Polygenic Risk Score (PRS) Introduction 101

GWAS, h^2 and prediction as the foundation

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

- the multiple hypothesis testing issue inherent in GWAS
- the (high) variability inherent in $\hat{\beta}$, the β estimates
- heritability h^2 as a function of both β and MAF
- the 'genetic effect size' of a SNP $= \beta^2 \cdot \text{MAF} \cdot (1 - \text{MAF})$
- a conceptual PRS construction based on the ground truth, PRS.oracle
- DIY ROC plotting and AUC calculation for a PRS-based prediction

GWAS is the foundation of PRS, providing J and $\hat{\beta}_j$ in $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$

$$Y \text{ (phenotype)} = \beta_0 + \beta_j G_j \text{ (genotype)} + \beta_E E \text{ (envir.)} + e \text{ (error)},$$
$$H_0 : \beta_j = 0,$$

where $e \sim N(0, \sigma^2)$, $j = 1 \ldots > 10^6$ **for all SNPs across the genome**.
(Could be more complex: multiple $E's$ and G's, GxE, and GxG interactions)

G_j: Genotype of a (bi-allelic, autosomal) SNP j

- coded 0, 1 and 2 for aa, Aa and AA
- a = the reference allele
- A = the alternative allele (often the minor allele with MAF of p)
- freq. of aa, Aa and AA: $(1-p)^2$, $2p(1-p)$ and p^2 under HWE

GWAS Paper '0'

WTCCC (2007). *Nature*. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls.

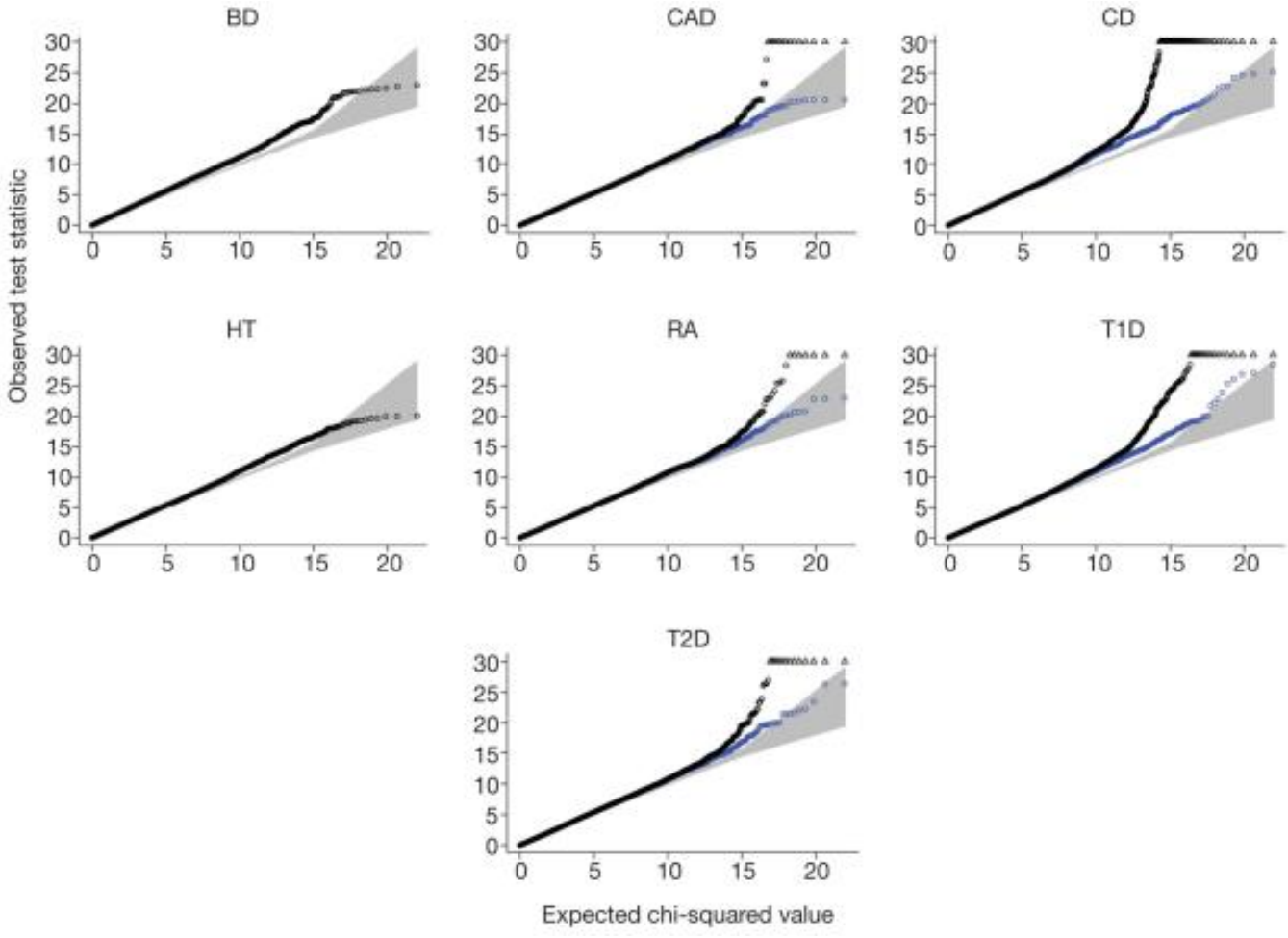
- Phenotypes: Seven major diseases, e.g. Bipolar, Hypertension
- Samples: $\approx$ 2000 cases and (shared) 3000 controls for each disease
- SNPs: Affymetrix 500K
- Analyses: **much effort on quality control (QC)**, simple association tests, novel imputation method.
- Results: 24 independent association signals at p-value $< 5 \cdot 10^{-7}$

  almost all true positives based on previous or replication studies

  Some of the loci confer risk for multiple diseases

  58 additional loci at $10^{-5} <$ p-value $< 5 \cdot 10^{-7}$

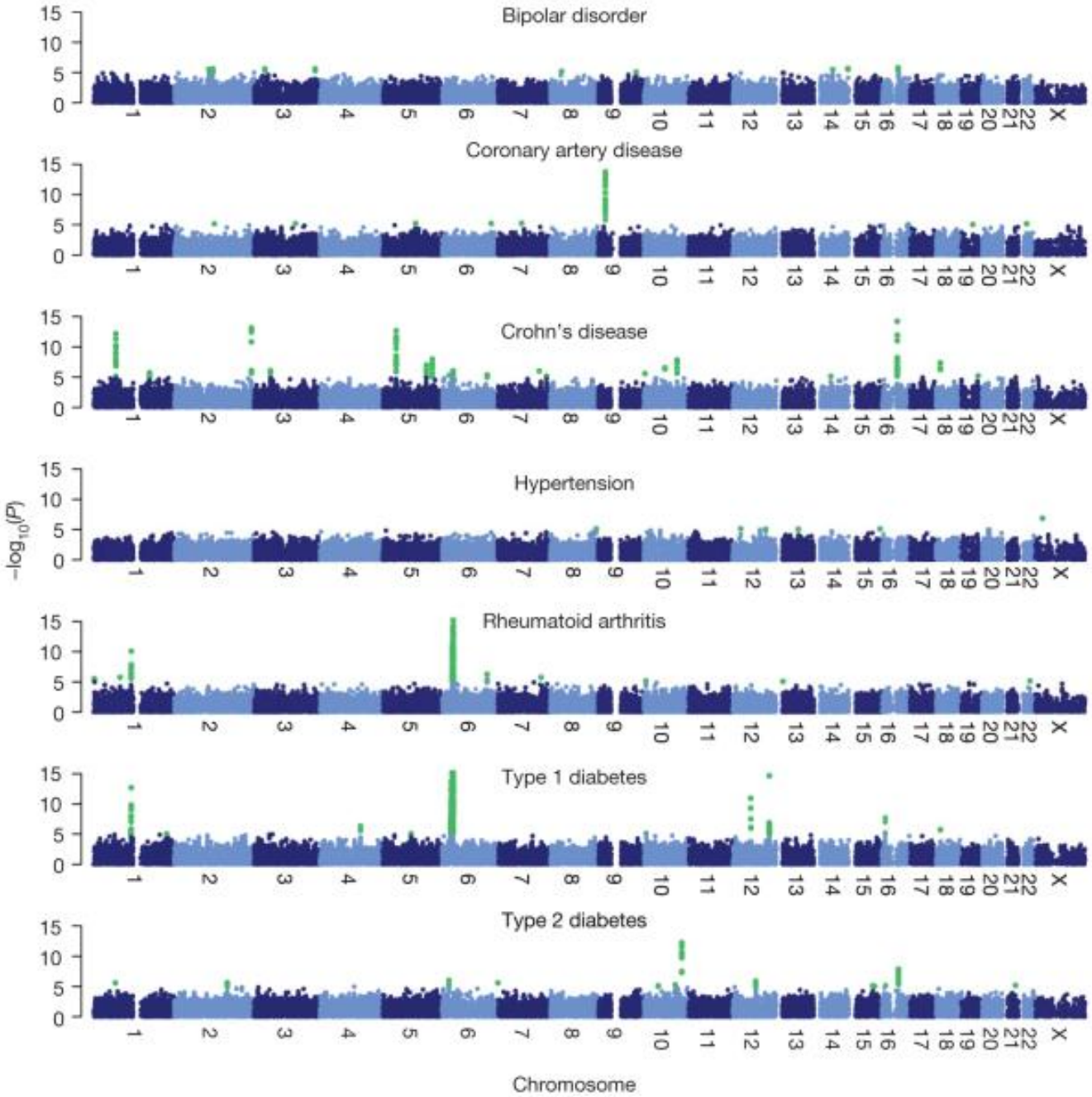
If interested: QQ-plot, Figure 3 of WTCCC 2007



Black: post-QC SNPs, MAF >1% and missing data rate <1%. SNPs at which the test statistic exceeds 30 are represented by triangles. (Most current GWASs: on the -log10(p-value) scale with no confidence band but with a main diagonal line.)

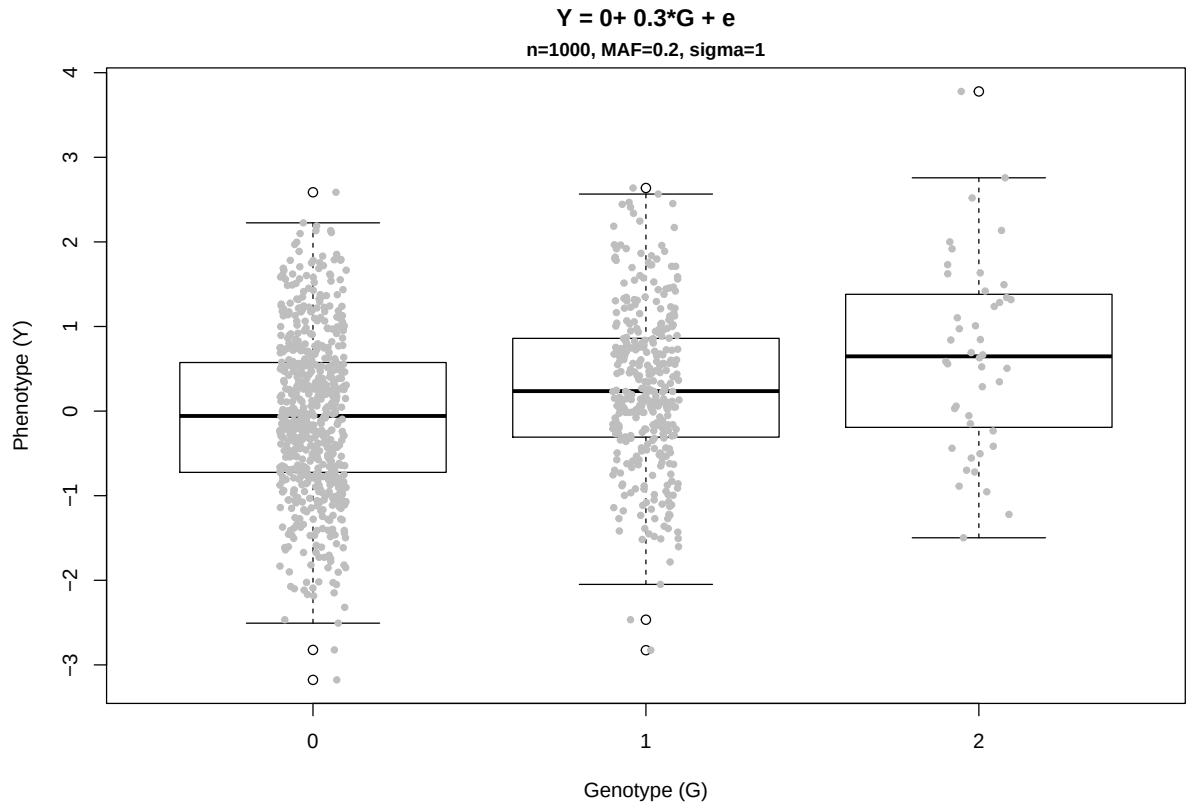
Blue: excluding SNPs located in the regions of association listed in Table 3 ($< 5 \cdot 10^{-7}$) (for BD: no visible effect on the plot, and for HT: no such SNPs).

