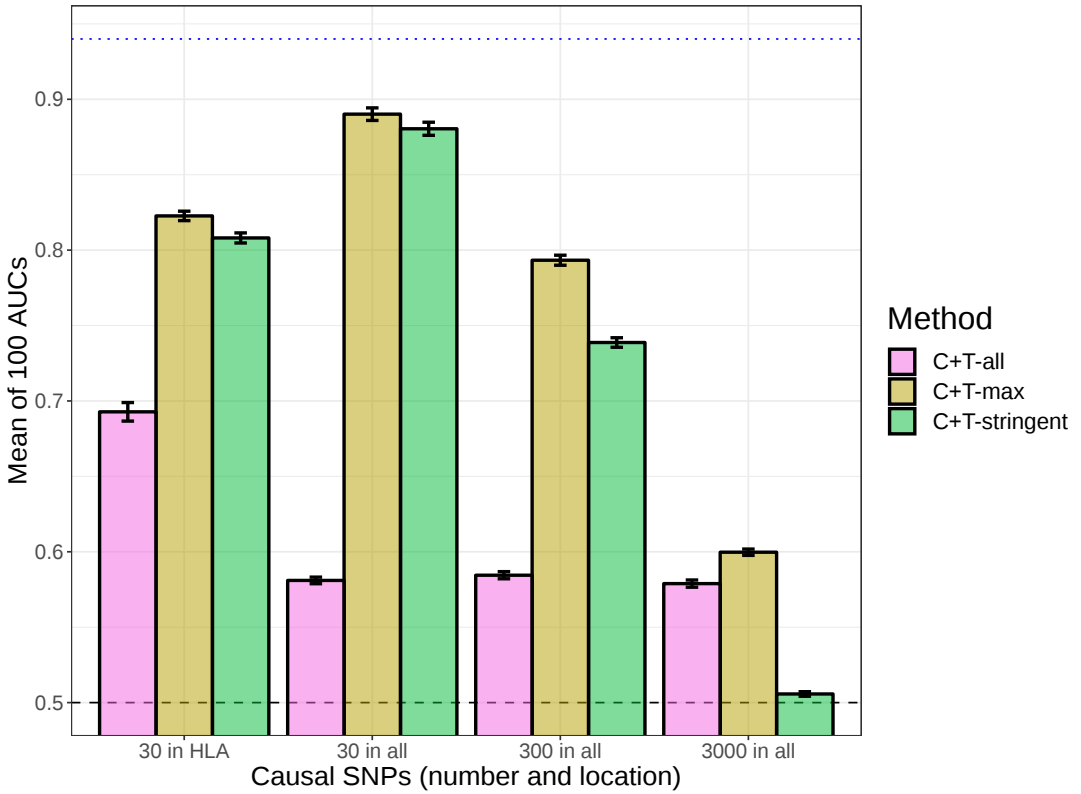
Results

Higher predictive performance with PLR



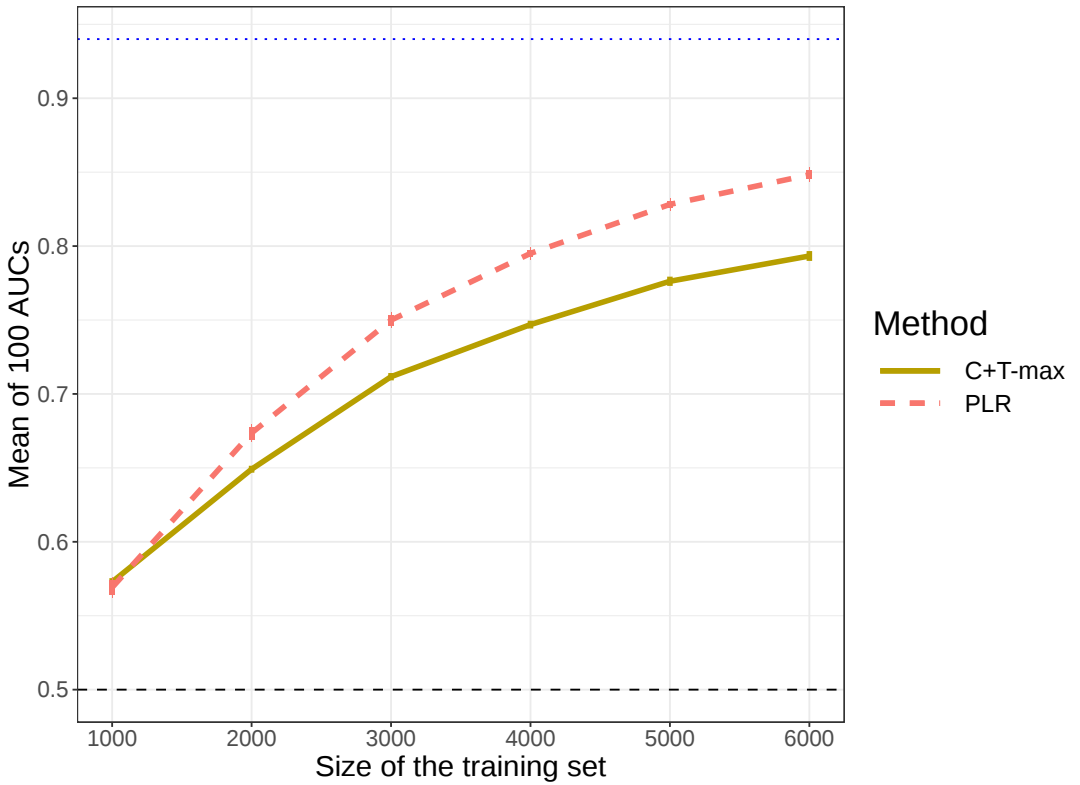
Penalized logistic regression consistently provides higher predictive performance, especially when there are correlated variables.

