Polygenic Risk Score (PRS) Introduction 201

basic PRS calculation and performance evaluation

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At the end of this lecture, a **deeper** understanding of

- the complexity of constructing a good PRS even under the simplest setting *without* LD or any heterogeneities..
- the trouble introduced by false positives, due to multiple hypothesis testing and low power.
- ‘the more is not always better’ statement: PRS based on 6 gw-significant SNPs vs. 66 0.01-significant SNPS.
- the various over-fitting or selection biases, and winner’s curse in $\hat{\beta}$ for both false positives and true positives.

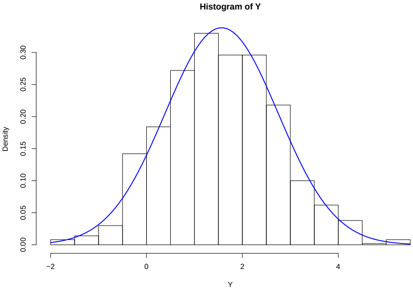
Recall the illustrative ‘polygenic’ model simulation study

10 out 5000 indep. SNPs with **varying ‘moderate-large’ effects** are truly associated with Y (**all** $\beta = 0.3$ **but MAF vary**).

$$Y_i = \sum_{j=1}^{10} \beta_j G_{ij} + e, \text{ where } \beta_j = 0.3$$

$$\text{MAF} \sim \text{ Unif(0.05,0.5)}, \ e \sim N(0,1).$$

```
nsnp.true=10 # number of truly associated SNPs
beta.true=0.3 # "large" effect (also MAF, the error term, and the sample size)
```



Recall (NOT realistic!) $PRS_{i,oracle} = \sum_{j=1}^{J=10} 0.3 \cdot G_{ij}$

The MAF of the 10 truly associated SNPs

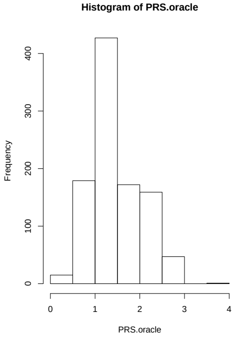
```
##  [1] 0.217 0.070 0.369 0.346 0.162 0.185 0.313 0.200 0.330 0.296
```

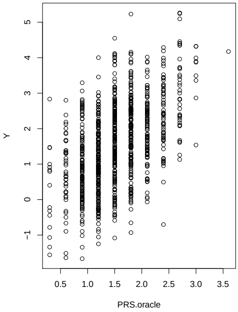
The SNP heritability vary, despite all $\beta_j = 0.3$

```
##  [1] 0.025 0.010 0.034 0.033 0.020 0.022 0.032 0.024 0.033 0.031
```

The true heritability, h^2

```
## [1] 0.243
```

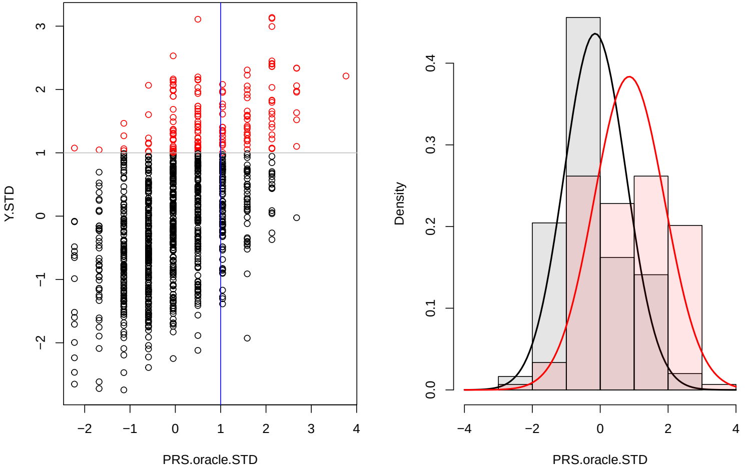




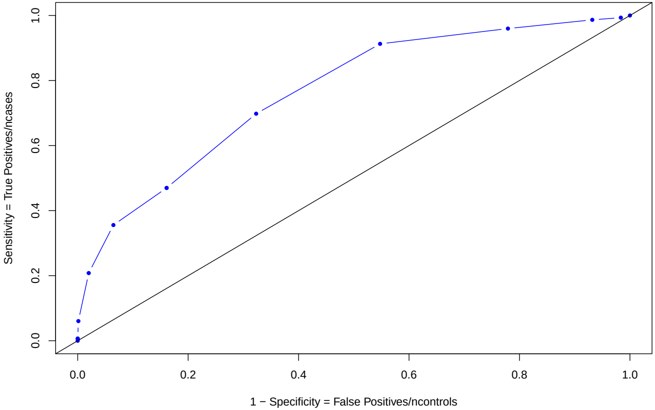
Recall the (highly significant) association between PRS.orcale and the trait

```
##
## Call:
## lm(formula = Y.STD ~ PRS.oracle.STD)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.71113 -0.60843 -0.01341  0.60283  2.86310
##
## Coefficients:
##                  Estimate Std. Error t value Pr(>|t|)
## (Intercept)    -6.748e-17  2.750e-02    0.00        1
## PRS.oracle.STD  4.942e-01  2.752e-02   17.96   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.8698 on 998 degrees of freedom
## Multiple R-squared:  0.2442, Adjusted R-squared:  0.2435
## F-statistic: 322.5 on 1 and 998 DF,  p-value: < 2.2e-16
```