If interested: Manhattan plot, Figure 4 of WTCCC 2007



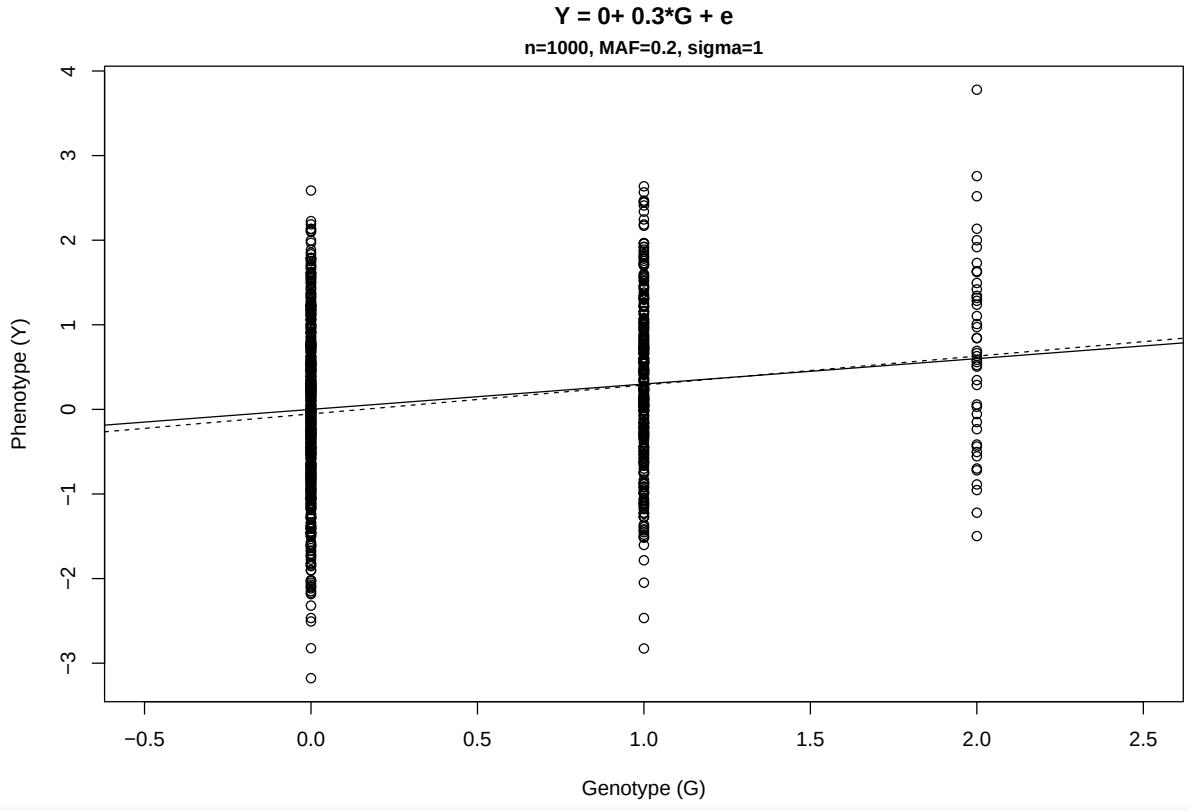
If interested: A refresher Y-on-G association test via simulation

```
set.seed(101)

nsample=1000; maf=0.2; beta=0.3; beta.0=0; sigma=1 # no E for simplicity
nG=rmultinom(1,size=nsample,prob=c((1-maf)^2,2*maf*(1-maf), maf^2)) # assume HWE
G=c(rep(0,nG[1]),rep(1,nG[2]),rep(2,nG[3]))
e=rnorm(nsample,mean=0,sd=sigma)
Y=beta.0+beta*G+e

boxplot(Y~G,main=paste("Y = ",beta.0, "+ ",beta,"*G + e",sep=""), ylab="Phenotype (Y)", xlab="Genotype (G)
stripchart(Y~G,vertical=T,method="jitter",add=T,pch=20,col="gray")
title(line=0.5,paste("n=",nsample,", MAF=",maf,", sigma=",sigma, sep=""),cex.main=0.9)
```



In interested: The true (solid) and fitted (dotted) regression lines

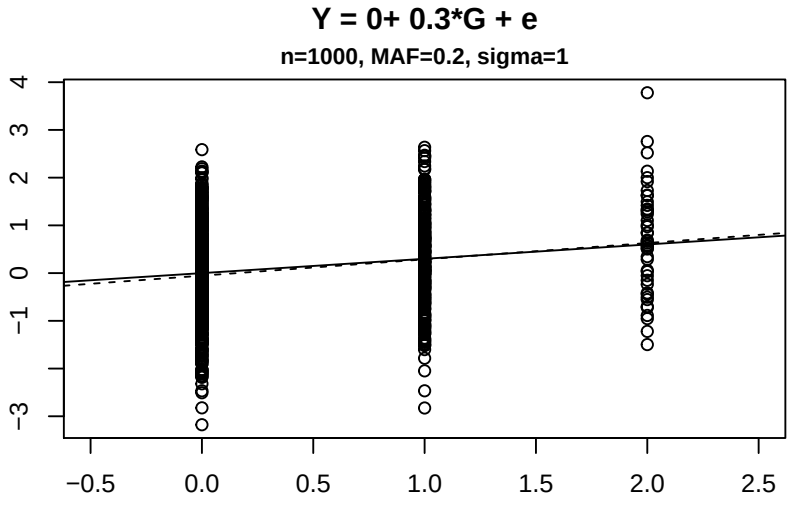
```
plot(G,Y,main=paste("Y = ",beta.0, "+ ",beta,"*G + e",sep=""), ylab="Phenotype (Y)", xlab="Genotype (G)",
title(line=0.5,paste("n=",nsample,", MAF=",maf,", sigma=",sigma, sep=""),cex.main=0.9)
fit=lm(Y~G)
abline(a=fit$coef[1],b=fit$coef[2],lty=2) # fitted regression (dotted) line
abline(a=beta.0,b=beta) # true regression (solid) line
```



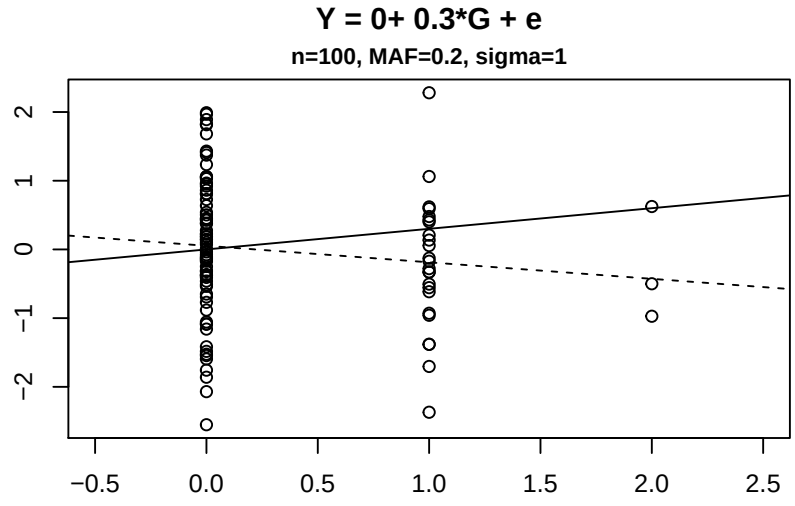

```
fit$coef
```

```
## (Intercept)           G
## -0.05350324  0.34152970
```

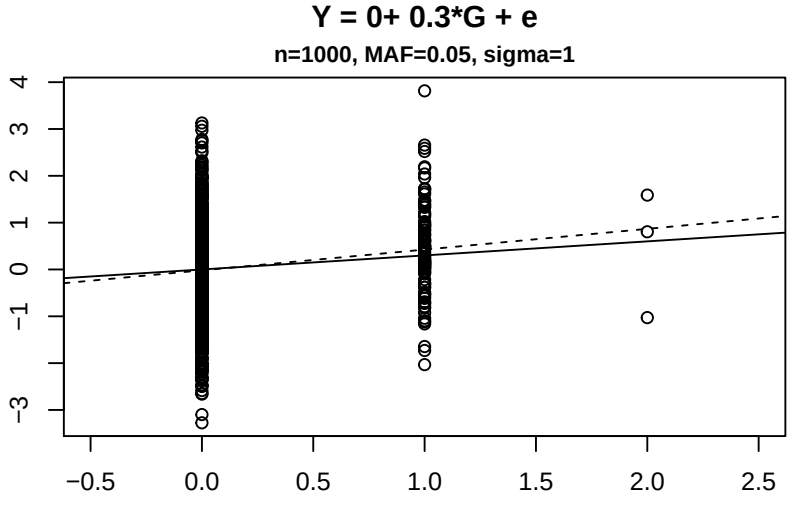
Quiz: difference between the same Y=0+0.3*G+e regression?



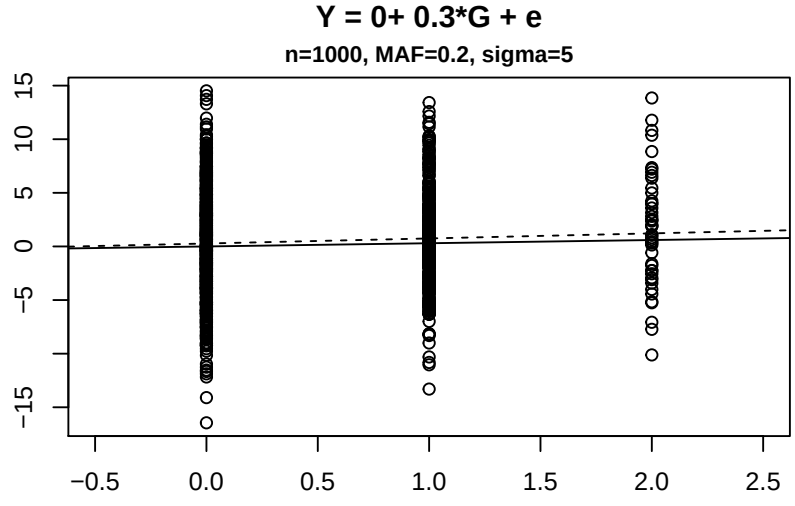
beta.0.hat=−0.05(0.04), beta.hat=0.34(0.05)



beta.0.hat=0.05(0.12), beta.hat=−0.24(0.2)



beta.0.hat=−0.02(0.03), beta.hat=0.44(0.1)



beta.0.hat=0.27(0.19), beta.hat=0.47(0.27)

If interested: What if Y is binary for a case-control study?