Predictive performance of C+T method varies with threshold



Recall that prediction of C+T-max is an upper-bound of the prediction provided by the C+T method.

Prediction with PLR is improving faster (Scenario #3)



Performance of methods improve with larger sample size. Yet, PLR is improving faster than C+T.

Real data

Celiac disease

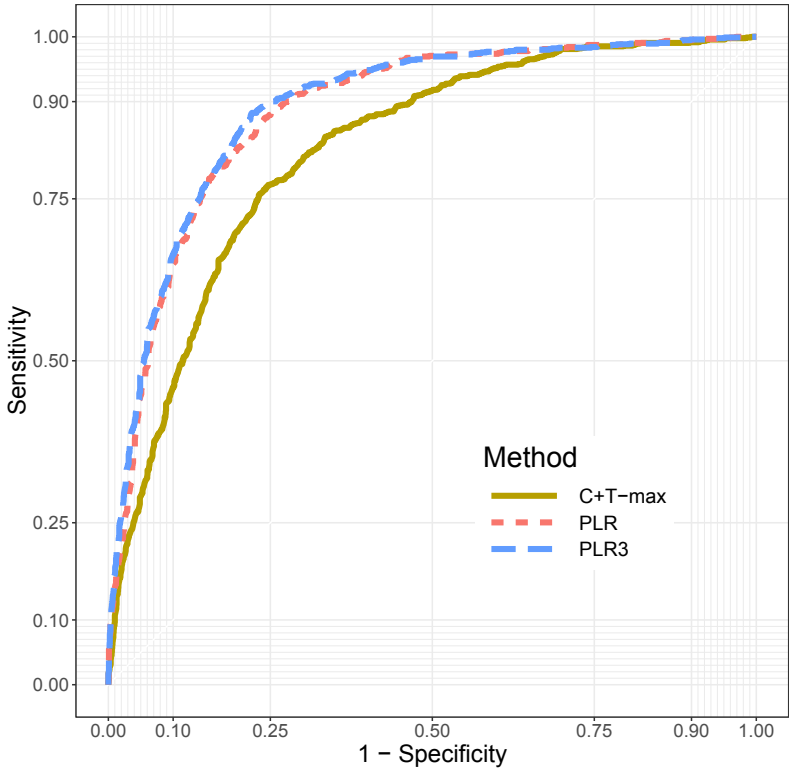
- intolerance to gluten
- only treatment: gluten-free diet
- heritability: 57-87% (Nisticò et al. 2006)
- prevalence: 1-6%

Case-control study for the celiac disease (WTCCC, Dubois et al. 2010)

- ~15,000 individuals
- ~280,000 SNPs
- ~30% cases

Results: real Celiac phenotypes

Method	AUC	pAUC	# predictors	Execution time (s)
C+T-max	0.825 (0.000664)	0.0289 (0.000187)	8360 (744)	130 (0.143)
PLR	0.887 (0.00061)	0.0411 (0.000224)	1570 (46.4)	190 (1.21)
PLR3	0.891 (0.000628)	0.0426 (0.000219)	2260 (56.1)	296 (2.03)



Discussion

Summary of our penalized regression as compared to the C+T method

- A more **optimal** approach for predicting complex diseases
- models that are **linear** and very **sparse**
- very **fast**
- **automatic choice** for the regularization parameter
- can be extended to capture also recessive and dominant effects

Prospects: future work using the UK Biobank

- use of external summary statistics to improve models
- better generalization to multiple populations
- integration of clinical and environmental data