Recall the liability model, and the case-control stratified PRS distributions



Recall the ROC curve and AUC using PRS_{oracle}



```
## [1] "AUC of ROC.oracle=" "0.763"
```

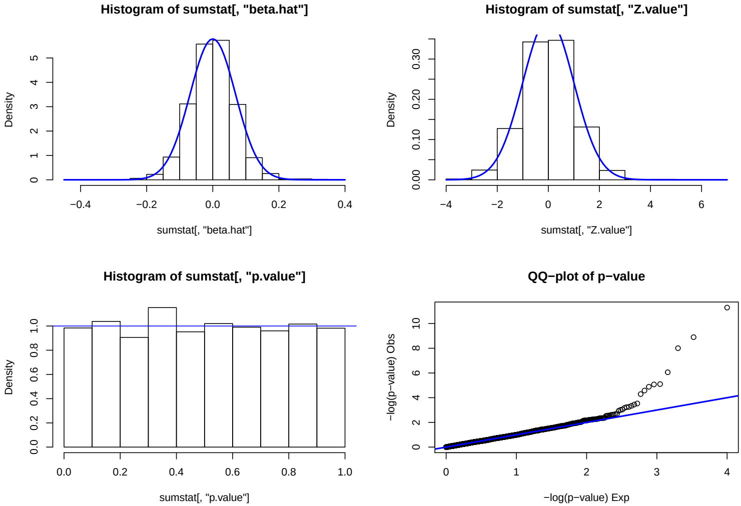
Recall the **BUT**,

$$\mathbf{PRS_{i,oracle}} = \sum_{j=1}^{J=10} \beta_j (= 0.3) G_{ij} \text{ \textbf{is NOT} } \mathbf{PRS_{i,parctice}}!$$

- J is unknown, to be determined
- β_j is unknown, to be estimated
- G_{ij} **cannot be directly from the same data used to infer** J **and** β_j.

  Otherwise: over-fitting/double-dipping/data-dredging/p-hacking/selection-bias!
- Not to mention LD and other considerations in real data settings.

What we have: $\hat{\beta}$, Z and p-values



Histogram of sumstat[, "beta.hat"]

Histogram of sumstat[, "Z.value"]

Histogram of sumstat[, "p.value"]

QQ−plot of p−value

Recall the sumstat (the true beta and MAF are here thanks to simulation)

```
##              MAF MAF.hat beta    beta.hat         se     Z.value      p.value
##  [1,] 0.21748927  0.2215  0.3  0.29257288 0.06536792  4.47578705 8.489445e-06
##  [2,] 0.06972117  0.0610  0.3  0.33145758 0.10935747  3.03095507 2.500692e-03
##  [3,] 0.36935781  0.3780  0.3  0.23908858 0.05323916  4.49084039 7.922031e-06
##  [4,] 0.34596068  0.3480  0.3  0.38889542 0.05565755  6.98728935 5.116550e-12
##  [5,] 0.16243508  0.1695  0.3  0.30892955 0.07052329  4.38053229 1.308960e-05
##  [6,] 0.18502467  0.1995  0.3  0.37606430 0.06503910  5.78212649 9.859505e-09
##  [7,] 0.31318998  0.3375  0.3  0.33166110 0.05410586  6.12985587 1.264930e-09
##  [8,] 0.20006021  0.2020  0.3  0.28159164 0.06670313  4.22156565 2.647447e-05
##  [9,] 0.32990538  0.3360  0.3  0.23025579 0.05661344  4.06715744 5.134017e-05
## [10,] 0.29562285  0.2905  0.3  0.28906539 0.05841261  4.94868102 8.766086e-07
## [11,] 0.44590808  0.4445  0.0  0.09584075 0.05424572  1.76678916 7.756916e-02
## [12,] 0.36809363  0.3745  0.0 -0.02245388 0.05302784 -0.42343559 6.720687e-01
## [13,] 0.37938767  0.3750  0.0 -0.06366768 0.05424574 -1.17368994 2.407993e-01
## [14,] 0.46923549  0.4740  0.0  0.03095466 0.05222091  0.59276375 5.534736e-01
## [15,] 0.25480427  0.2485  0.0  0.05966600 0.06226877  0.95820104 3.381935e-01
## [16,] 0.31564388  0.3205  0.0 -0.03353920 0.05695716 -0.58884957 5.560954e-01
## [17,] 0.41919624  0.4345  0.0 -0.08589125 0.05307934 -1.61816710 1.059426e-01
## [18,] 0.15085332  0.1410  0.0  0.03167344 0.07632138  0.41500089 6.782304e-01
## [19,] 0.23525007  0.2515  0.0 -0.05445552 0.05876396 -0.92668222 3.543156e-01
## [20,] 0.06737475  0.0740  0.0 -0.10570983 0.10173334 -1.03908733 2.990158e-01
## [21,] 0.36532020  0.3595  0.0  0.06726877 0.05527611  1.21695922 2.239074e-01
## [22,] 0.48057686  0.4785  0.0  0.00804454 0.05286361  0.15217538 8.790794e-01
## [23,] 0.14600840  0.1400  0.0 -0.06318882 0.07458090 -0.84725206 3.970578e-01
## [24,] 0.34747768  0.3405  0.0 -0.00162502 0.05702567 -0.02849630 9.772720e-01
## [25,] 0.46549350  0.4590  0.0  0.07744989 0.05301480  1.46091065 1.443547e-01
## [26,] 0.40807389  0.4185  0.0  0.02135427 0.05247701  0.40692616 6.841495e-01
## [27,] 0.08204565  0.0820  0.0 -0.00372138 0.09588876 -0.03880935 9.690502e-01
## [28,] 0.22523350  0.2240  0.0 -0.09720419 0.06372866 -1.52528210 1.275056e-01
## [29,] 0.23290305  0.2455  0.0 -0.03611566 0.05999003 -0.60202767 5.472925e-01
## [30,] 0.34670979  0.3425  0.0  0.04700733 0.05368057  0.87568618 3.814114e-01
```