A continuous trait: $E(Y) = \beta_0 + \beta_j G_j$ (no E for notation simplicty)

A binary trait: $E(Y) = 1 \cdot \text{Prob}(Y = 1) + 0 \cdot \text{Prob}(Y = 0) = \text{Prob}(Y = 1)$

Instead of studying $E(Y) =$ Prob$(Y = 1)$ directly, use a 'smart' transformation, $g(E(Y))$,

$$logit(E(Y)) = logit(\text{Prob}(Y = 1)) = log(\frac{\text{Prob}(Y = 1)}{1 - \text{Prob}(Y = 1)}) \in (-\infty, \infty)$$

Logistic regression, a generalized linear model (GLM),

$$g(E(Y)) = logit(E(Y)) = log(\frac{\text{Prob}(Y = 1)}{1 - \text{Prob}(Y = 1)}) = \beta_0 + \beta_j G_j$$

Interpretation: $\{\beta$ **is the logOR}** and

$$\textbf{Prob}(Y = 1) = \frac{exp(\beta_0 + \beta_j G_j)}{1 + exp(\beta_0 + \beta_j G_j)}$$

Binary trait simulation study (not discussed here)

NOT easy!

We can use **a liability/threshold model** to create cases and controls from a continuous outcome, similar to a population-based case-control study using e.g. the UK Biobank data.

Can we talk about $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$ now?
NOT yet: A deeper understanding of GWAS is needed!

Even determining J, the 'top' associated/ranked SNPs, is not that simple! Several complications:

- multiple hypothesis testing (mht; here)
- weak-moderate genetic effect size (low power; next)
- correlated tests (LD; more complicated: consider LD prior or post GWAS?)
- ...

mht: from $\alpha = 0.05$ to $\alpha = 5 \times 10^{-8}$, the genome-wide (GW) significance level

Dudbridge and Gusnanto (2008). *Genetic Epidemiology*. Estimation of significance thresholds for genomewide association scans.

$$g(E(Y)) = \beta_0 + \beta_j G_j; \quad H_0 : \beta_j = 0 \text{ for } j = 1, \ldots \approx 10^6 \text{ SNPs.}$$

- $\alpha = 0.05$**: many 'significant' SNPs per GWAS/family of tests**.
- If all SNPs are not associated, p-values are Unif(0,1) distributed.
- $\alpha = 5 \times 10^{-8}$**: family/GWAS-wise error rate (FWER) of 0.05**,

  Prob(at least one false positive SNP per GWAS) ≤ 0.05.

An illustrative simulation study: no SNPs associated

Using $\alpha = 0.05$ leads to 256 significant SNPs (all false positives) in this one single 'GWAS.null'! No significant findings at $\alpha = 0.05/5000$

```
set.seed(101)
nsample=1000; nsnp=5000 # less than 10^6 and no LD for now
G=matrix(-9,nrow = nsample,ncol = nsnp) # the genotype matrix
maf=runif(nsnp,min=0.05,max=0.5) # MAF randomly drawn from Unif(0,05,0.5) for simplicity
maf.hat=rep(-9,nsnp)
nsnp.true=0 # number of truly associated SNPs
beta.true=0 # no effect to study type 1 error
beta=c(rep(beta.true,nsnp.true),rep(0,(nsnp-nsnp.true))) # beta vector
betaG=rep(0,nsample) # the initial beta*G vector
for(j in 1:nsnp){ # using the loop function slows down the computation but adds clarity for teaching.
  nG=rmultinom(1,size=nsample,prob=c((1-maf[j])^2,2*maf[j]*(1-maf[j]), maf[j]^2))
  maf.hat[j]=(2*nG[3]+nG[2])/(2*nsample) # MAF estimated from the sample
  G[,j]=sample(c(rep(0,nG[1]),rep(1,nG[2]),rep(2,nG[3]))) # shuffle the G; no LD
  betaG=betaG+beta[j]*G[,j]
}
beta.0=0;sigma=1;e=rnorm(nsample,mean=0,sd=sigma)
Y=beta.0+betaG+e # the phenotype vector
sum.stat=matrix(-9,nrow=nsnp,ncol=7)
colnames(sum.stat)=c("MAF", "MAF.hat", "beta", "beta.hat", "se", "Z.value", "p.value")
for(j in 1:nsnp){
  fit=lm(Y~G[,j]); sum.stat[j,]=c(maf[j],maf.hat[j], beta[j], summary(fit)$coefficients[2,])
}
sum(sum.stat[,"p.value"]<=0.05) # many "significant" SNPs in this one single "GWAS"
```

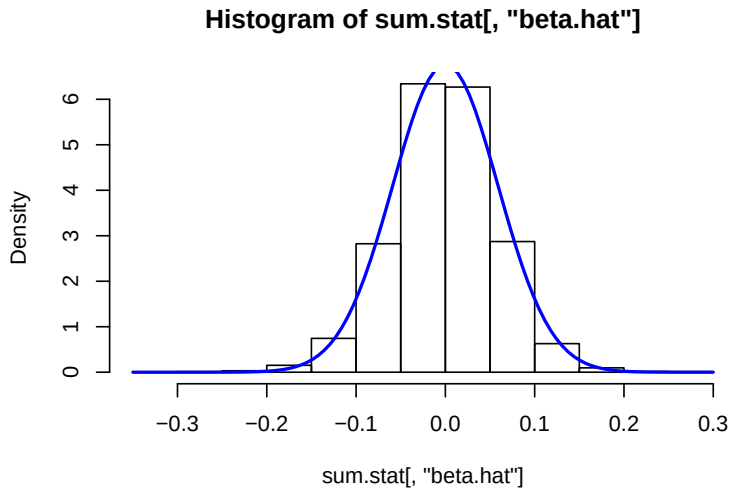
```
## [1] 256
```

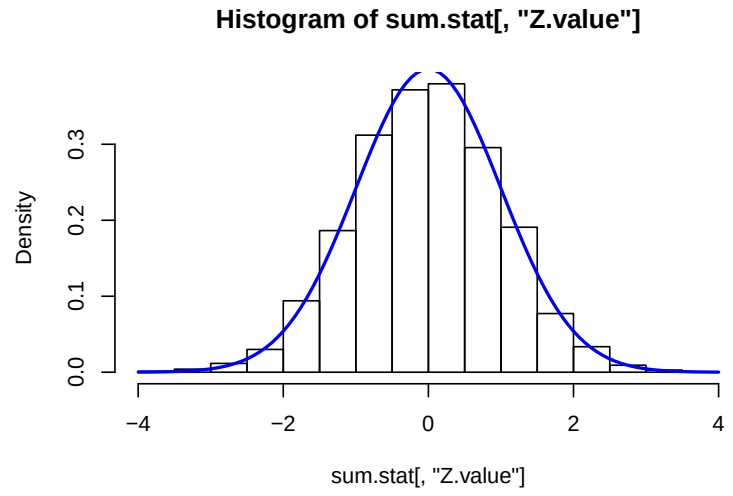
```
sum(sum.stat[,"p.value"]<=0.05/nsnp) # using the Bonferroni correction for FWER of 0.05
```

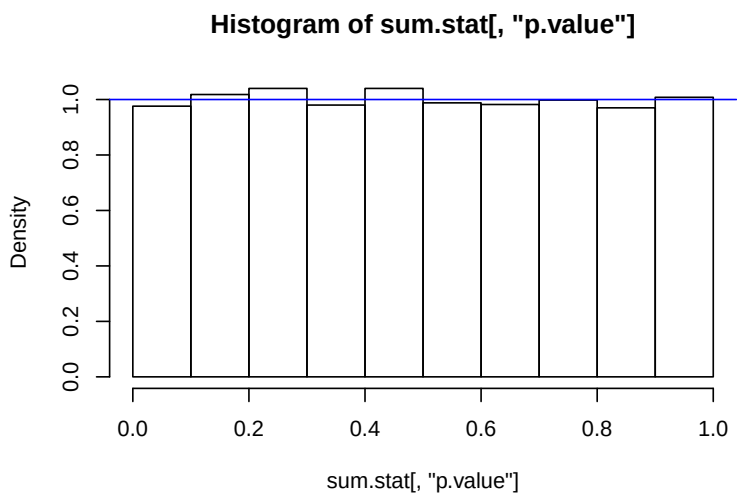
```
## [1] 0
```

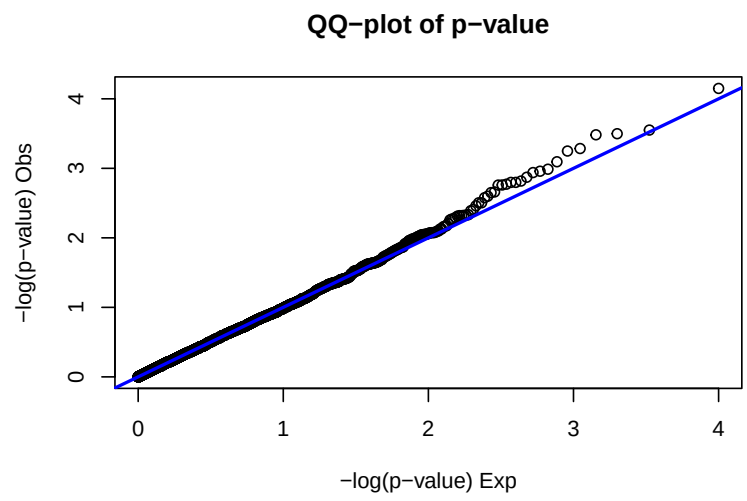
Pay attention to the spread of $\hat{\beta}_j$ histogram (top-left plot)

No association here, true $\beta_j = 0$ for all SNPs.