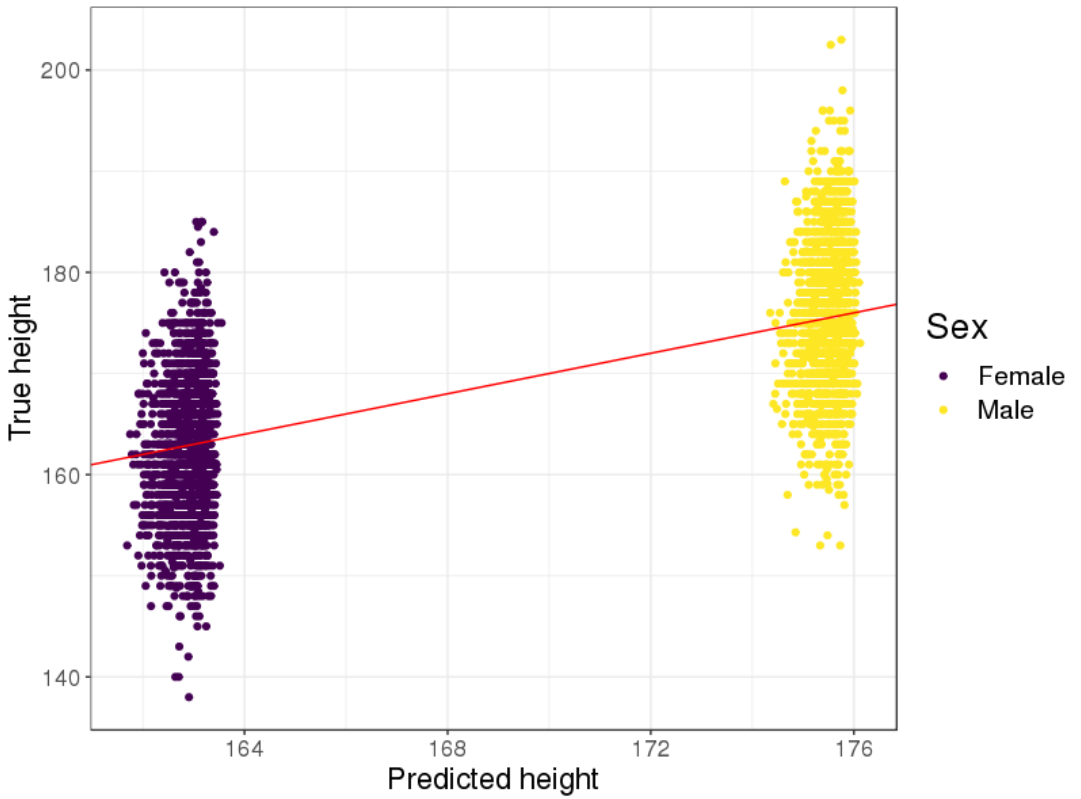
Planning for 3rd year

+ early results usink the UK biobank

Pitfalls of penalized regression

Penalization is too strong when there are large effects (sex for height)

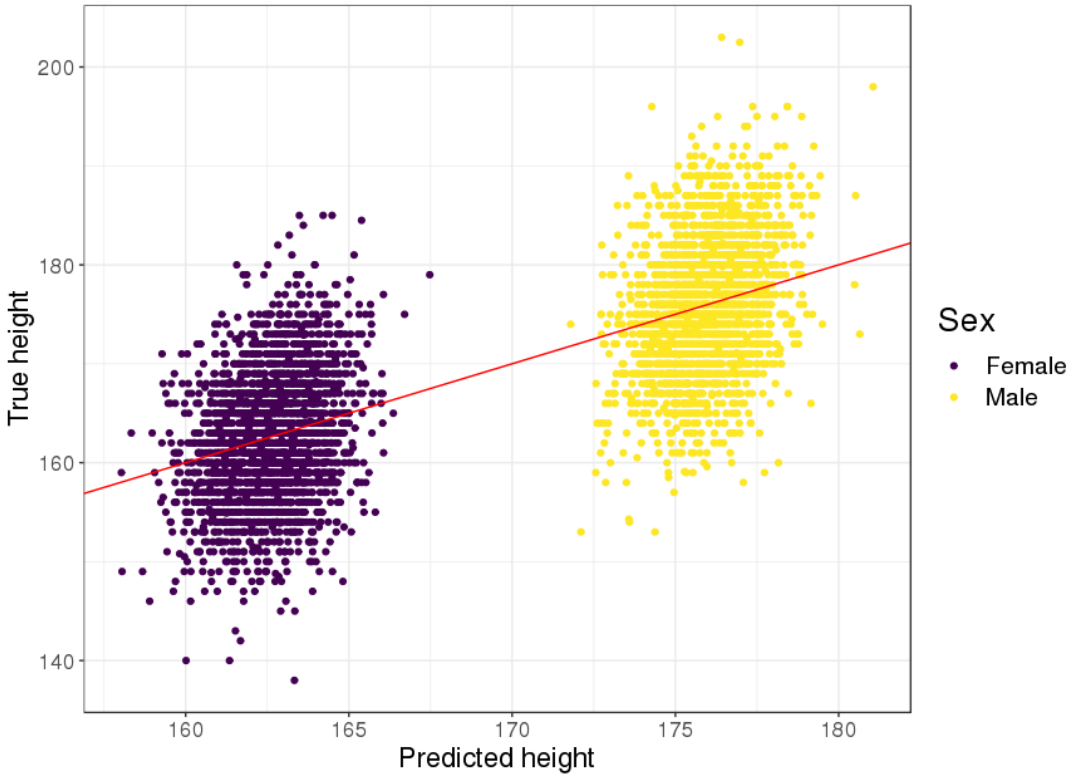
$$\text{height} \sim \text{SNPs} + \text{PCs} + \text{sex}$$