Determine J and Estimate β_j using GW significance level

```
J.index=which(sumstat[,"p.value"]<=0.05/nsnp) #10^-5 here for 5000 SNPs
J.index # the index for the significant SNPs
```

```
## [1]  1  3  4  6  7 10
```

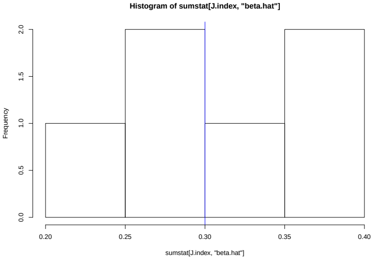
```
c(length(J.index),sum(J.index<=nsnp.true)) # positives, true positives
```

```
## [1] 6 6
```

```
round(sumstat[J.index,"beta.hat"],2) # beta estimates for the significant SNPs
```

```
## [1] 0.29 0.24 0.39 0.38 0.33 0.29
```

```
hist(sumstat[J.index,"beta.hat"]); abline(v=beta.true,col="blue")
```



A less stringent significance level, say $\alpha = 0.01$?

Trade-off: between false positives (56) and power (10 out 10)

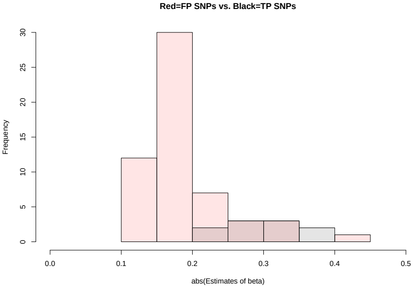
```
J.index=which(sumstat[,"p.value"]<=0.01)
J.index # the index for significant SNPs
```

```
##  [1]    1    2    3    4    5    6    7    8    9   10  324  349  358  385  509
## [16]  610  681  709  720  803  923  941 1248 1249 1275 1284 1346 1388 1451 1575
## [31] 1597 1651 1673 1702 1764 1782 1784 1835 1945 2343 2390 2518 2531 2561 2606
## [46] 2708 2726 2827 2909 3125 3207 3358 3372 3453 3584 3622 3646 3656 3871 3879
## [61] 3889 4182 4304 4472 4588 4935
```

```
c(length(J.index),sum(J.index<=nsnp.true)) # positives, true positives
```

```
## [1] 66 10
```

Trouble ahead: $|\hat{\beta}_j|$ of the FP SNPs are competitive!



Top associated SNPs for $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$: J

Genome-wide significance level ($\alpha = 10^{-5}$ here for 5000 SNPs)

- $J = 6$
- find only 6 out 10 truly associated SNPs
- but 0 false positives

A less stringent significance level ($\alpha = 0.01$)

- $J = 66$
- find all 10 truly associated SNP
- but 56 false positives

Live Quiz 1: Which α threshold will leads to a better PRS (higher AUC)?

A: using 6 SNPS with GW significance
B: using 66 SNPs with p< 0.01
C: ~same

Effect size estimates in $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$: $\hat{\beta}_j$

Genome-wide significance level

```
J.index=which(sumstat[,"p.value"]<=0.05/nsnp)
round(sumstat[J.index,"beta.hat"],2)
```

```
## [1] 0.29 0.24 0.39 0.38 0.33 0.29
```

A less stringent significance level

```
J.index=which(sumstat[,"p.value"]<=0.01)
round(sumstat[J.index,"beta.hat"],2)
```

```
##  [1]  0.29  0.33  0.24  0.39  0.31  0.38  0.33  0.28  0.23  0.29 -0.20  0.15
## [13]  0.15 -0.17 -0.23 -0.25 -0.17 -0.17 -0.18 -0.31  0.17  0.18 -0.15 -0.16
## [25] -0.18  0.16  0.27 -0.19  0.19  0.19 -0.16 -0.16  0.33 -0.15 -0.15  0.17
## [37] -0.18  0.14 -0.14 -0.16  0.14 -0.24 -0.14  0.15  0.14 -0.14 -0.22 -0.17
## [49] -0.18  0.17 -0.20  0.15  0.14 -0.18  0.19 -0.21 -0.22 -0.43  0.33  0.15
## [61] -0.14 -0.15 -0.19 -0.22  0.26  0.18
```

That was too easy! **More considerations** later:

- Winner's curse (a result of low power) and the MAF connection
- heterogeneity and transportability
- LD

Quiz: patterns for the signicant SNPs?