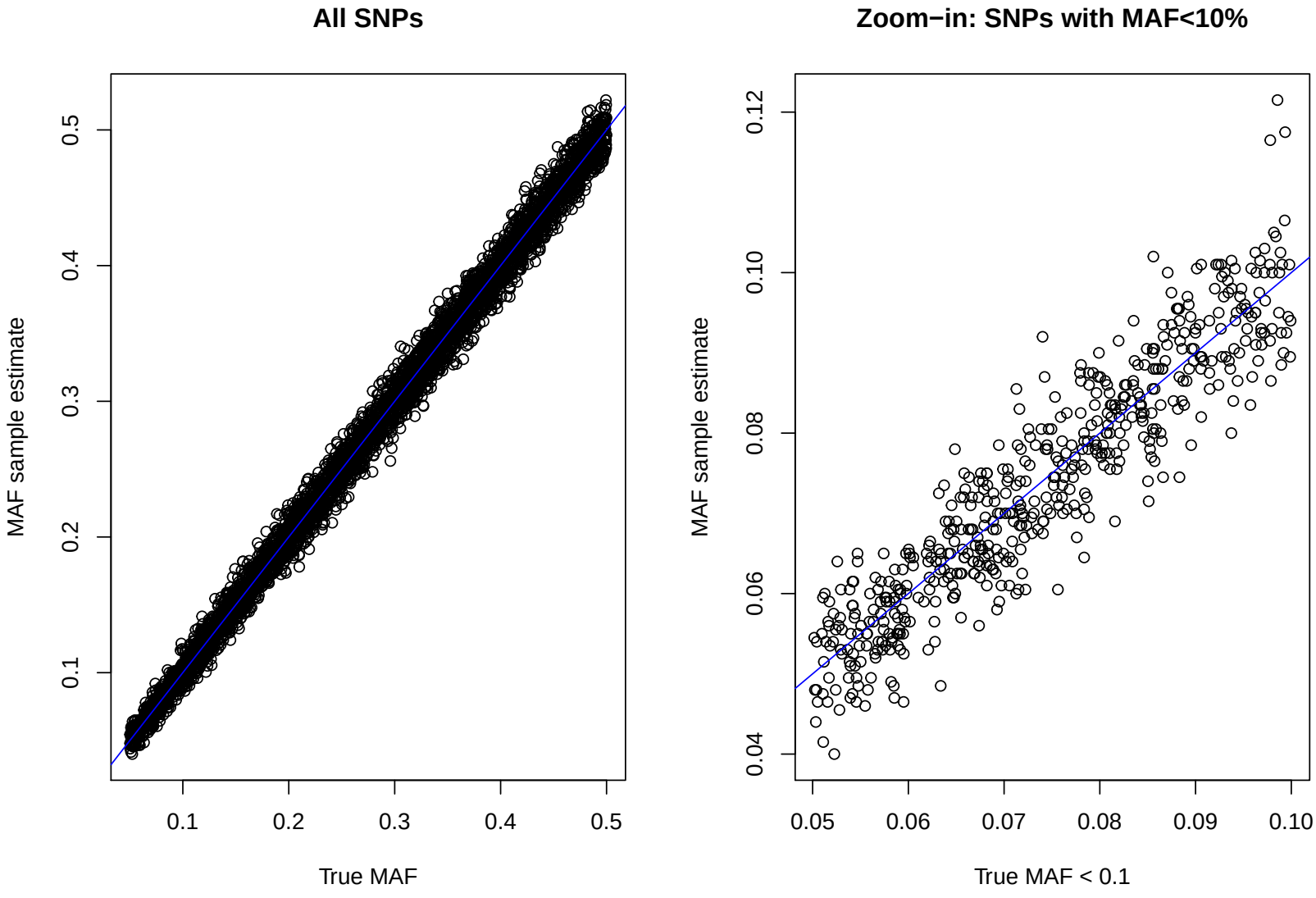








If interested: Also pay attention to the uncertainty in MAF estimates



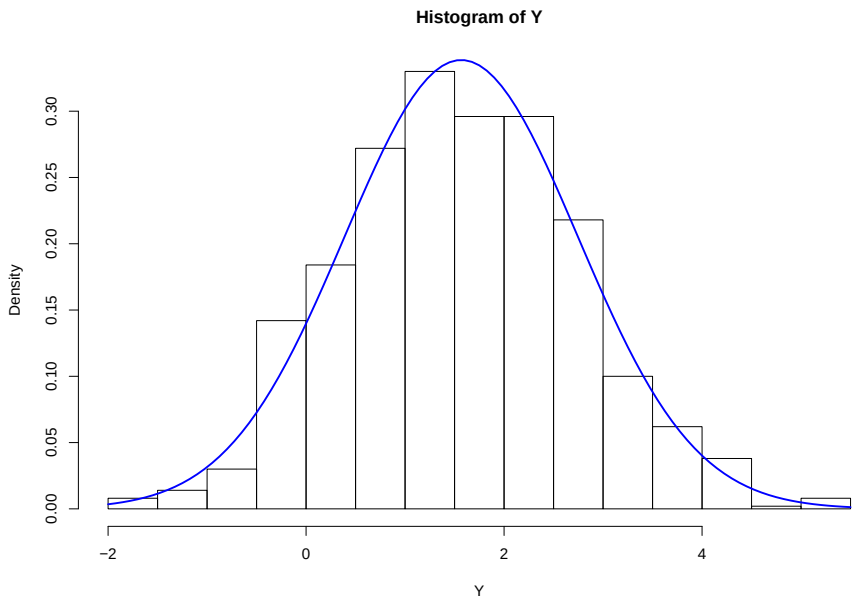
An illustrative 'polygenic' model simulation study

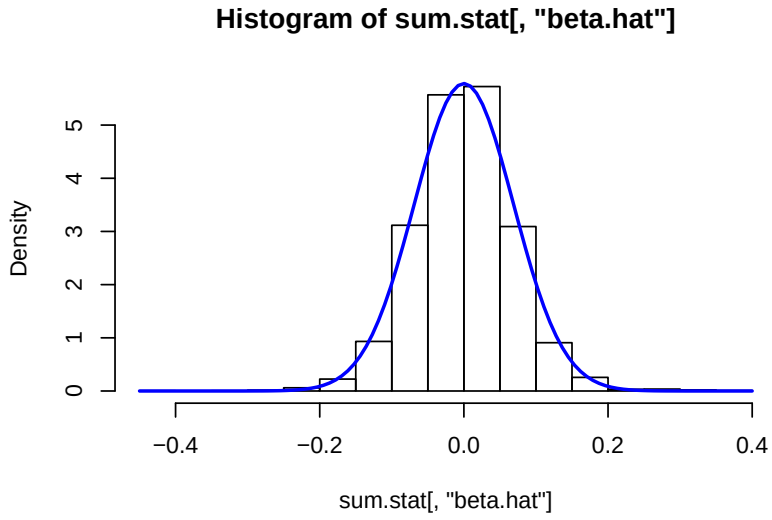
10 out 5000 indep. SNPs with **varying 'moderate-large' effects** are truly associated with Y (**all** $\beta = 0.3$ **but MAF vary**).

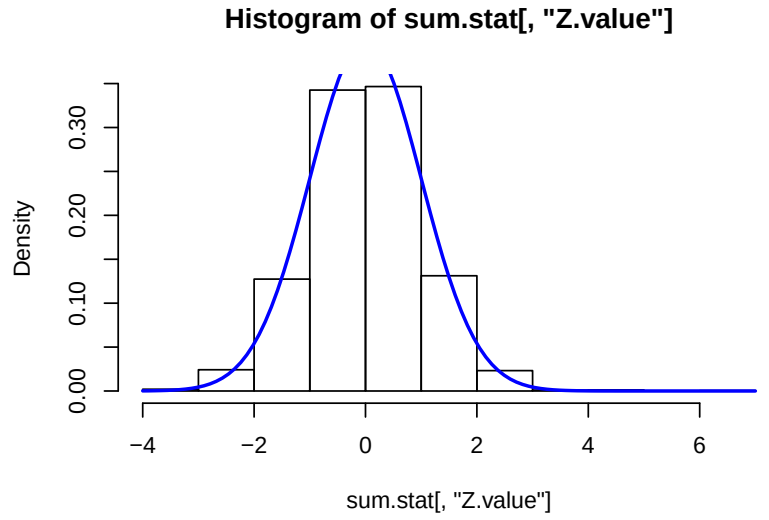
$$Y_i = \sum_{j=1}^{10} \beta_j G_{ij} + e, \text{ where } \beta_j = 0.3$$

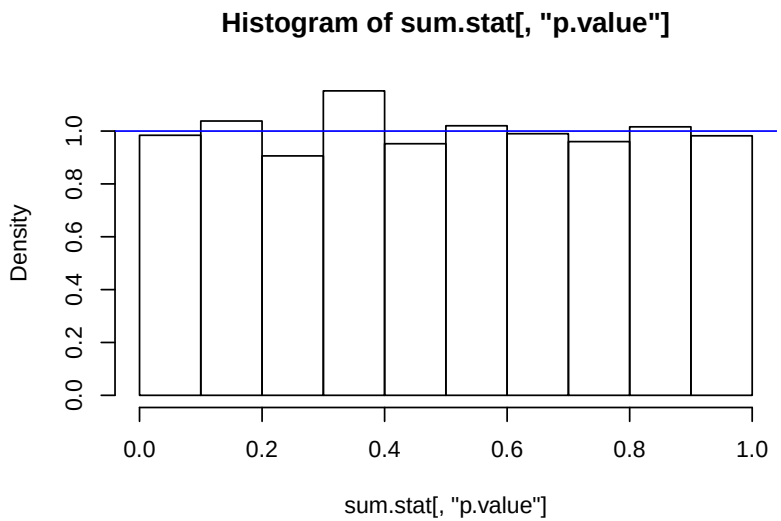
$$\text{MAF} \sim \text{ Unif}(0.05,0.5), \; e \sim N(0,1).$$

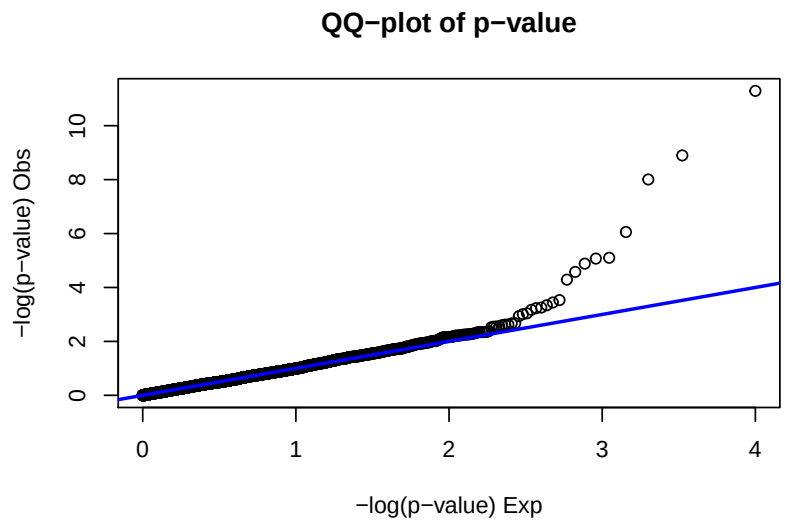
```
nsnp.true=10 # number of truly associated SNPs
beta.true=0.3 # "large" effect (also MAF, the error term, and the sample size)
```







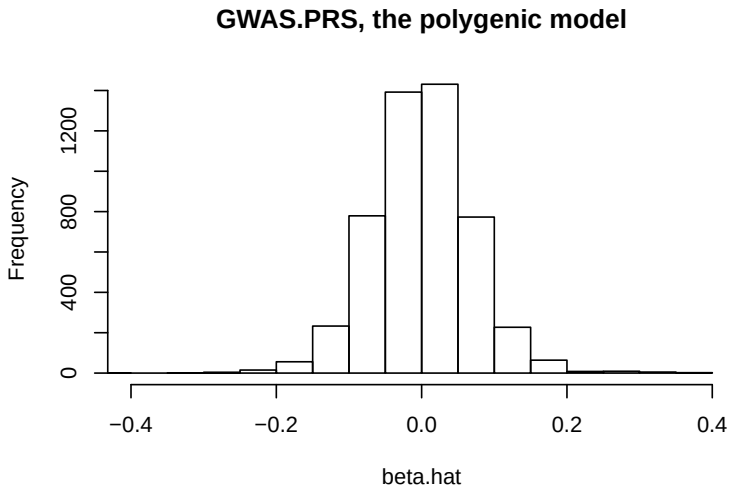


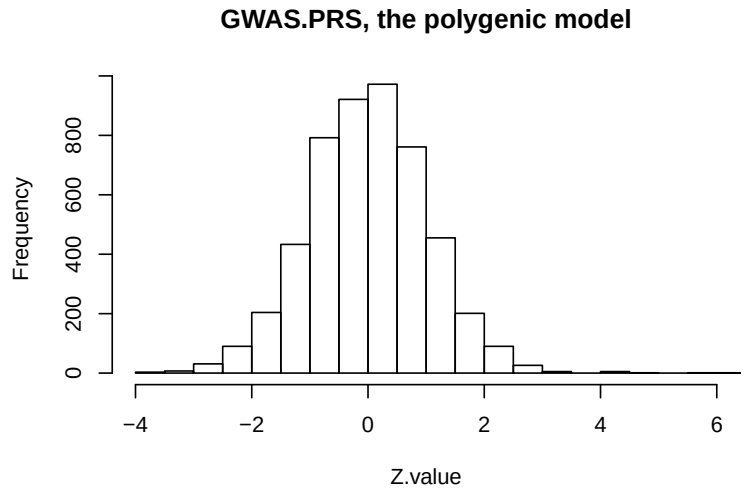


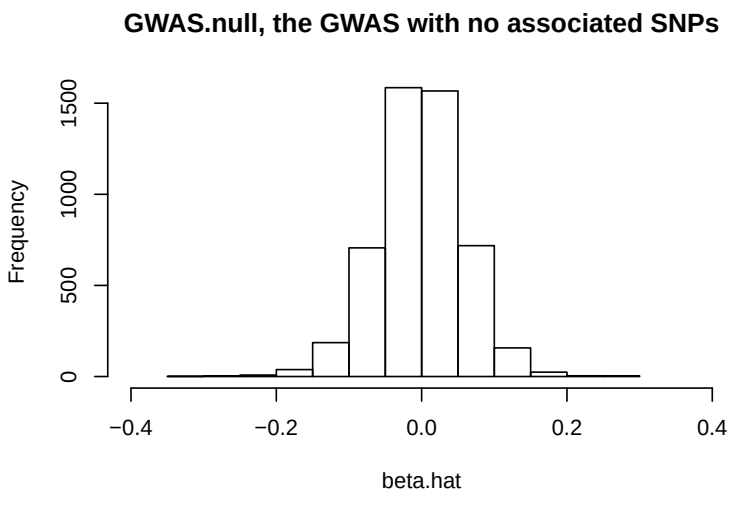
N.B. Histogram and QQ-plot carry different types of information!