Better prediction, but still too conservative

$$\text{base: } \text{height} \sim \text{sex}$$

$$\text{pred: } \text{height} \sim \text{base} + \text{SNPs} + \text{PCs} + \text{sex}$$

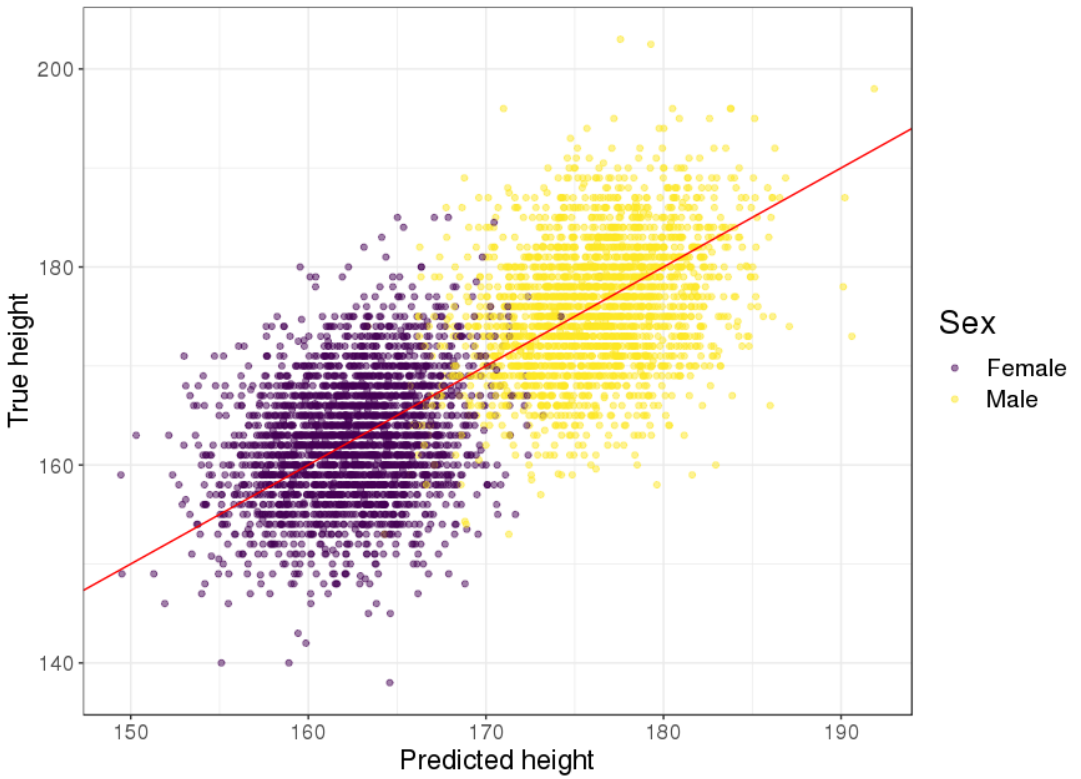


Post-process with some linear regression

$$\text{base: height} \sim \text{sex}$$

