Polygenic Risk Score (PRS) Introduction 501

LD and Concluding Remarks

Drs. Lei Sun, Wei Deng, Yanyan Zhao

Department of Statistical Sciences, FAS

Division of Biostatistics, DLSPH

University of Toronto

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At the end of this lecture, some basic understanding of our **limited understanding of LD**

- No heterogeneity between ex.data and my.data.
- Only SNPs in perfect LD, $r^2 = 1$, and
- But vary the number tagging SNPs
- No allelic heterogeneity, and
- No multiple causual SNPs within a locus.

First

Live Final Quiz 8

Adding two perfectly tagging SNPs to each of the 10 causal SNP, the AUC of PRS.gw will

A: decrease
B: increase
C: ~same
D: identical

Recall the baseline model without any heterogeneity

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

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

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

```
# external data
ex.nsnp.true=10; ex.beta.true=0.3
ex.nsnp=5000; ex.nsample=1000; ex.sigma=1; ex.seed=101
ex.sumstat=generate.ex.sumstat(ex.seed,ex.nsample,ex.nsnp,ex.nsnp.true,ex.beta.true,ex.sigma)

# my data
my.nsnp.true=10; my.beta.true=0.3; my.maf=ex.sumstat[,"MAF"]
my.nsnp=5000; my.nsample=1000; my.sigma=1; my.seed=102
my.data=generate.my.data(my.seed,my.nsample,my.nsnp,my.nsnp.true,my.beta.true,my.sigma,my.maf)
```

Total and SNP h^2 of the external model

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

```
##  [1] 0.023 0.009 0.032 0.031 0.019 0.021 0.029 0.022 0.030 0.028
```

The index of the six 'genome-wide' significant ones

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

Total and SNP h^2 of my model

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

```
##  [1] 0.023 0.009 0.032 0.031 0.019 0.021 0.029 0.022 0.030 0.028
```

Recall the different $PRS_i = \sum_{j=1}^{J} \hat{\beta}_j G_{ij}$

Using the GW threshold on the external data

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

Using $\alpha = 0.01$ (and also add $\alpha = 0.1$) on the external data

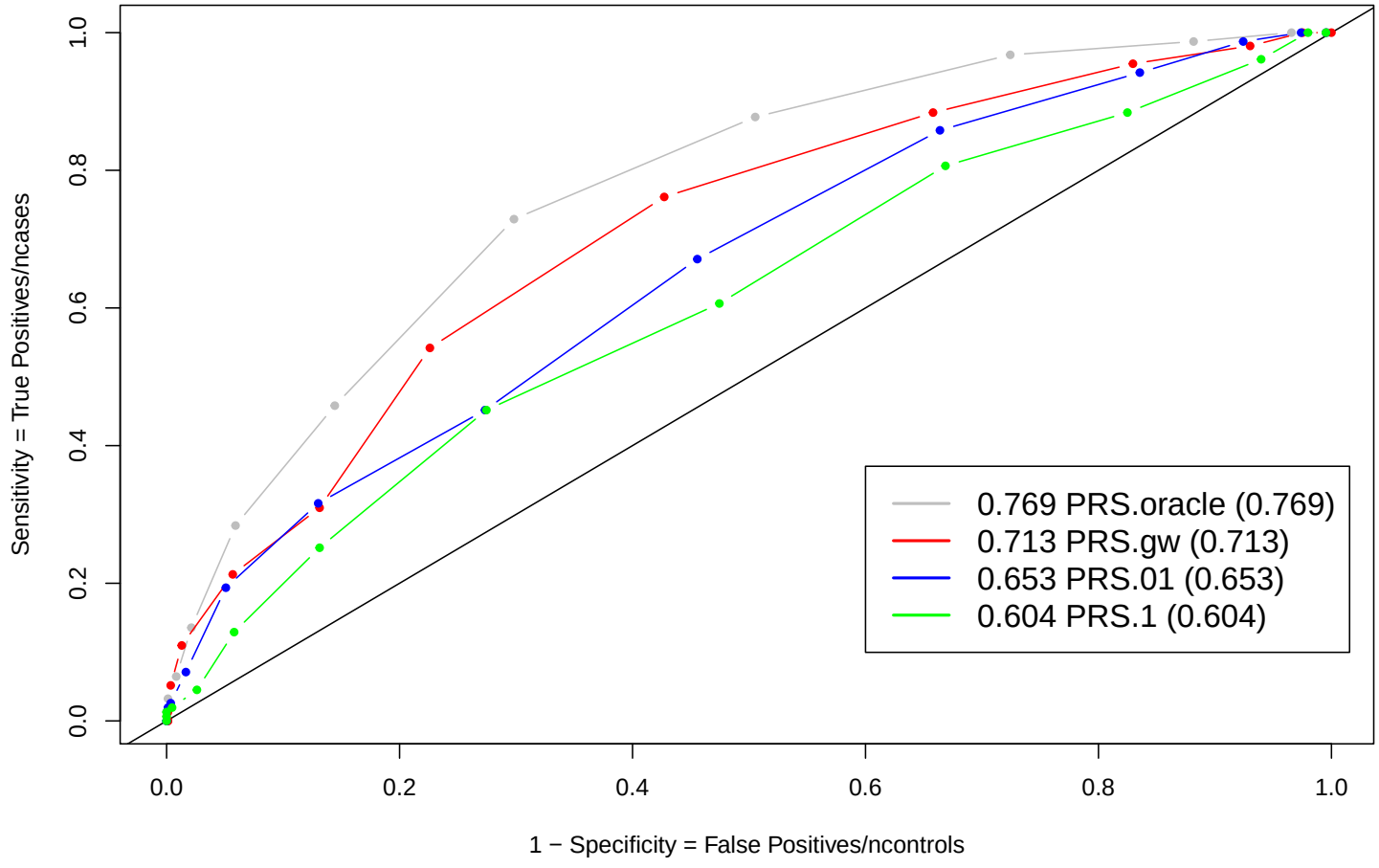
$$my.PRS_{.01} \text{ (or } my.PRS_{.1}) = \sum_{j=1}^{66 \text{ (or } 492)} \hat{\beta}_j^{external} \times G_{ij}^{my.data}$$