MAF of the 10 truly associated SNPs

```
##  [1] 0.22 0.07 0.37 0.35 0.16 0.19 0.31 0.20 0.33 0.30
```

MAF of the 6 significant SNPs at the GW level

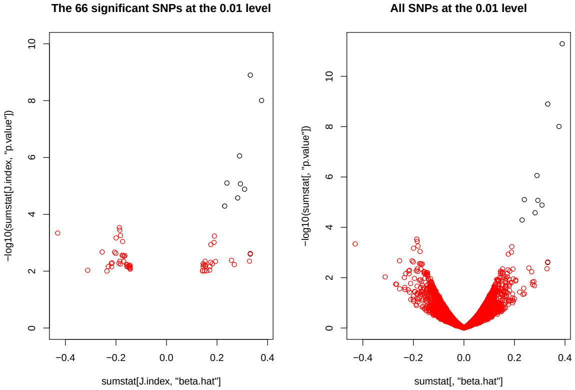
```
## [1] 0.22 0.37 0.35 0.19 0.31 0.30
```

Sample estimates of the 6 significant SNPs at the GW level

```
## [1] 0.22 0.38 0.35 0.20 0.34 0.29
```

Quiz cont'd, -log(GWAS p-value) vs. $\hat{\beta}_j$

(Red = FP SNPs vs. Black = TP SNPs)



Sun et al. (2011). *Human Genetics*. BR-squared: a practical solution to the winner's curse in genome-wide scans.

Can we construct $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$ now?

What we have using GW $\alpha = 10^{-5}$ (for 5000 SNPs):

The number of SNPs, J

```
## [1] 6
```

Which specific SNPs

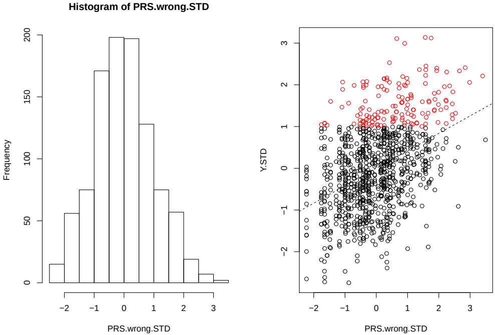
```
## [1]  1  3  4  6  7 10
```

$\hat{\beta}_j$ **of these SNPS**

```
## [1] 0.29 0.24 0.39 0.38 0.33 0.29
```

WRONG if using G_{ij} from the same data!

$$PRS_{i,wrong} = \sum_{j=1}^{6} \hat{\beta}_j G_{ij}$$



This PRS.wrong appears to be ~normally distributed and highly predictive of the outcome, BUT **due to over-fitting!**

If you are not fully convinced of the over-fitting issue:

Using $\alpha = 0.01$ BUT exclude the all the true positives. That is, **using only the following 56 false positive SNPs to construct PRS:**

```
## [1] 56
```

```
##  [1]  324  349  358  385  509  610  681  709  720  803  923  941 1248 1249 1275
## [16] 1284 1346 1388 1451 1575 1597 1651 1673 1702 1764 1782 1784 1835 1945 2343
## [31] 2390 2518 2531 2561 2606 2708 2726 2827 2909 3125 3207 3358 3372 3453 3584
## [46] 3622 3646 3656 3871 3879 3889 4182 4304 4472 4588 4935
```

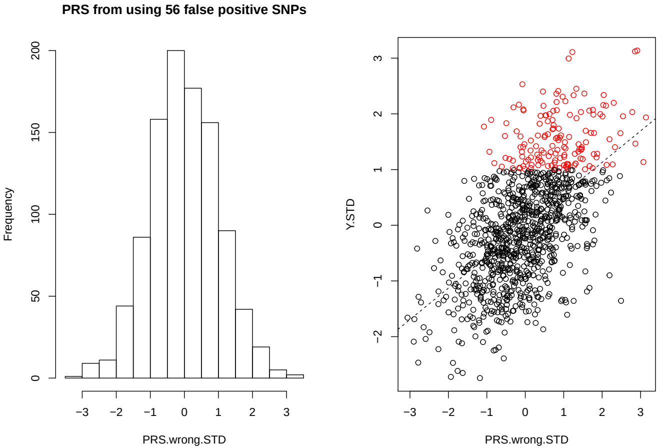
Their effect size sample estimates:

```
##  [1] -0.20  0.15  0.15 -0.17 -0.23 -0.25 -0.17 -0.17 -0.18 -0.31  0.17  0.18
## [13] -0.15 -0.16 -0.18  0.16  0.27 -0.19  0.19  0.19 -0.16 -0.16  0.33 -0.15
## [25] -0.15  0.17 -0.18  0.14 -0.14 -0.16  0.14 -0.24 -0.14  0.15  0.14 -0.14
## [37] -0.22 -0.17 -0.18  0.17 -0.20  0.15  0.14 -0.18  0.19 -0.21 -0.22 -0.43
## [49]  0.33  0.15 -0.14 -0.15 -0.19 -0.22  0.26  0.18
```