$$\text{pred: height} \sim \text{base} + \text{SNPs} + \text{PCs} + \text{sex}$$

$$\text{post\_pred: height} \sim \text{pred} \times \text{sex}$$



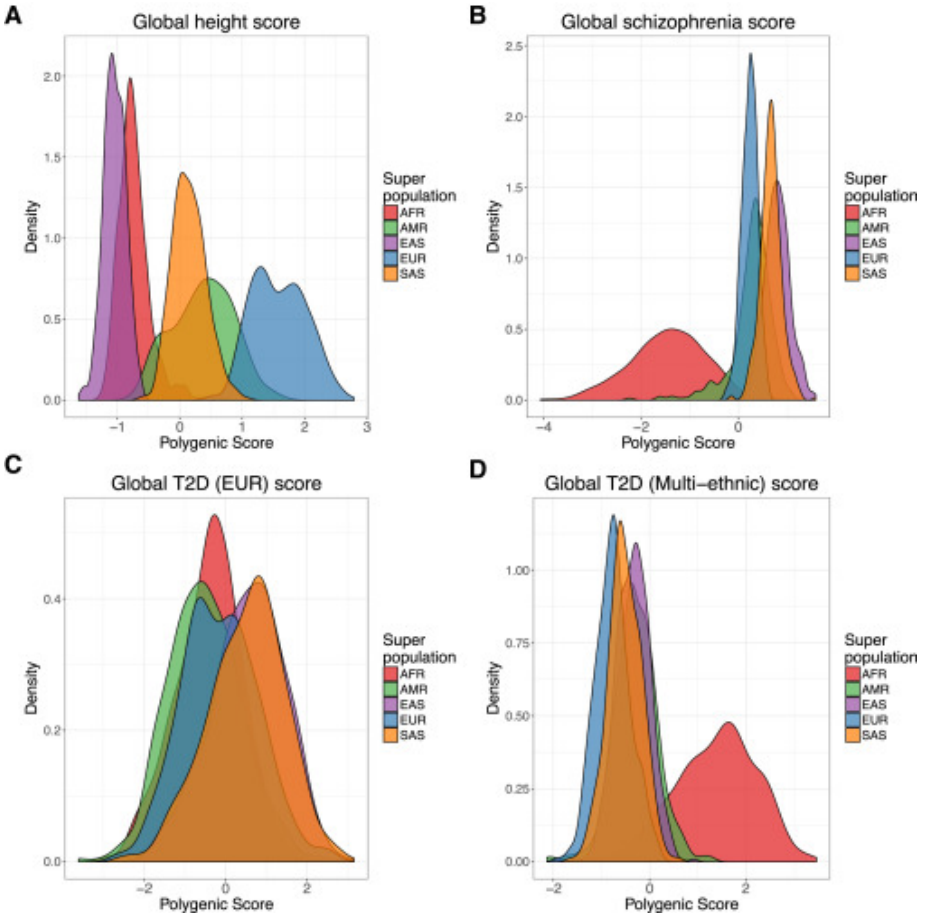
How to combine the information of multiple studies?

(possibly of different populations)

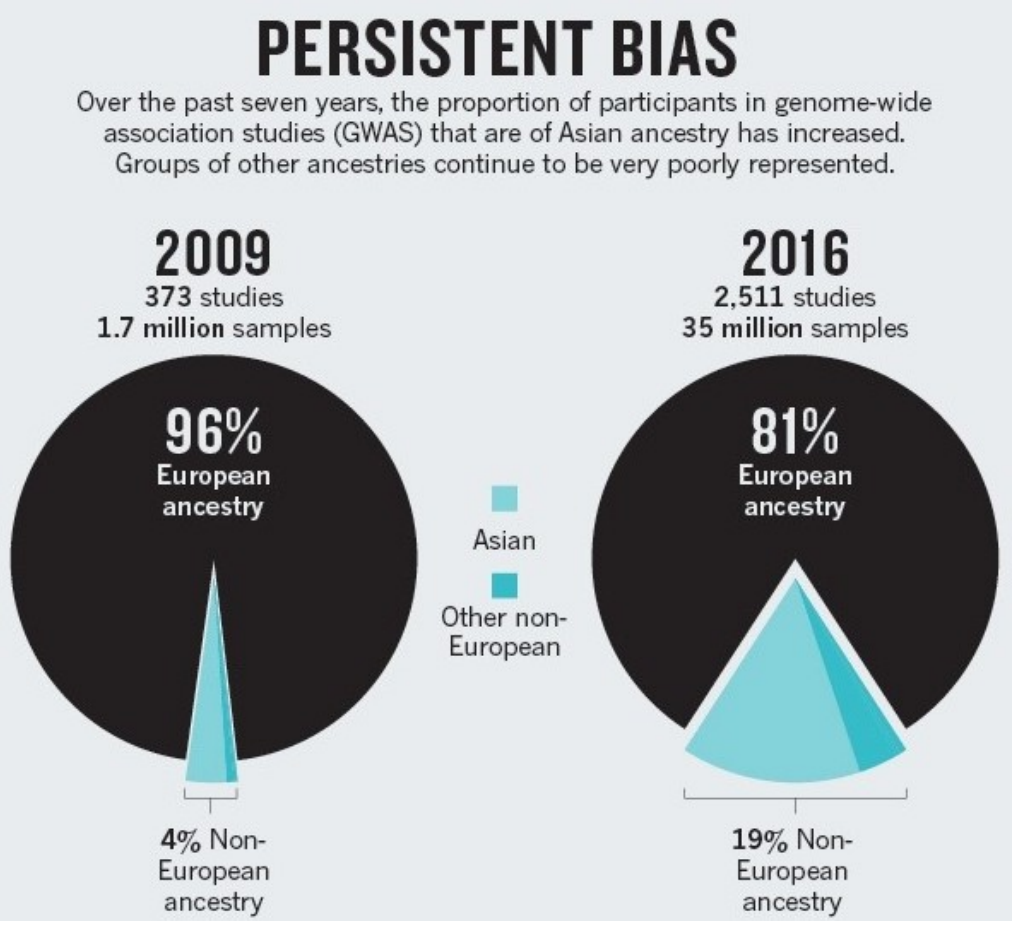
Genetics are different between populations