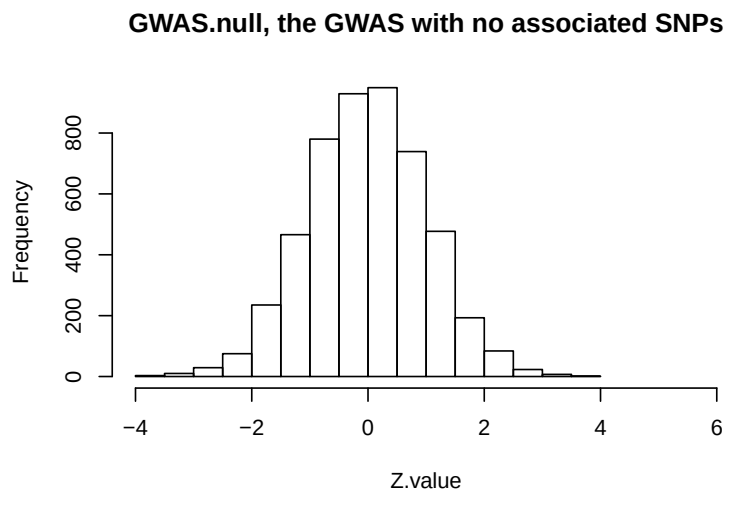
A closer look at the histograms of $\hat{\beta}$ and $Z = \hat{\beta}/SE$

Trouble ahead: similar between the GWAS.PRS (top) and GWAS.null (bottom)









If interested: GWAS-type of summary statistics (with true MAF and beta shown)

```
##              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
```

If interested: SNP1 output

```
##
## Call:
## lm(formula = Y ~ G[, 1])
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.3958 -0.8050  0.0109  0.7912  3.8070
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  1.43764    0.04691  30.647  < 2e-16 ***
## G[, 1]       0.29257    0.06537   4.476 8.49e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.167 on 998 degrees of freedom
## Multiple R-squared:  0.01968,    Adjusted R-squared:  0.0187
## F-statistic: 20.03 on 1 and 998 DF,  p-value: 8.489e-06
```

If interested: SNP2 output

```
##
## Call:
## lm(formula = Y ~ G[, 2])
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.2024 -0.8023 -0.0395  0.8466  3.7030
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept)  1.52681    0.03943  38.723   <2e-16 ***
## G[, 2]       0.33146    0.10936   3.031   0.0025 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.173 on 998 degrees of freedom
## Multiple R-squared:  0.009121,   Adjusted R-squared:  0.008128
## F-statistic: 9.187 on 1 and 998 DF,  p-value: 0.002501
```

IF we knew which set of SNPs to include (getting into the PRS direction but not yet)

```
# not realistic: no GWAS needed if we already know which SNPs are associated!
summary(lm(Y~G[,1]+G[,2]+G[,3]+G[,4]+G[,5]+G[,6]+G[,7]+G[,8]+G[,9]+G[,10]))
```

```
##
## Call:
## lm(formula = Y ~ G[, 1] + G[, 2] + G[, 3] + G[, 4] + G[, 5] +
##     G[, 6] + G[, 7] + G[, 8] + G[, 9] + G[, 10])
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.2616 -0.7070 -0.0004  0.6983  3.3557
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -0.03884    0.09679  -0.401  0.68830
## G[, 1]       0.30033    0.05783   5.193 2.51e-07 ***
## G[, 2]       0.29903    0.09607   3.112  0.00191 **
## G[, 3]       0.31183    0.04731   6.592 7.06e-11 ***
## G[, 4]       0.35997    0.05006   7.190 1.27e-12 ***
## G[, 5]       0.32629    0.06260   5.212 2.27e-07 ***
## G[, 6]       0.38079    0.05782   6.586 7.33e-11 ***
## G[, 7]       0.31377    0.04840   6.482 1.42e-10 ***
## G[, 8]       0.32870    0.05901   5.570 3.28e-08 ***
## G[, 9]       0.27331    0.05002   5.464 5.90e-08 ***
## G[, 10]      0.27448    0.05183   5.296 1.46e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.027 on 989 degrees of freedom
## Multiple R-squared:  0.2471, Adjusted R-squared:  0.2395
## F-statistic: 32.46 on 10 and 989 DF,  p-value: < 2.2e-16
```

What kind of model (heritability, h^2) did we simulate?

$$Y = \sum_{j=1}^{10} \beta_j G_j + e, \text{ where } \beta_j = 0.3, \ e \sim N(0, \sigma^2 = 1),$$

The MAF of the 10 truly associated SNPs, ranging from 0.07 to 0.37:

```
round(maf[1:nsnp.true],2)
```

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

```
V.G=sum(beta[1:nsnp.true]^2*maf[1:nsnp.true])
V.e=sigma^2
h2=V.G/(V.G+V.e)
round(c(V.G,V.e,h2),3)
```

```
## [1] 0.224 1.000 0.183
```

True (not estimated) heritability:

$$h^2 = \frac{V_G}{V_G + V_e} = \frac{0.224}{0.224 + 1} = 18.3\%$$

Analytical details of h^2 of this **simple** model

(linear, fixed-effect, additive, no LD, no interaction)

$$Y = \sum_{j=1} \beta_j G_j + e, \text{ where } e \sim N(0, \sigma^2).$$

$$V_Y = Var(Y) = \sum_j \beta_j^2 Var(G_j) + \sigma^2 = V_G + V_e,$$

- G_j: p_j as MAF for A
- coded additively: $0 = aa$, $1 = Aa$ and $2 = AA$
- genotype frequency under HWE: $(1-p_j)^2$, $2p_j(1-p_j)$ and p_j^2
- $E(G_j) = 2p_j$; $Var(G_j) = 2p_j(1-p_j)$

$$\text{(narrow) } h^2 = \frac{V_G}{V_G + V_e} = \frac{\sum_j \beta_j^2 Var(G_j)}{Var(Y)} = \frac{\sum_j \beta_j^2 2p_j(1-p_j)}{\sum_j \beta_j^2 2p_j(1-p_j) + \sigma^2}.$$

Heritability of GWAS 'loci', h_j^2 contributed by each individual, independent SNP j in our case

$$\text{(narrow) } h_j^2 = \frac{\beta_j^2 2p_j(1-p_j)}{\sum_j \beta_j^2 2p_j(1-p_j) + \sigma^2}.$$

$\beta_j = 0.3$ **for all 10 causal SNPs but MAFs differ:**

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

Thus, (true not estimated) h_j^2's differ:

```
##  [1] 0.016 0.005 0.027 0.025 0.012 0.014 0.023 0.015 0.024 0.022
```

Worth repeating: What is the effect size of a SNP?

All 10 SNPs have $\beta = 0.3$, but their (true not estimated) h^2 contributions vary

from 0.5% (MAF=0.07, SNP2)

to 2.7% (MAF=0.37, SNP3)

$\sum_j \beta_j^2 2p_j(1-p_j)$

Effect interpretation also depends on MAF and σ^2.

n comes in later when we try to find these SNPs using data.

In practice, β_j must be estimated and

Large n is then critical!

MAF p_j and σ^2 also need to be estimated.

If interested: Connection with Explained Variatation (EV) and R^2 from regression

(linear, fixed-effect, additive, no LD, no interaction)

$$Y = \sum_{j=1} \beta_j G_j + e, \text{ where } e \sim N(0, \sigma^2).$$

$$EV = \frac{\text{variation of Y explained by G}}{\text{total variation of Y}} = \frac{Var(E(Y|G))}{Var(Y)}$$
$$= \frac{\sum_j \beta_j^2 2p_j(1-p_j)}{\sum_j \beta_j^2 2p_j(1-p_j) + \sigma^2} = h^2.$$

$$R^2 = \frac{SS_{explained}}{SS_{total}} = 1 - \frac{SS_{residual}}{SS_{total}}$$
$$= 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y})^2} \approx h^2$$

Recall: multi-SNP regression **IF** we knew the true model

```
##
## Call:
## lm(formula = Y ~ G[, 1] + G[, 2] + G[, 3] + G[, 4] + G[, 5] +
##     G[, 6] + G[, 7] + G[, 8] + G[, 9] + G[, 10])
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.2616 -0.7070 -0.0004  0.6983  3.3557
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -0.03884    0.09679  -0.401  0.68830
## G[, 1]       0.30033    0.05783   5.193 2.51e-07 ***
## G[, 2]       0.29903    0.09607   3.112  0.00191 **
## G[, 3]       0.31183    0.04731   6.592 7.06e-11 ***
## G[, 4]       0.35997    0.05006   7.190 1.27e-12 ***
## G[, 5]       0.32629    0.06260   5.212 2.27e-07 ***
## G[, 6]       0.38079    0.05782   6.586 7.33e-11 ***
## G[, 7]       0.31377    0.04840   6.482 1.42e-10 ***
## G[, 8]       0.32870    0.05901   5.570 3.28e-08 ***
## G[, 9]       0.27331    0.05002   5.464 5.90e-08 ***
## G[, 10]      0.27448    0.05183   5.296 1.46e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.027 on 989 degrees of freedom
## Multiple R-squared:  0.2471, Adjusted R-squared:  0.2395
## F-statistic: 32.46 on 10 and 989 DF,  p-value: < 2.2e-16
```

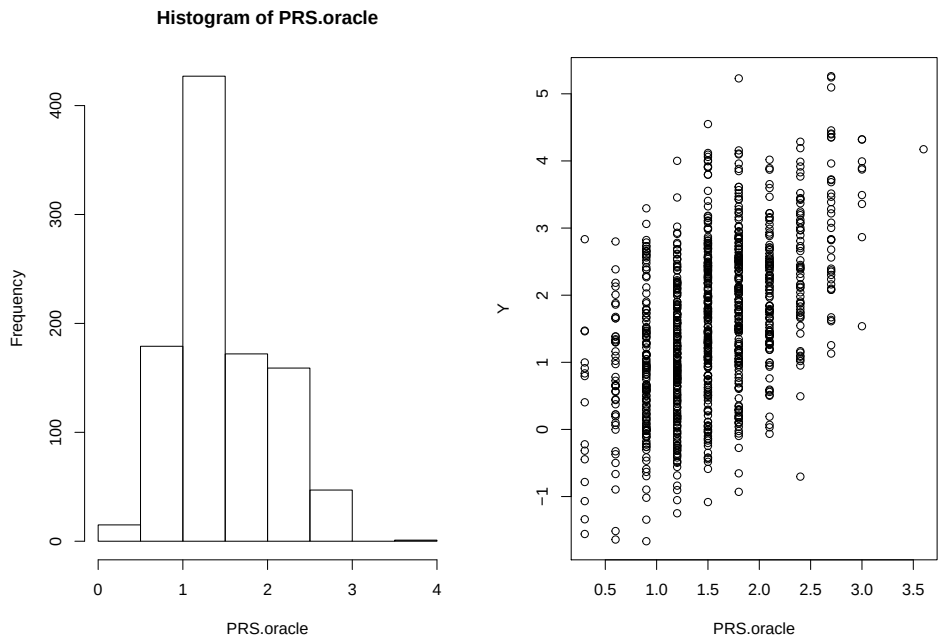
From multi-SNP to one-super-SNP (PRS) association!