Their MAF sample estimates:

```
##  [1] 0.29 0.37 0.34 0.47 0.10 0.12 0.28 0.30 0.19 0.05 0.20 0.41 0.37 0.29 0.29
## [16] 0.23 0.08 0.50 0.20 0.30 0.35 0.34 0.06 0.33 0.40 0.23 0.20 0.43 0.46 0.32
## [31] 0.36 0.10 0.37 0.28 0.41 0.37 0.12 0.32 0.45 0.23 0.19 0.46 0.32 0.47 0.37
## [46] 0.19 0.14 0.05 0.06 0.29 0.46 0.37 0.19 0.13 0.09 0.21
```

PRS, using only null SNPs, is predictive: clearly WRONG!



Obtaining a significant result $\neq$ a correct result!

This PRS.wrong, constructed from the 56 null SNPs, is actually more significantly associated with the phenotype than PRS.oracle: clearly wrong!

```
##
## Call:
## lm(formula = Y.STD ~ PRS.wrong.STD)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -2.76357 -0.52506 -0.01203  0.54337  2.57385
##
## Coefficients:
##                 Estimate Std. Error t value Pr(>|t|)
## (Intercept)   -1.493e-16  2.611e-02    0.00        1
## PRS.wrong.STD  5.646e-01  2.613e-02   21.61   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.8258 on 998 degrees of freedom
## Multiple R-squared:  0.3188, Adjusted R-squared:  0.3181
## F-statistic:   467 on 1 and 998 DF,  p-value: < 2.2e-16
```

Cannot be overemphasized

A predictive (and normally distributed) PRS, on its own, is not evidence for correct PRS calculation!

Remember the superscripts in your PRS calculation:

$$\hat{\beta}_j^{external\,(base,\,discovery)} \times G_{ij}^{my.data\,(target,\,validation)}$$

Surely we will not make this rookie mistake! BUT,

over-fitting can appear in other (subtler) forms, e.g. overlapping samples between the external and my data, or pleitropy studies of multiple phenotypes from a single sample

How to construct $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$ then? e.g. **The simplest scenario**

Obtain the J and $\hat{\beta}_j$ from **an external data set**.

The external data set resembles our own data set perfectly, i.e. **no heterogeneity** in population, sampling design etc.

Calculate the PRS_i for each individual i in our own sample for prediction:

$$PRS_i^{my.data} = \sum_{j=1}^{J} \hat{\beta}_j^{external} G_{ij}^{my.data}$$

Simulate an independent set of data, my.data

```
# Assume the previous data was the external data
# the external model was
# nsnp=5000; nsnp.true=10; beta.true=0.3; beta.0=0; sigma=1

# Use the SAME MODEL but a DIFFERNT SEE to generate new independent data

set.seed(102)

my.nsample=1000 # my. is for my own data for prediction or validation
my.nsnp=nsnp # no heterogeneity: the same number of SNPs
my.maf=maf # no heterogeneity: the same MAF as before
my.nsnp.true=nsnp.true # no heterogeneity: the same number of truly associated S
my.beta.true=beta.true # no heterogeneity: the same effect size as before
my.beta=c(rep(my.beta.true,my.nsnp.true),rep(0,(my.nsnp-my.nsnp.true)))
```

Using the same model as above (no heterogeneity):
10 out 5000 SNPs are truly associated with ‘moderate-large’ effect

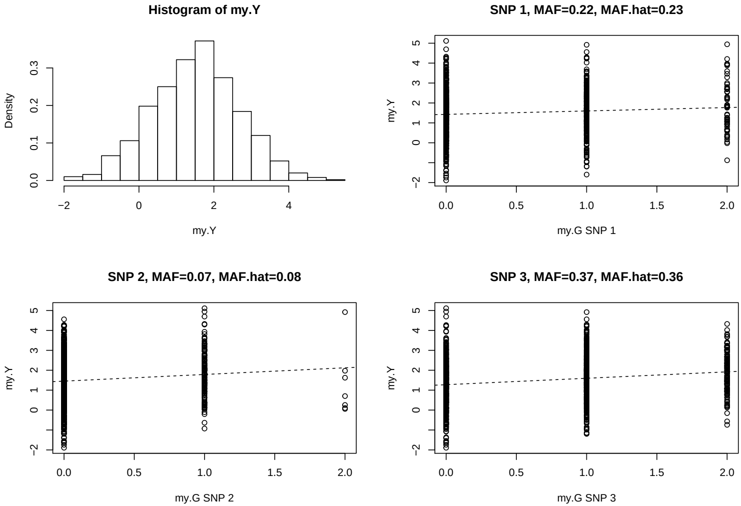
$$Y_i^{my.data} = \sum_{j=1}^{10} 0.3 \times G_{ij}^{my.data} + e^{my.data}, \text{ where } e^{my.data} \sim N(0,1)$$

MAFs stay the same as the external data (no heterogeneity), and recall the MAFs of the 10 truly associated SNPs:

```
##  [1] 0.22 0.07 0.37 0.35 0.16 0.19 0.31 0.20 0.33 0.30
```

The sample size does not have to be the same, but for now we use my.nsample=1000.