Produced with our R packages (450K people from the UK biobank)

which makes predictions fail on external populations



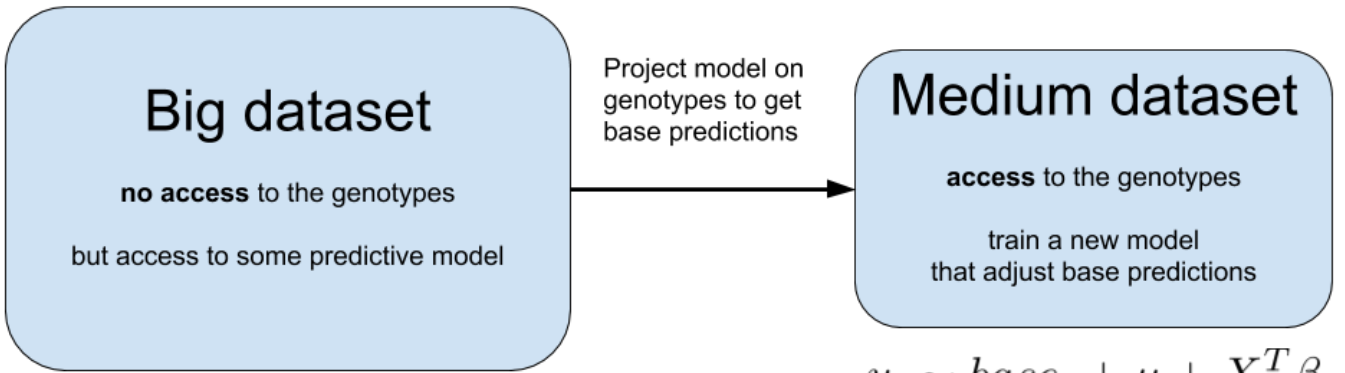
Genomics is failing on diversity



Source: 10.1038/538161a

What can we do about it?

We can use information from other studies (possibly in other populations)



Will this improve prediction?

Planning for 3rd year

End of 2018

- Publication of second paper
- Exploratory analysis for 3rd paper
- Starting thesis writing

Early 2019

- Teaching (Advanced R for doctoral school + statistics at ENSIMAG)
- Final analysis + writing of third paper
- Getting my DNA sequenced and analyzing it!

Until July 2019

- Submission of 3rd paper
- Finishing writing thesis
- International R Conference useR!2019 in Toulouse

The end

- Answer reviews for 3rd paper
- Thesis defense

Thanks!

Presentation: https://privefl.github.io/thesis-docs/suivi-these2.html

R package {bigstatsr}: https://github.com/privefl/bigstatsr

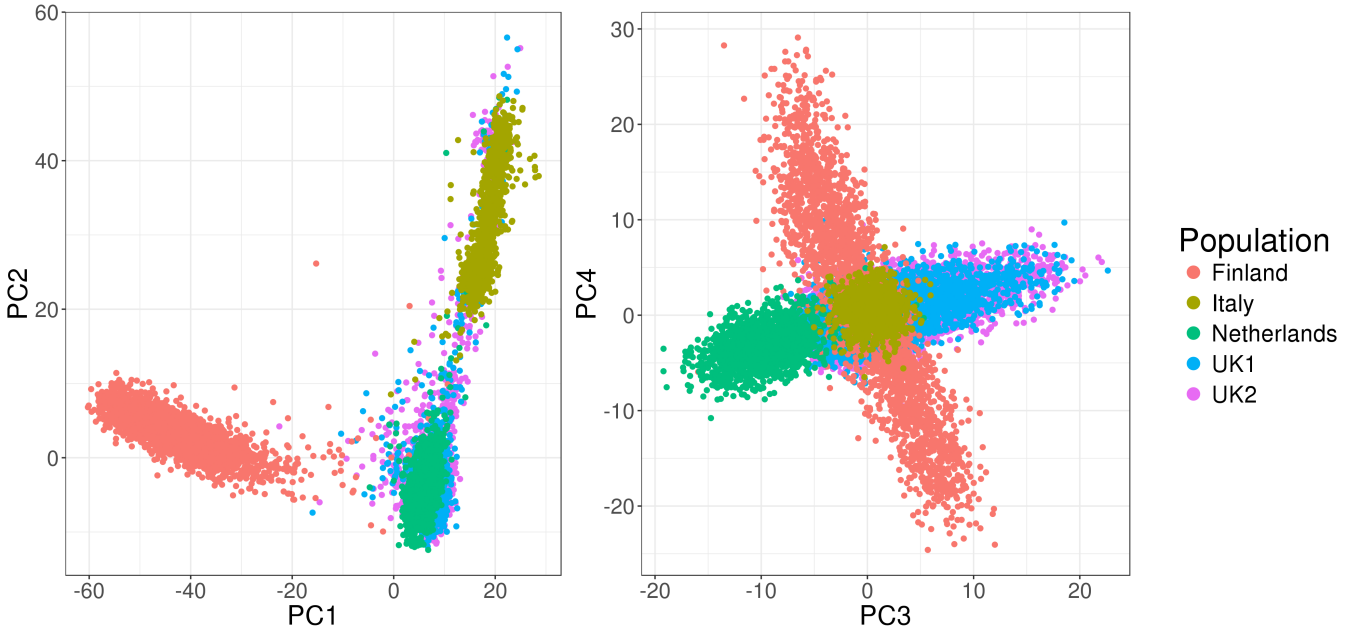
R package {bigsnpr}: https://github.com/privefl/bigsnpr