The oracle one (benchmarking the upper bound)

$$my.PRS_{oracle} = \sum_{j=1}^{10} 0.3 \times G_{ij}^{my.data}$$

The baseline model ROC and AUC

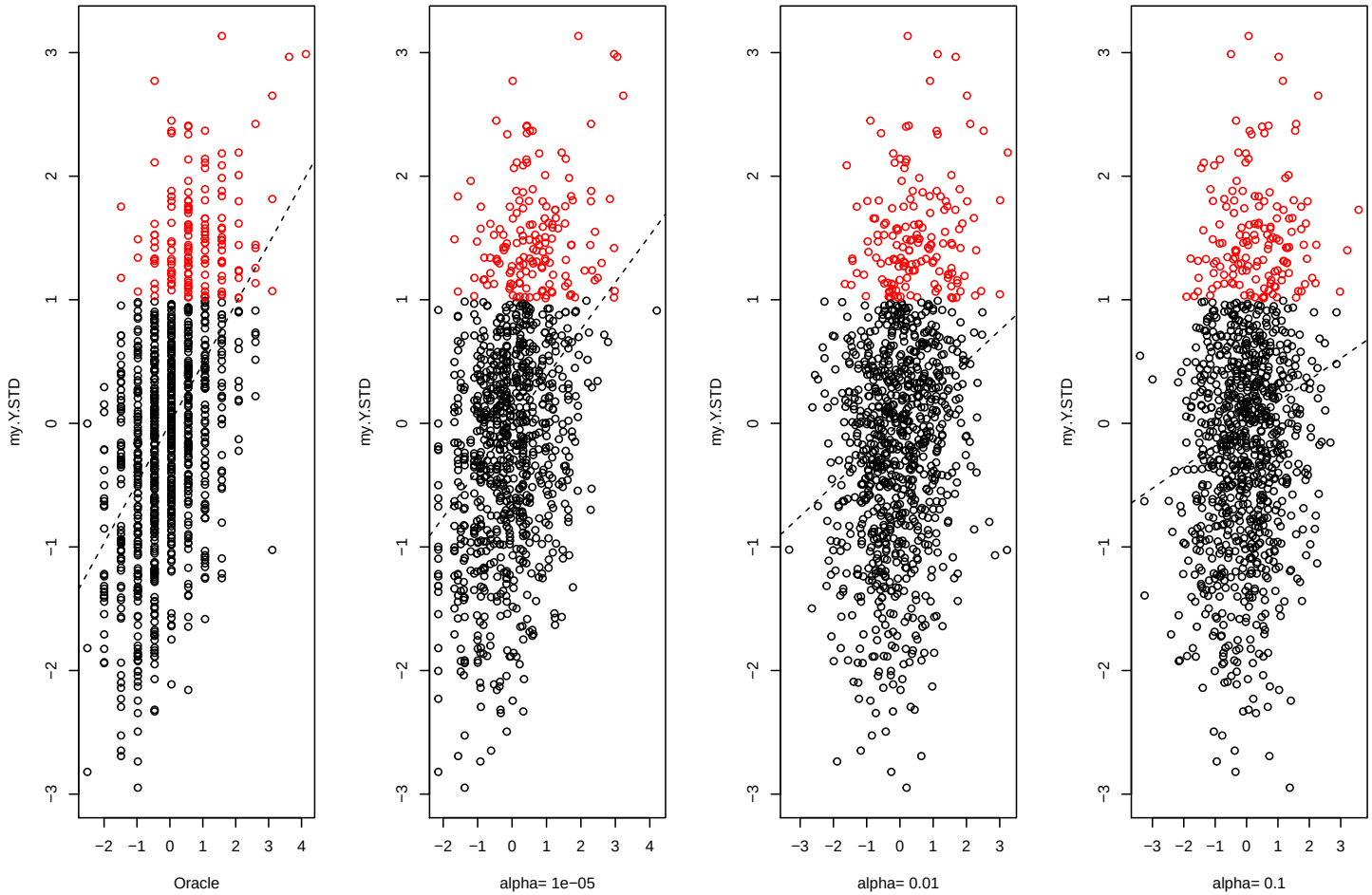
```
# generate the ROC plots
my.PRS.output=generate.my.PRS.output(ex.sumstat,my.data,alpha.level,l.threshold)
generate.ROC.plot(my.PRS.output)
```




```
##       alpha   J TP  FP
## [1,] 1e-05   6  6   0
## [2,] 1e-02  66 10  56
## [3,] 1e-01 492 10 482
```