EDA (exploratory data analysis) of my.data



my.sumstat (the true beta and MAF are here thanks to simulation)

```
##              MAF MAF.hat beta    beta.hat         se    Z.value      p.value
##  [1,] 0.21748927  0.2270  0.3  0.17164714 0.06066349  2.8294965 4.755586e-03
##  [2,] 0.06972117  0.0755  0.3  0.33447059 0.09604226  3.4825358 5.182232e-04
##  [3,] 0.36935781  0.3555  0.3  0.32234988 0.05230483  6.1629085 1.034940e-09
##  [4,] 0.34596068  0.3545  0.3  0.25019642 0.05335395  4.6893703 3.121234e-06
##  [5,] 0.16243508  0.1530  0.3  0.32262395 0.06958963  4.6360925 4.021553e-06
##  [6,] 0.18502467  0.1800  0.3  0.28017270 0.06679596  4.1944557 2.978552e-05
##  [7,] 0.31318998  0.3045  0.3  0.36190034 0.05517189  6.5595060 8.652840e-11
##  [8,] 0.20006021  0.1780  0.3  0.35342514 0.06681630  5.2895046 1.507249e-07
##  [9,] 0.32990538  0.3300  0.3  0.31052039 0.05197947  5.9739043 3.218822e-09
## [10,] 0.29562285  0.2960  0.3  0.33840898 0.05429097  6.2332464 6.731015e-10
## [11,] 0.44590808  0.4465  0.0  0.04515026 0.05043254  0.8952605 3.708637e-01
## [12,] 0.36809363  0.3580  0.0 -0.02127391 0.05509213 -0.3861515 6.994668e-01
## [13,] 0.37938767  0.3870  0.0 -0.02908571 0.05264218 -0.5525171 5.807178e-01
```

compared with the **ex.sumstat** from the external data

```
##              MAF MAF.hat beta    beta.hat         se    Z.value      p.value
##  [1,] 0.21748927  0.2215  0.3  0.29257288 0.06536792  4.4757871 8.489445e-06
##  [2,] 0.06972117  0.0610  0.3  0.33145758 0.10935747  3.0309551 2.500692e-03
##  [3,] 0.36935781  0.3780  0.3  0.23908858 0.05323916  4.4908404 7.922031e-06
##  [4,] 0.34596068  0.3480  0.3  0.38889542 0.05565755  6.9872894 5.116550e-12
##  [5,] 0.16243508  0.1695  0.3  0.30892955 0.07052329  4.3805323 1.308960e-05
##  [6,] 0.18502467  0.1995  0.3  0.37606430 0.06503910  5.7821265 9.859505e-09
##  [7,] 0.31318998  0.3375  0.3  0.33166110 0.05410586  6.1298559 1.264930e-09
##  [8,] 0.20006021  0.2020  0.3  0.28159164 0.06670313  4.2215657 2.647447e-05
##  [9,] 0.32990538  0.3360  0.3  0.23025579 0.05661344  4.0671574 5.134017e-05
## [10,] 0.29562285  0.2905  0.3  0.28906539 0.05841261  4.9486810 8.766086e-07
## [11,] 0.44590808  0.4445  0.0  0.09584075 0.05424572  1.7667892 7.756916e-02
## [12,] 0.36809363  0.3745  0.0 -0.02245388 0.05302784 -0.4234356 6.720687e-01
## [13,] 0.37938767  0.3750  0.0 -0.06366768 0.05424574 -1.1736899 2.407993e-01
```

Finally, $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$

Using GW threshold on the external data

$$my.PRS_{GW} = \sum_{j=1}^{6\ Positives\ (all\ TP)} \hat{\beta}_j^{external} \times G_{ij}^{my.data}$$

Using the $\alpha = 0.01$ threshold on the external data

$$my.PRS_{.01} = \sum_{j=\{1:10,324,\ldots,4935\}}^{66\ Positives\ (10\ TP)} \hat{\beta}_j^{external} \times G_{ij}^{my.data}$$