privefl privefl F. Privé

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

Real genotype data

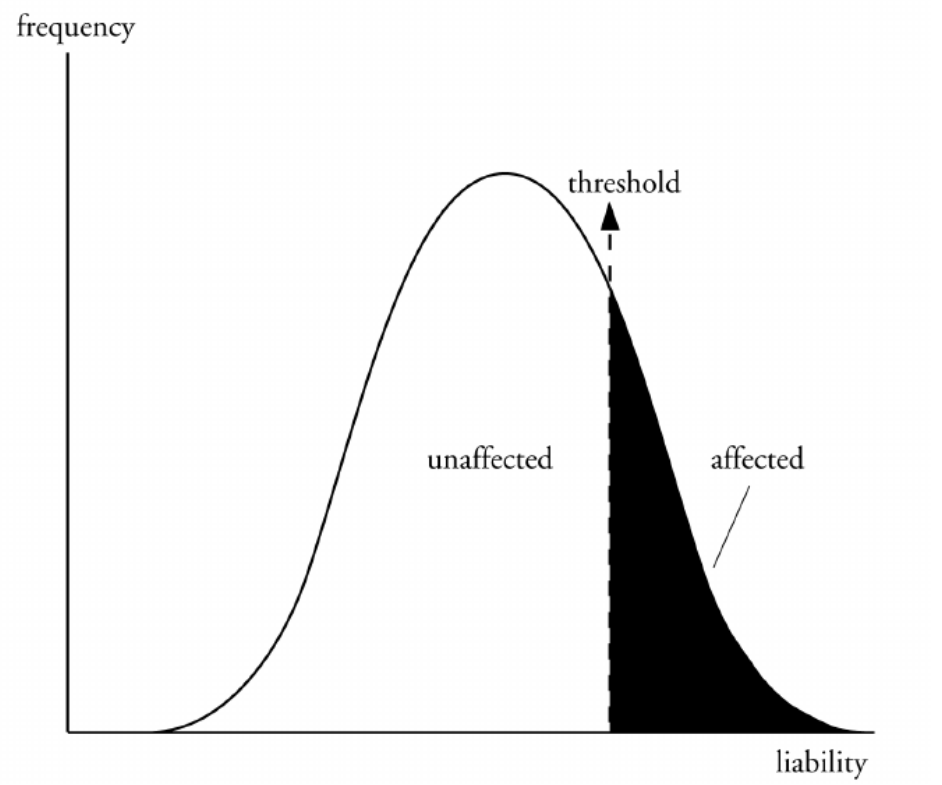
Use real data from a case-control study for the Celiac disease.



Keep only **controls** from the **UK** and **not deviating from the robust Malahanobis distance**.

Simulate new phenotypes

The liability-threshold model



Two models of liability

Model "ADD"

$$y_i = \underbrace{\sum_{j \in S_{\text{causal}}} w_j \cdot \widetilde{G_{i,j}}}_{\text{genetic effect}} + \underbrace{\epsilon_i}_{\text{environmental effect}}$$

Model "COMP"

$$y_i = \underbrace{\sum_{j \in S^{(1)}_{\text{causal}}} w_j \cdot \widetilde{G_{i,j}}}_{\text{linear}} + \underbrace{\sum_{j \in S^{(2)}_{\text{causal}}} w_j \cdot \widetilde{D_{i,j}}}_{\text{dominant}} + \underbrace{\sum_{\substack{k=1 \\ j_1 = e_k^{(3.1)} \\ j_2 = e_k^{(3.2)}}}^{k=\left|S^{(3.1)}_{\text{causal}}\right|} w_{j_1} \cdot \widetilde{G_{i,j_1} G_{i,j_2}}}_{\text{interaction}} + \epsilon_i$$

- w_j are **weights** (generated with a Gaussian or a Laplace distribution)
- $G_{i,j}$ is the **allele count** of individual i for SNP j
- $D_{i,j} = 1\left\{G_{i,j} \neq 0\right\}$