IF we knew the true model: PRS_{oracle}

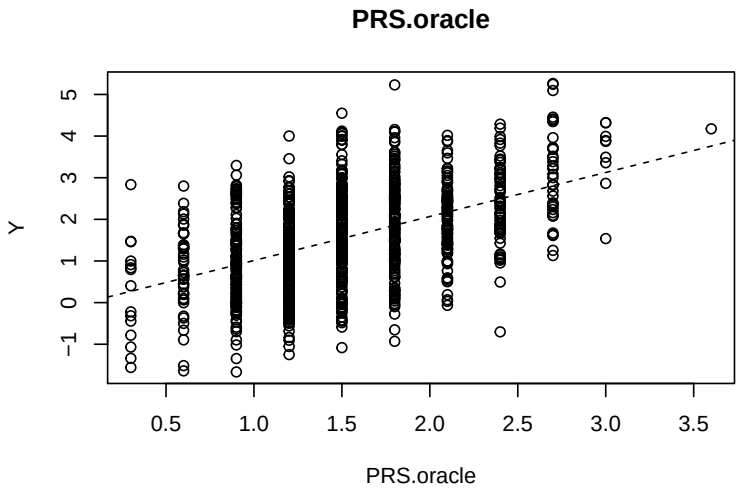
Not realistic: only to demonstrate the value of PRS **conceptually**.

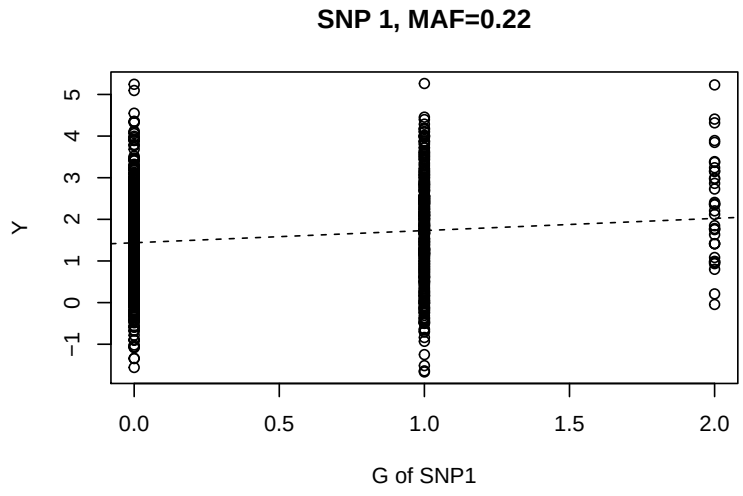
$$PRS_{i,oracle} = \sum_{j=1}^{J=10} \beta_j G_{ij} + e, \text{ where } \beta_j = 0.3$$

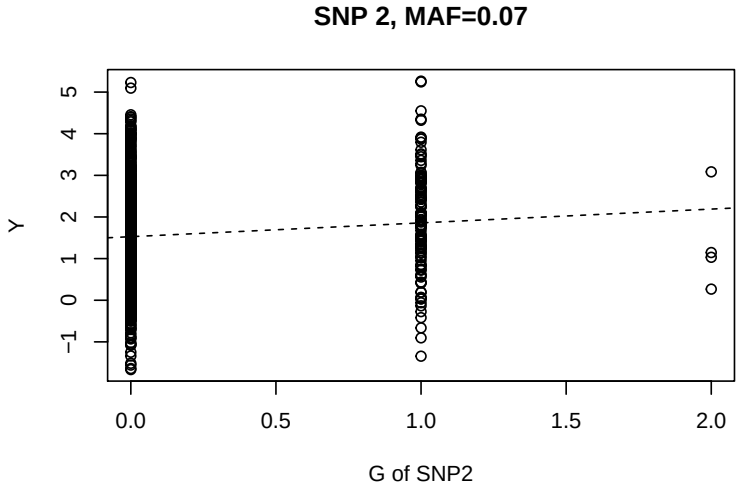
```
PRS.oracle=rep(0,nsample)  # PRS vector
for (i in 1:nsample) # for each individual i
  for (j in 1:nsnp.true) # sum over the J selected SNPs
    PRS.oracle[i] = PRS.oracle[i]+beta[j]*G[i,j]
par(mfrow=c(1,2))
hist(PRS.oracle) # not quite normal as J=10 here
plot(PRS.oracle,Y) # much more predictive than individual SNPs
```

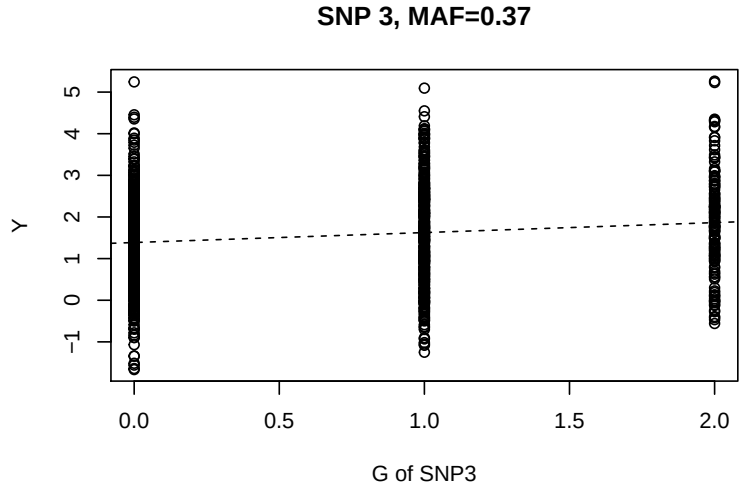


(Good) PRS is more significantly associated with the trait than one single SNP









```
summary(lm(Y~PRS.oracle))
```

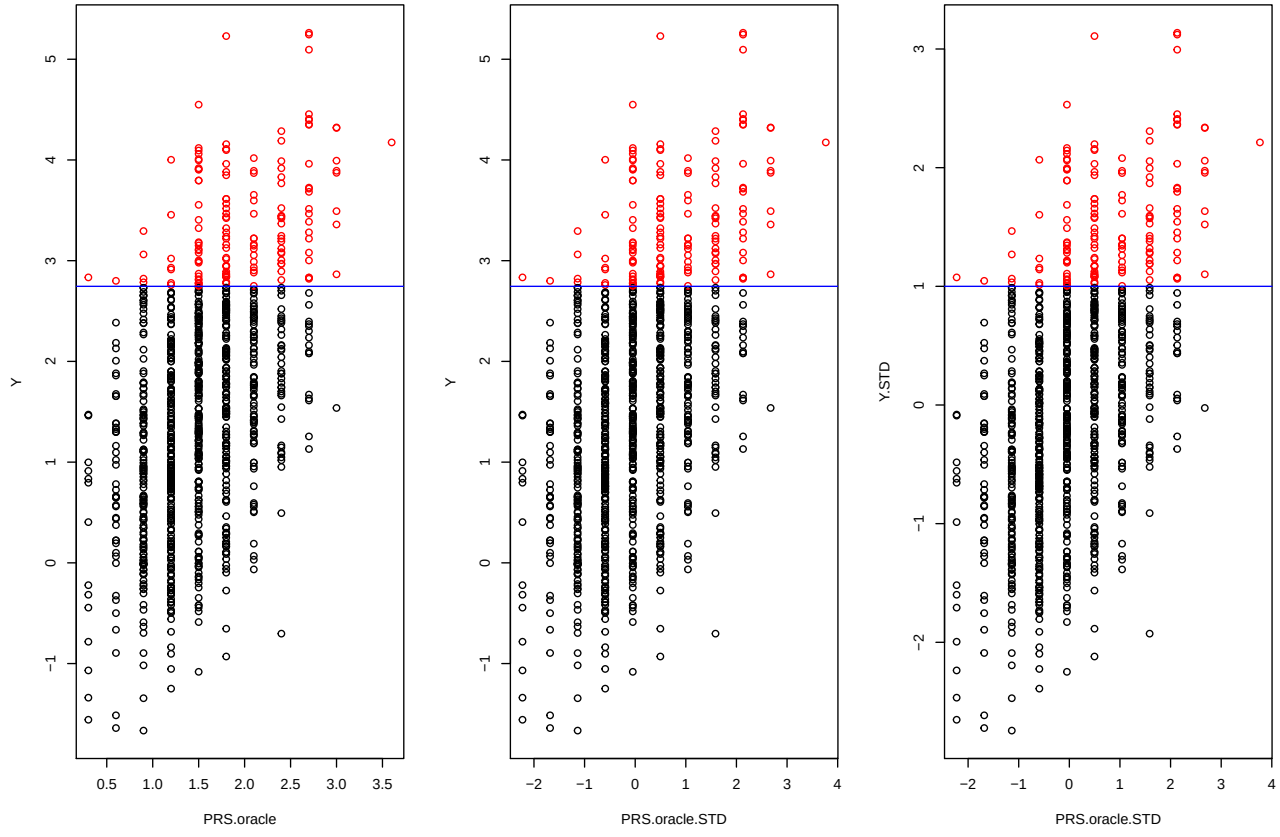
```
##
## Call:
## lm(formula = Y ~ PRS.oracle)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -3.1940 -0.7168 -0.0158  0.7102  3.3731
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) -0.04598    0.09549  -0.482     0.63
## PRS.oracle   1.05710    0.05886  17.959   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.025 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
```

From PRS-based association to PRS-based prediction!

Standardization (STD) and a liability/threashold model

```
Y.STD=(Y-mean(Y))/sqrt(var(Y))
PRS.oracle.STD=(PRS.oracle-mean(PRS.oracle))/sqrt(var(PRS.oracle))
case.index=which(Y.STD>1);control.index=which(Y.STD<=1) # 1 is a subjective choice
c(length(Y[case.index]),length(Y[control.index])) # numbers of cases and controls
```

```
## [1] 149 851
```