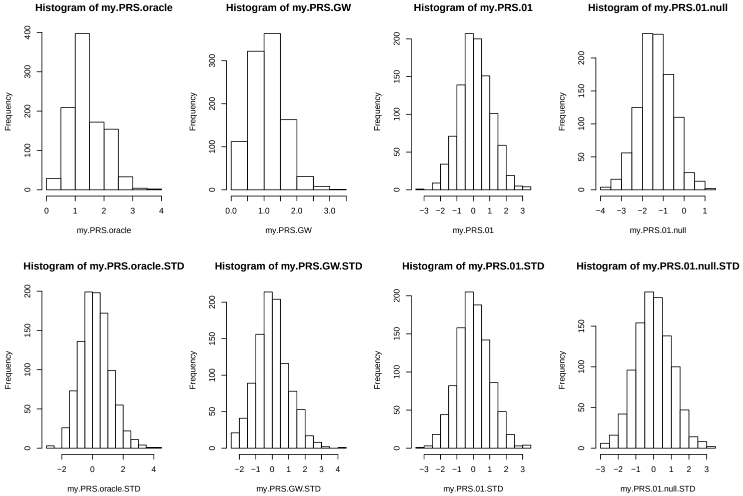
Using the $\alpha = 0.01$ threshold on the external data AND use only the false positives (made possible by the simulation and should NOT be predictive when calculated correctly!)

$$my.PRS_{.01.null} = \sum_{j=\{324,\ldots,4935\}}^{56\ False\ Positives} \hat{\beta}_j^{external} \times G_{ij}^{my.data}$$

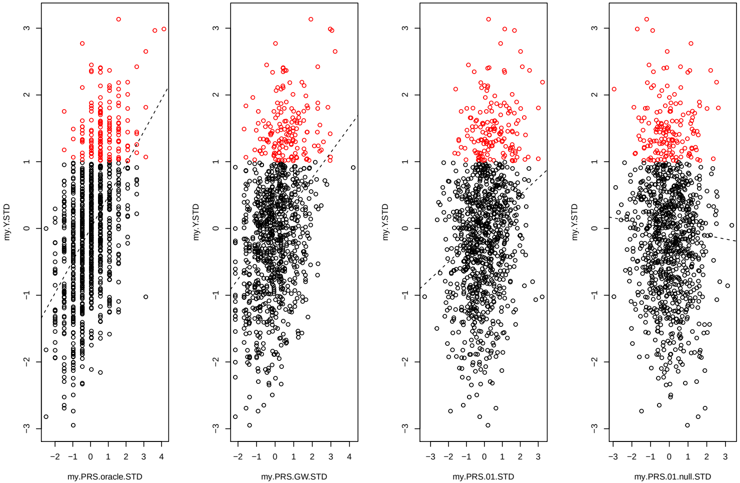
The oracle one (made possible by the simulation)

$$my.PRS_{Oracle} = \sum_{j=1}^{all\ 10\ causal\ ones} 0.3 \times G_{ij}^{my.data}$$

Raw and standardized (STD) of the PRSs constructed



Performance of the PRSs, from the association perspective



```
## [1] "slope.hat" "0.484"     "0.38"      "0.251"     "-0.053"

## [1] "Z.value" "17.467"  "12.983"  "8.185"   "-1.675"

## [1] "p.value"   "8.131e-60" "1e-35"     "8.22e-16"  "0.094"
```

$PRS.01.null$ is NOT associated with the trait as expected!

```
##                          Estimate Std. Error       t value   Pr(>|t|)
## (Intercept)         1.345526e-17 0.03159422  4.258771e-16 1.00000000
## my.PRS.01.null.STD -5.295421e-02 0.03161003 -1.675234e+00 0.09420154
```

PRS_{oracle} is the best, but PRS_{oracle} is not realistic!

```
##                       Estimate Std. Error      t value     Pr(>|t|)
## (Intercept)       1.642237e-15 0.02768826 5.931169e-14 1.000000e+00
## my.PRS.oracle.STD 4.838675e-01 0.02770211 1.746681e+01 8.130893e-60
```

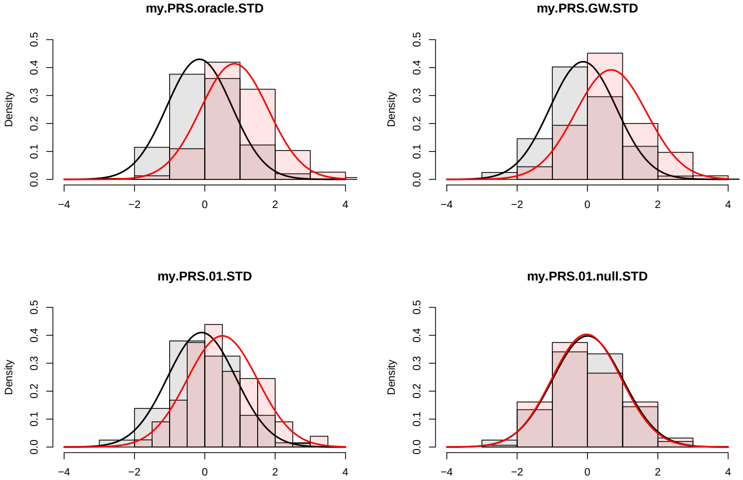
PRS_{GW} is significantly associated with the phenotype, but less so than PRS_{oracle} as it should be

```
##                    Estimate Std. Error       t value     Pr(>|t|)
## (Intercept)   -4.464004e-17 0.02926376 -1.525438e-15 1.000000e+00
## my.PRS.GW.STD  3.801176e-01 0.02927841  1.298287e+01 1.000642e-35
```