the baseline model

```
generate.association.plot(my.PRS.output)
```




```
##      [,1]                [,2]          [,3]          [,4]          [,5]
## [1,] "slope.hat"         "0.484"       "0.38"        "0.251"       "0.175"
## [2,] "Z.value"           "17.467"      "12.983"      "8.185"       "5.628"
## [3,] "p.value"           "8.131e-60"   "1.001e-35"   "8.225e-16"   "2.364e-08"
## [4,] "n, case, control"  "1000"        "155"         "845"         " "
```

the baseline model

```
ex.sumstat[1:13,]
```

```
##              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
```

```
my.data$my.sumstat[1:13,]
```

```
##              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
```

Consider LD now

```
# First save the baseline noLD model results for later comparison
ex.nsnp.noLD=ex.nsnp
ex.sumstat.noLD=ex.sumstat
my.data.noLD=my.data
my.nsnp.noLD=my.nsnp
my.PRS.output.noLD=my.PRS.output

# Second, specify the ntag.T for each of the nsnp.true, start with 2 for each
# For now, no null SNPs are tagged, the extreme version of the assumption
# that `truly associated SNPs are more likely to be tagged than null SNPs'

# external data
ex.nsnp.true=10; ex.beta.true=0.3

# specify the ntag.T for each of the nsnp.true
ex.ntag.T=rep(2,ex.nsnp.true)
#ex.ntag.T=c(1,2,3,4,5,6,7,8,9,10)
#ex.ntag.T=c(10,9,8,7,6,5,4,3,2,1)
#ex.ntag.T=c(2,2,1,4,3,10,2,3,7,5)

ex.nsnp=(5000+sum(ex.ntag.T)); ex.nsample=1000; ex.sigma=1; ex.seed=101

# use a new LD-aware data and summary stat function
ex.sumstat=generate.ex.sumstat.LD(ex.seed,ex.nsample,ex.nsnp,ex.nsnp.true,ex.be
```