higher PRS_{oracle} $\Longrightarrow$ **higher risk/case**

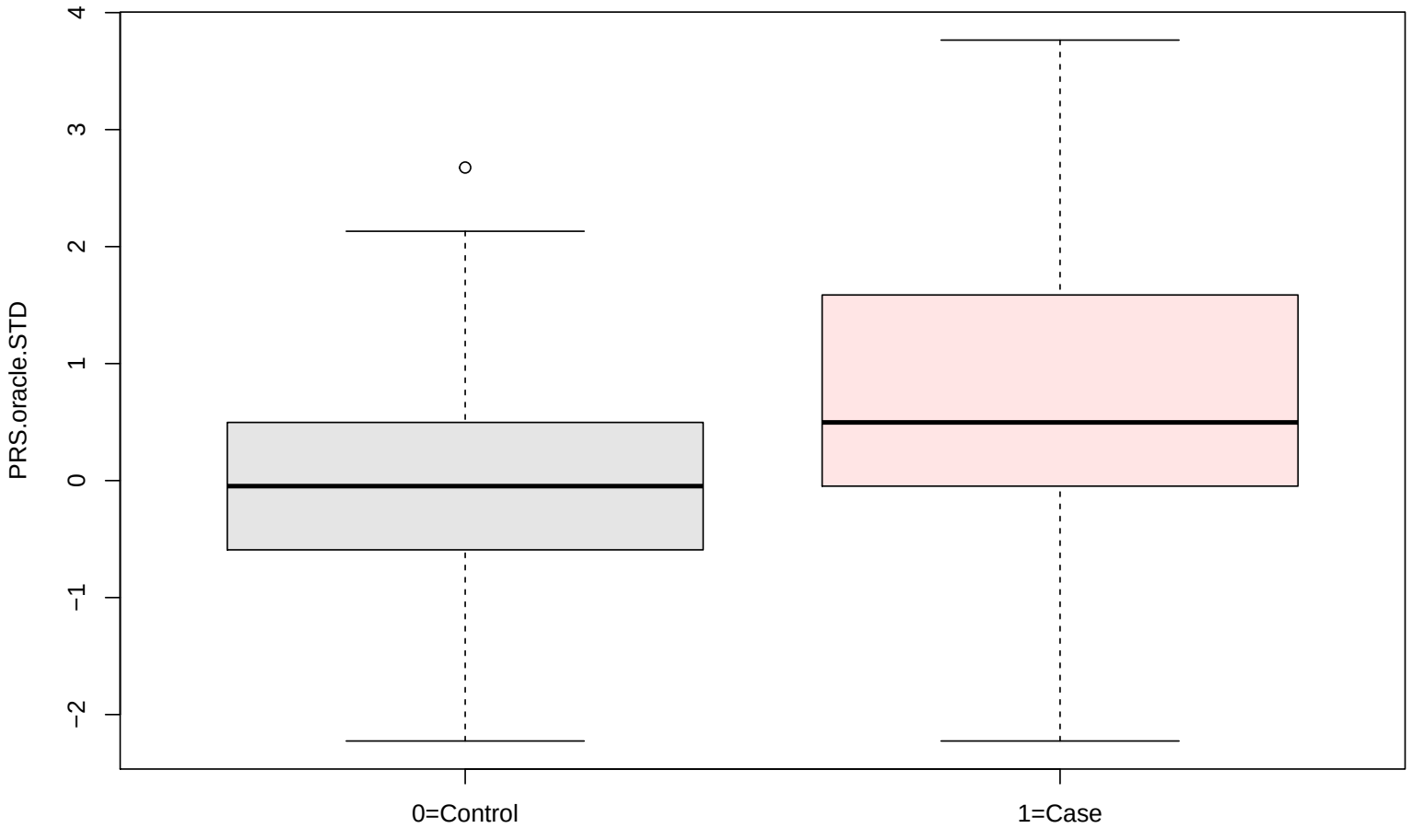
Quiz

Standardization (STD) is often done in practice and should not change interpretation.

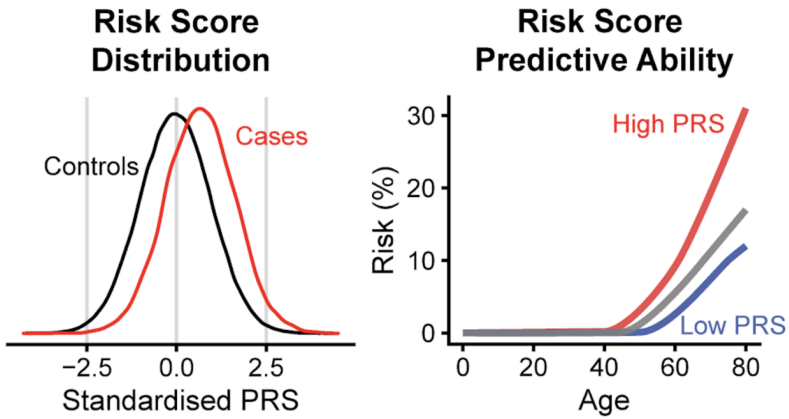
BUT, what are the potential pitfalls of STD?

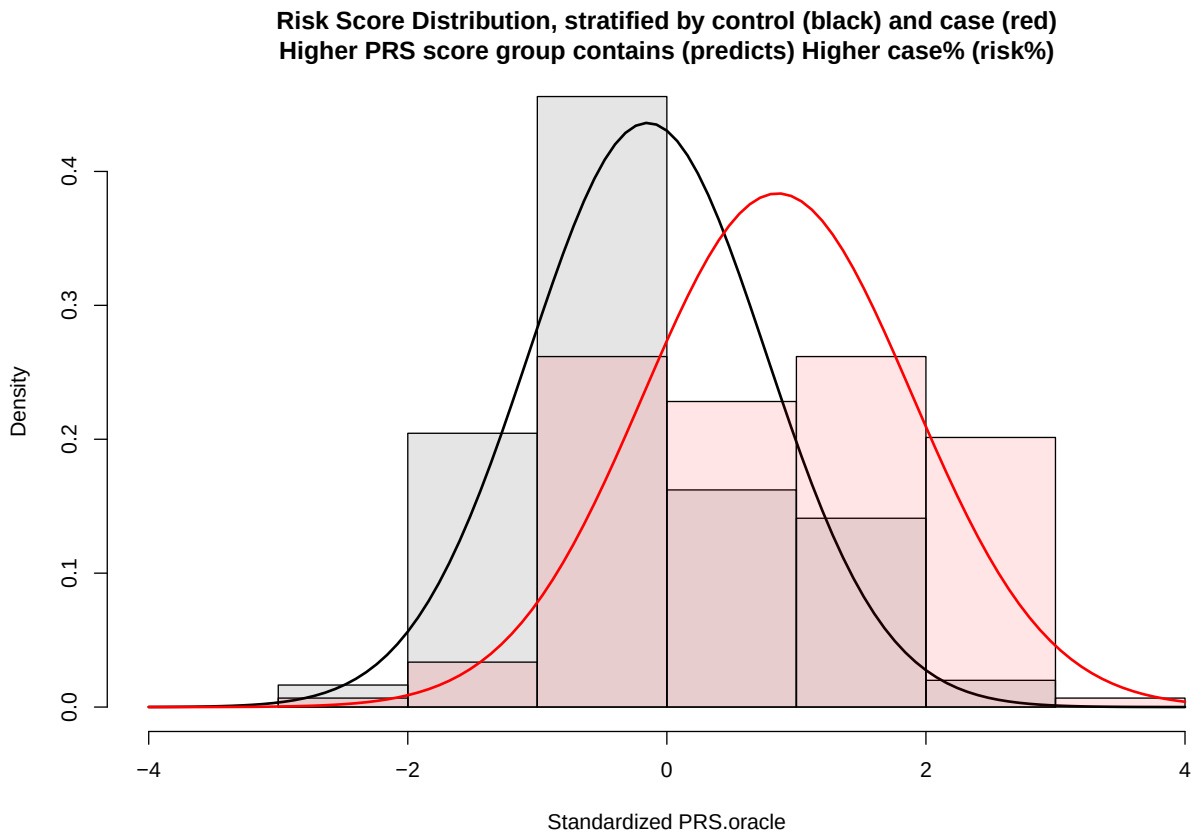
Different perspective but the same idea: PRS_{oracle}'s of cases tend to be higher than PRS_{orcale}'s of controls

```
Y.cc=rep("0=Control",nsample); Y.cc[case.index]="1=Case"
boxplot(PRS.oracle.STD~Y.cc,main="",xlab="",col=c(rgb(0,0,0,0.1),rgb(1,0,0,0.1)))
```



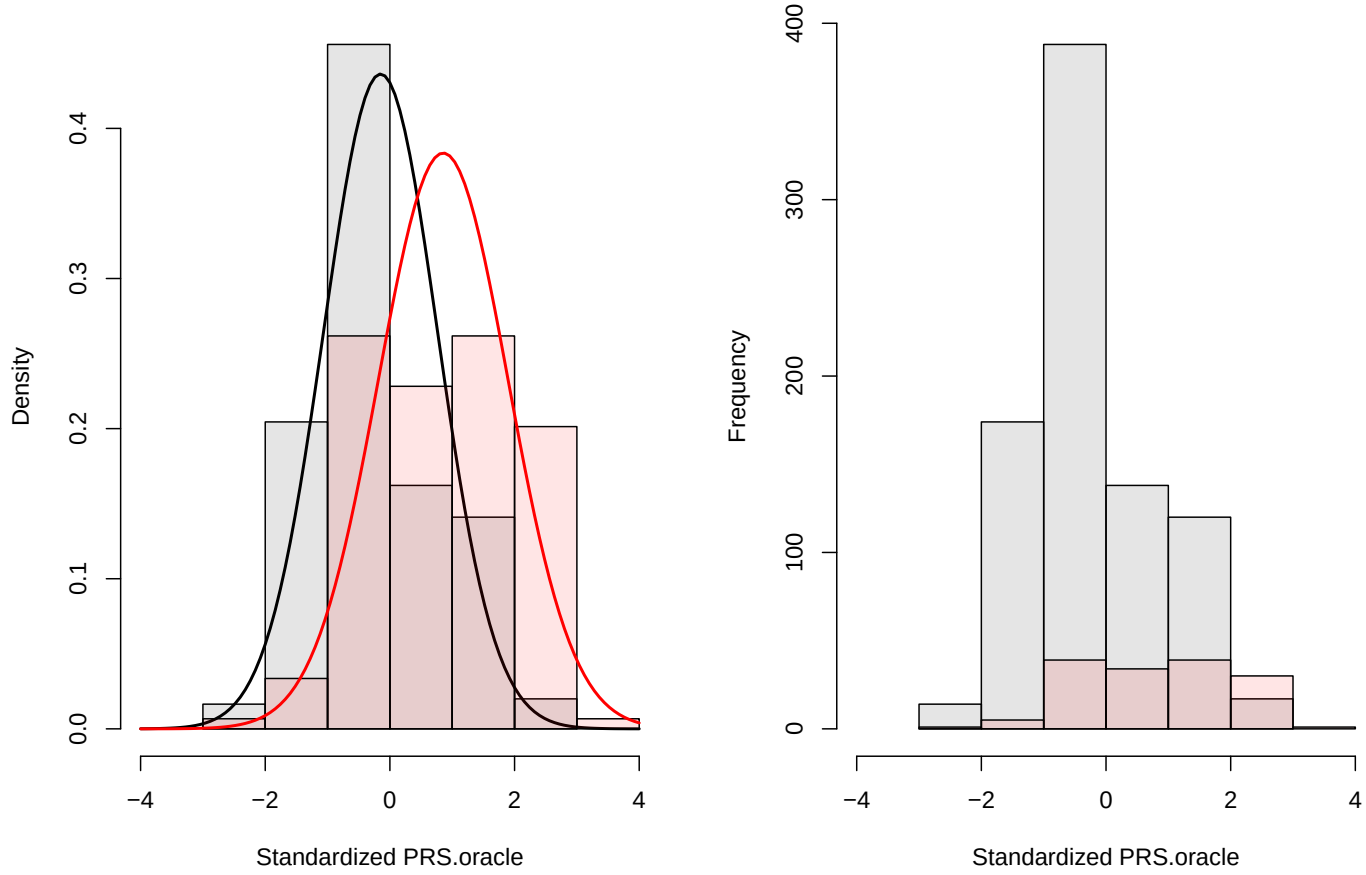
Recall and mimic the illustrative plots (2 in 1)





Quiz:

The standardized PRS.oracle value of an individual is 2.5. What is the **probability** of this individual having the disease/condition? (Hint in the two histrograms below and **relative risk** $\neq$ **absolute risk!**)