Extension via feature engineering

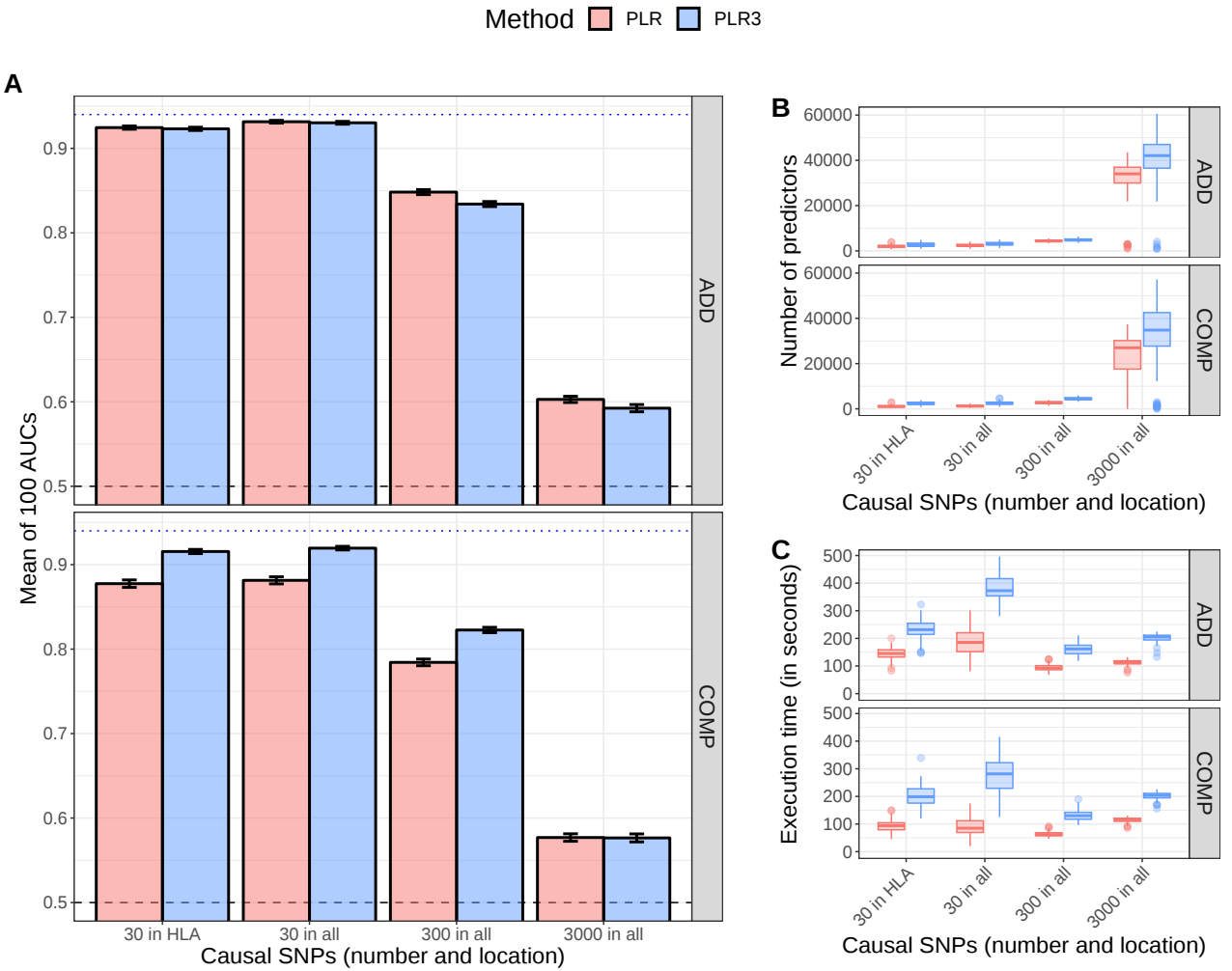
We construct a separate dataset with, for each SNP variable, two more variables coding for recessive and dominant effects.

	SNP1	SNP2
[1,]	0	2
[2,]	0	1
[3,]	1	1
[4,]	0	2
[5,]	0	0
[6,]	1	0
[7,]	1	1
[8,]	0	1
[9,]	0	1
[10,]	0	2

	SNP1.1	SNP1.2	SNP1.3	SNP2.1	SNP2.2	SNP2.3
[1,]	0	0	0	2	1	1
[2,]	0	0	0	1	1	0
[3,]	1	1	0	1	1	0
[4,]	0	0	0	2	1	1
[5,]	0	0	0	0	0	0
[6,]	1	1	0	0	0	0
[7,]	1	1	0	1	1	0
[8,]	0	0	0	1	1	0
[9,]	0	0	0	1	1	0
[10,]	0	0	0	2	1	1

We call these two methods "PLR" and "PLR3".

Feature engineering improves prediction



Prediction with PLR is improving faster (Scenario #2)