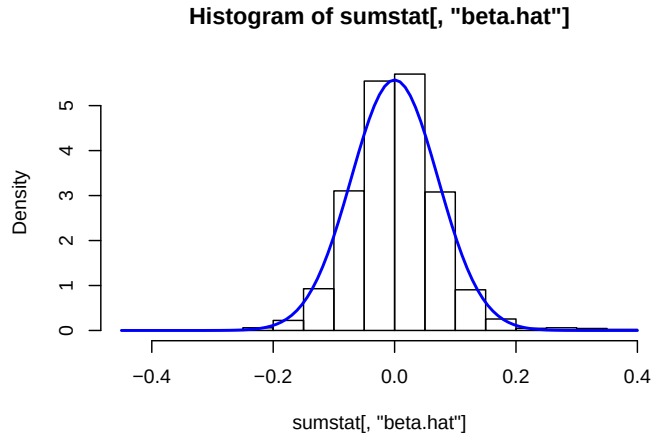
the LD

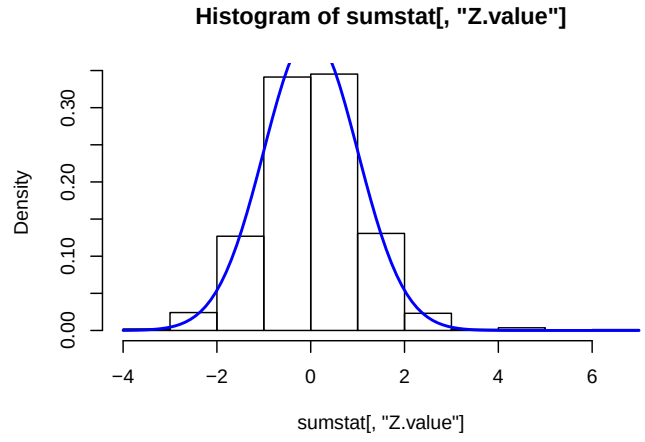
```
ex.sumstat[c(1:12,4999:ex.nsnp),]
```

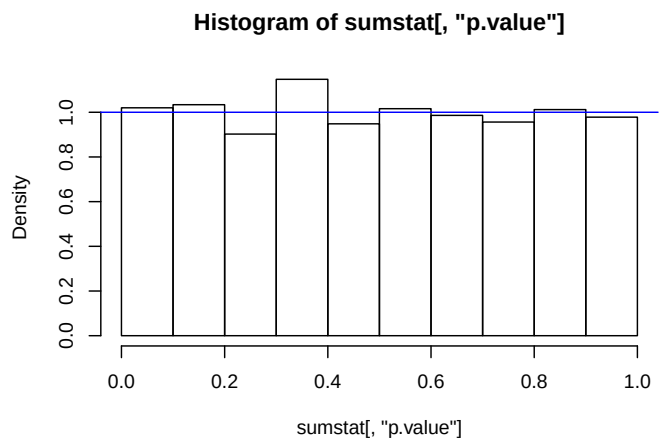
```
##              MAF MAF.hat beta    beta.hat         se    Z.value      p.value
##  [1,] 0.21748927  0.2215  0.3  0.29257288 0.06536792  4.4757871 8.489445e-06
##  [2,] 0.06972117  0.0610  0.3  0.33145758 0.10935747  3.0309551 2.500692e-03
##  [3,] 0.36935781  0.3780  0.3  0.23908858 0.05323916  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,] 0.37662575  0.3720  0.0  0.03703145 0.05527881  0.6699033 5.030744e-01
## [14,] 0.37629499  0.3815  0.0 -0.07125913 0.05474273 -1.3017095 1.933161e-01
## [15,] 0.21748927  0.2215  0.0  0.29257288 0.06536792  4.4757871 8.489445e-06
## [16,] 0.21748927  0.2215  0.0  0.29257288 0.06536792  4.4757871 8.489445e-06
## [17,] 0.06972117  0.0610  0.0  0.33145758 0.10935747  3.0309551 2.500692e-03
## [18,] 0.06972117  0.0610  0.0  0.33145758 0.10935747  3.0309551 2.500692e-03
## [19,] 0.36935781  0.3780  0.0  0.23908858 0.05323916  4.4908404 7.922031e-06
## [20,] 0.36935781  0.3780  0.0  0.23908858 0.05323916  4.4908404 7.922031e-06
## [21,] 0.34596068  0.3480  0.0  0.38889542 0.05565755  6.9872894 5.116550e-12
## [22,] 0.34596068  0.3480  0.0  0.38889542 0.05565755  6.9872894 5.116550e-12
## [23,] 0.16243508  0.1695  0.0  0.30892955 0.07052329  4.3805323 1.308960e-05
## [24,] 0.16243508  0.1695  0.0  0.30892955 0.07052329  4.3805323 1.308960e-05
## [25,] 0.18502467  0.1995  0.0  0.37606430 0.06503910  5.7821265 9.859505e-09
## [26,] 0.18502467  0.1995  0.0  0.37606430 0.06503910  5.7821265 9.859505e-09
## [27,] 0.31318998  0.3375  0.0  0.33166110 0.05410586  6.1298559 1.264930e-09
## [28,] 0.31318998  0.3375  0.0  0.33166110 0.05410586  6.1298559 1.264930e-09
## [29,] 0.20006021  0.2020  0.0  0.28159164 0.06670313  4.2215657 2.647447e-05
## [30,] 0.20006021  0.2020  0.0  0.28159164 0.06670313  4.2215657 2.647447e-05
## [31,] 0.32990538  0.3360  0.0  0.23025579 0.05661344  4.0671574 5.134017e-05
## [32,] 0.32990538  0.3360  0.0  0.23025579 0.05661344  4.0671574 5.134017e-05
## [33,] 0.29562285  0.2905  0.0  0.28906539 0.05841261  4.9486810 8.766086e-07
```