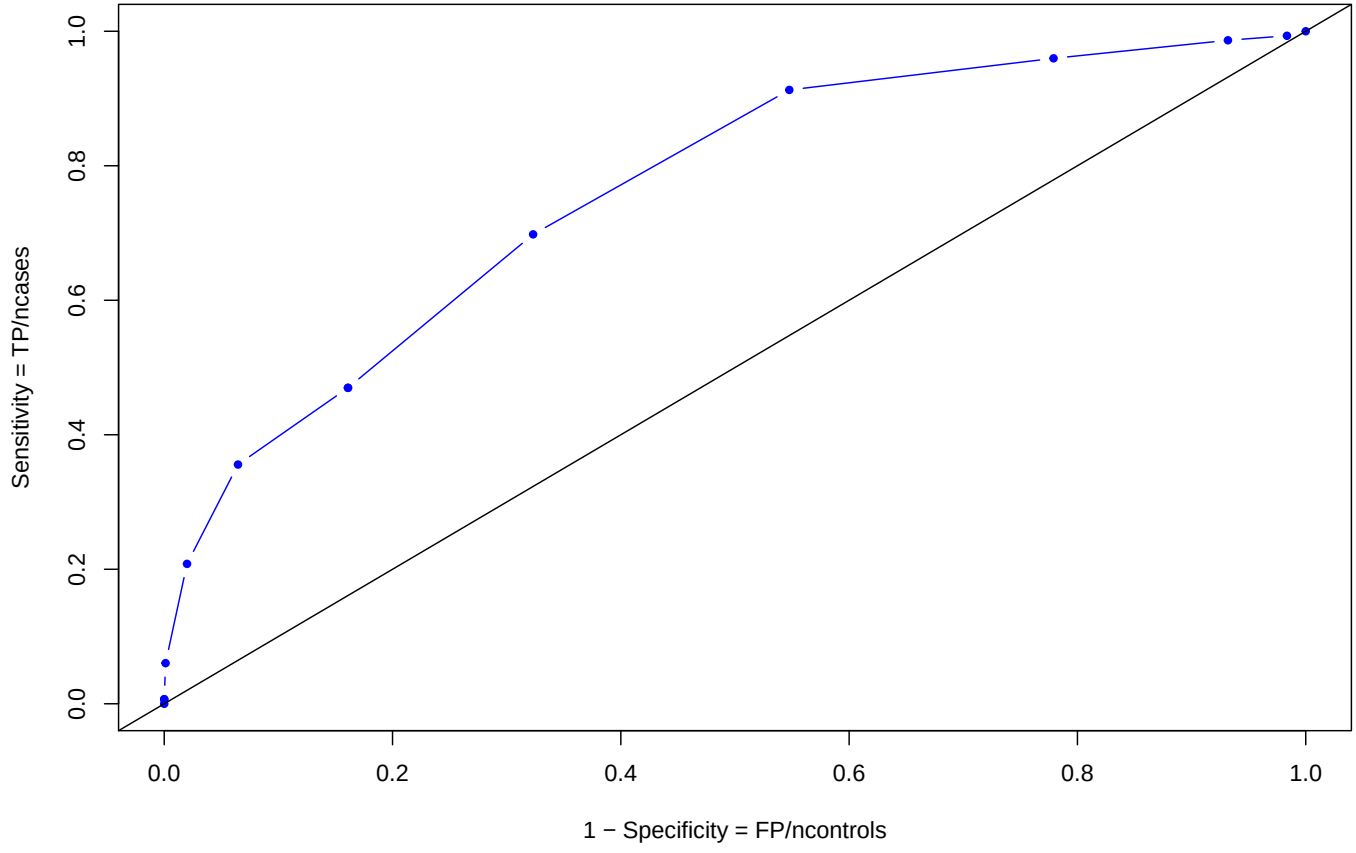


Another related quiz:

- cases: individuals with the disease/condition
- controls: individuals without the disease/condition
- a test or a decision rule, say Covid-19 testing or PRS-based prediction (e.g. standardized PRS >3 predicting case)
- Sensitivity = e.g. 90%
  $$\text{Sensitivity} = \Pr(\text{positive test result}|\text{case})$$
- Specificity = e.g. 90%
  $$\text{Specificity} = \Pr(\text{negative test result}|\text{control})$$

Is it possible that $\Pr(\text{case}|\text{PRS}>3) < 50\%$?
(hint: which information is missing from the above?)

Towards ROC (receiver operating characteristic) curve and AUC (area under the curve), using our simulated data and PRS.oracle



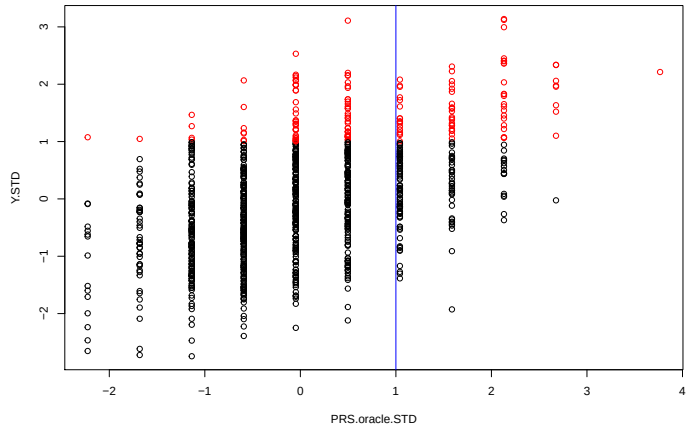

```
## [1] "AUC of ROC.oracle=" "0.763"
```

Undertanding each point on the ROC curve

```
plot(PRS.oracle.STD,Y.STD,col=color.index)
ncase=sum(Y.cc=="1=Case") # total number of cases
ncontrol=sum(Y.cc=="0=Control") # total number of controls
c(ncase,ncontrol)
```

```
## [1] 149 851
```

```
PRS.threshold=1;abline(v=PRS.threshold,col="blue")  # threshold used to call a sample positive/case
```




```
P=sum(PRS.oracle.STD>PRS.threshold) # number of Positives at this threshold
TP=sum(Y.cc[PRS.oracle.STD>PRS.threshold]=="1=Case") # True Positives
FP=sum(Y.cc[PRS.oracle.STD>PRS.threshold]=="0=Control") # False Positives
c(P,TP,FP)
```

```
## [1] 207  70 137
```

```
sensitivity=TP/ncase # sensitivity
specificity.1=FP/ncontrol # 1-specificity
c(sensitivity,specificity.1) # ONE point on the ROC curve: (y=sensitivity=0.47,x=1-specificity=0.16)
```

```
## [1] 0.4697987 0.1609871
```

A few more (sensitivity vs. 1-specificity) points for ROC

```
# increase the threshold: both sensitivity and 1-specificity decrease
PRS.threshold= -1.5
```

```
## [1] 940 147 793
```

```
## [1] 0.9865772 0.9318449
```

```
PRS.threshold=0
```

```
## [1] 379 104 275
```

```
## [1] 0.6979866 0.3231492
```

```
PRS.threshold=1.5
```

```
## [1] 108  53  55
```

```
## [1] 0.35570470 0.06462985
```

```
PRS.threshold=2
```

```
## [1] 48 31 17
```

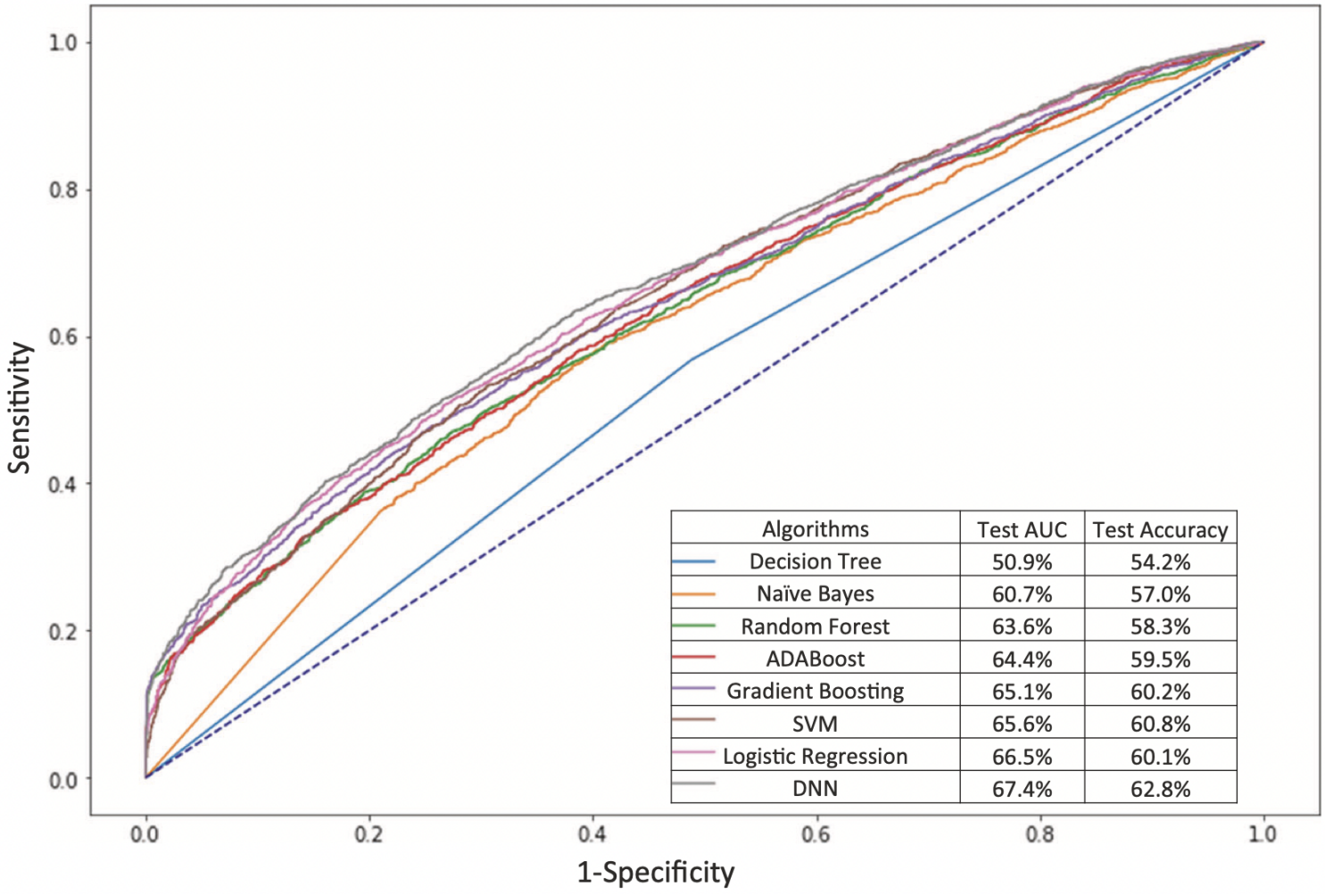
```
## [1] 0.2080537 0.0199765
```

```
PRS.threshold=2.5  # estimates are no longer stable as counts are small
```

```
## [1] 10  9  1
```

```
## [1] 0.060402685 0.001175088
```

Real-life ROC curves, e.g.



Algorithms	Test AUC	Test Accuracy
Decision Tree	50.9%	54.2%
Naïve Bayes	60.7%	57.0%
Random Forest	63.6%	58.3%
ADABoost	64.4%	59.5%
Gradient Boosting	65.1%	60.2%
SVM	65.6%	60.8%
Logistic Regression	66.5%	60.1%
DNN	67.4%	62.8%

Figure 3 of Badre et al. (2021). *Journal of Human Genetics*. Deep neural network improves the estimation of polygenic risk scores for breast cancer.

N.B. The classical logistic regression is competitive!

Because,

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

- 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's next: HOW to construct $\mathbf{PRS_{practice}}$ and do it CORRECTLY!

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

- the multiple hypothesis testing issue inherent in GWAS
- the (high) variability inherent in $\hat{\beta}$, the β estimates
- heritability h^2 as a function of both β and MAF
- the 'genetic effect size' of a SNP $= \beta^2 \cdot \text{MAF} \cdot (1 - \text{MAF})$
- a conceptual PRS construction based on the ground truth, PRS.oracle
- DIY ROC plotting and AUC calculation for a PRS-based prediction

What's next: How to construct $PRS_{practice}$ and do it correctly and compare results using different α level.