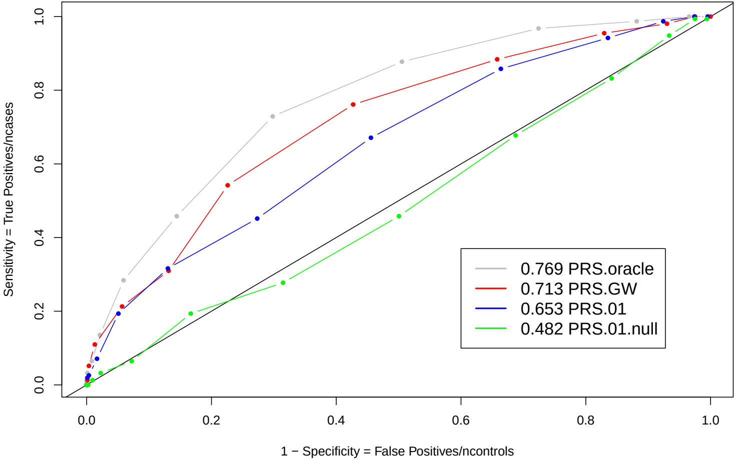
More is not necessarily better: $PRS_{.01}(J = 66)$ is worse than $PRS_{GW}(J = 6)$ in this case

```
##                    Estimate Std. Error       t value    Pr(>|t|)
## (Intercept)   -1.324645e-17 0.03062723 -4.325055e-16 1.00000e+00
## my.PRS.01.STD  2.508221e-01 0.03064256  8.185419e+00 8.22472e-16
```

Case-control stratified distributions of the different PRSs

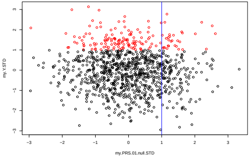


Performance of the PRSs, from the prediction perspective



Undertanding of the main diagonal line and AUC=50% of a non-predictive PRS

- Recall the scatter plot for the non-predictive PRS.0.01.null.STD



- Let $K < 1$ be the population prevalence of the disease, so out of a total of n samples, expect $n_{case} = n \cdot K$.

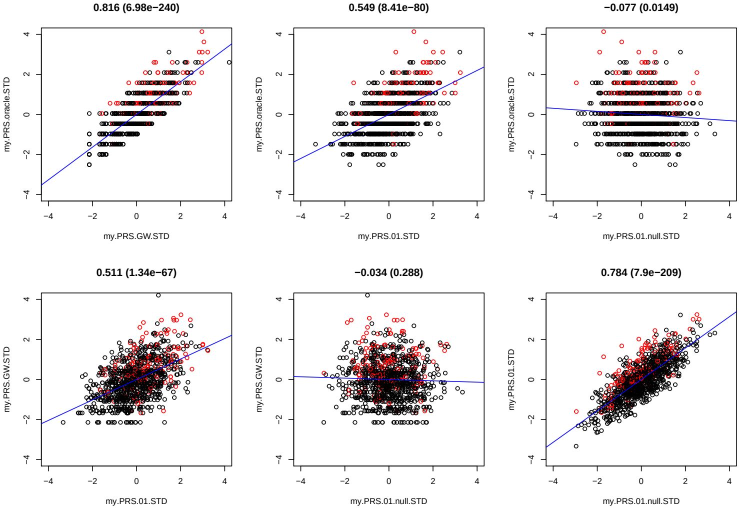
- For each threshold t used to call P_t samples positives (cases),

- Because the PRS used is not predictive, the expected true positives, $TP_t = P_t \cdot K$, and the expected sensitivity $= \frac{TP_t}{n_{case}} = \frac{P_t \cdot K}{n \cdot K} = \frac{P_t}{n}$.

- Similarly, the expected false positives, $FP_t = P_t \cdot (1 - K)$, and the expected $1 -$ specificity $= \frac{FP_t}{n_{control}} = \frac{P_t \cdot (1-K)}{n \cdot (1-K)} = \frac{P_t}{n}$.

- Thus, sensitivity (x) = 1-specificity (y) across the whole $\frac{P_t = 0}{n} = 0$ to $\frac{P_t = n}{n} = 1$ range. That is, ROC of a non-predictive PRS is (expected) to be the main diagonal line $(x = y)$, and AUC=50%.

Quiz: How can two PRSs with very different predictive performance be highly correlated?



Recap the goal of this lecture: a **deeper** understanding of

- the complexity of constructing a good PRS even under the simplest setting *without* LD or any heterogeneties.
- the trouble introduced by false positives, due to multiple hypothesis testing and low power.
- 'the more is not always better' statement: PRS based on 6 gw-significant SNPs vs. 66 0.01-significant SNPS.
- the various over-fitting or selection biases, $\hat{\beta}$ for a false positive or a true positive.

What's next

- Effects of ex.nsample and ex.beta.true on AUC: easy to answer.
- Answers to these Qs are less obvious: **If we decrease ex.beta.true from 0.3 to 0.1 but increase ex.nsnp.true from 10 to 90**,

  h^2 and SNP h^2?

  AUC in general?

  AUC between PRS.gw and PRS.01?