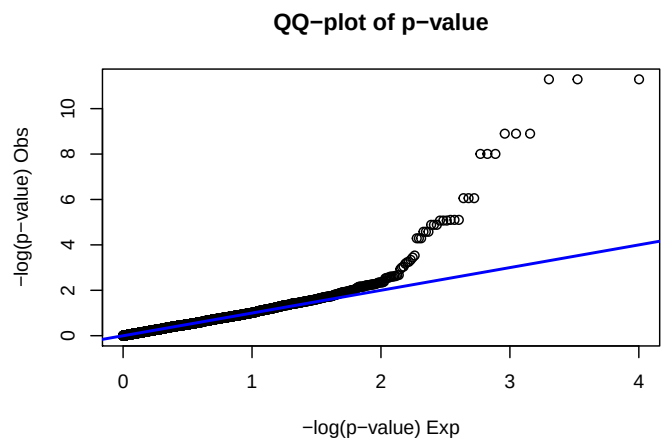
the LD ex.model, ntag.T=2

```
generate.sumstat.plot(ex.sumstat,ex.nsnp)
```



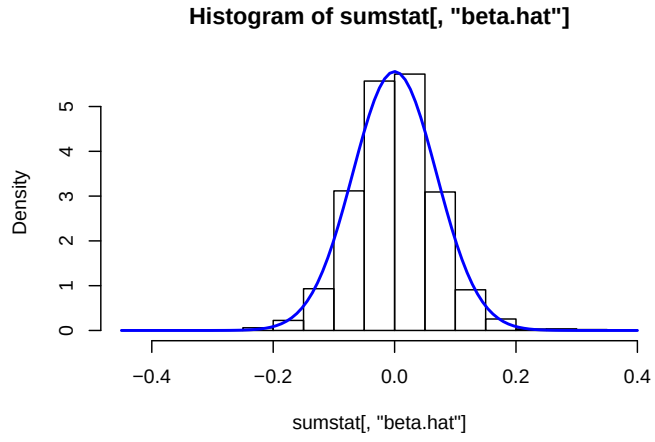


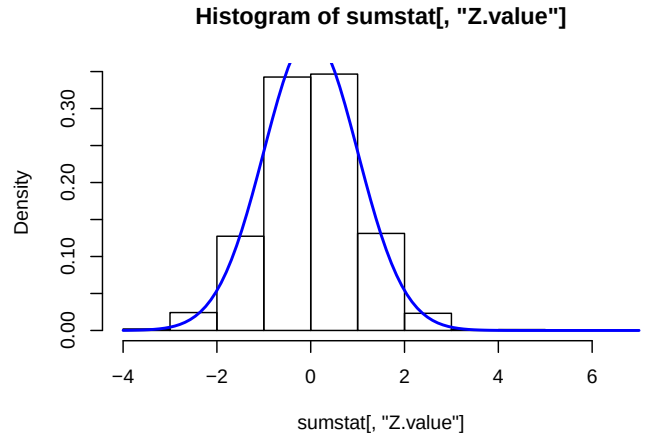


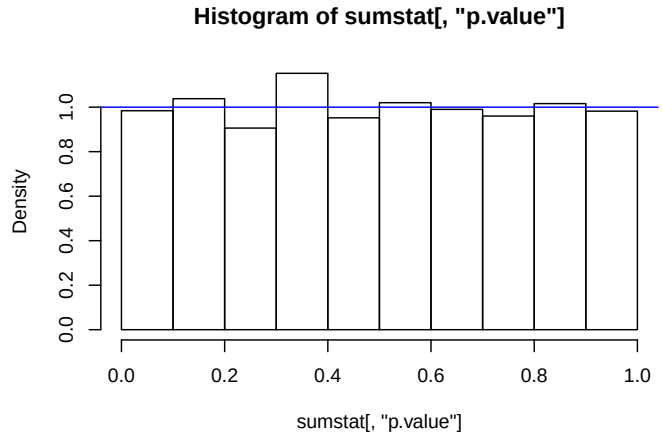


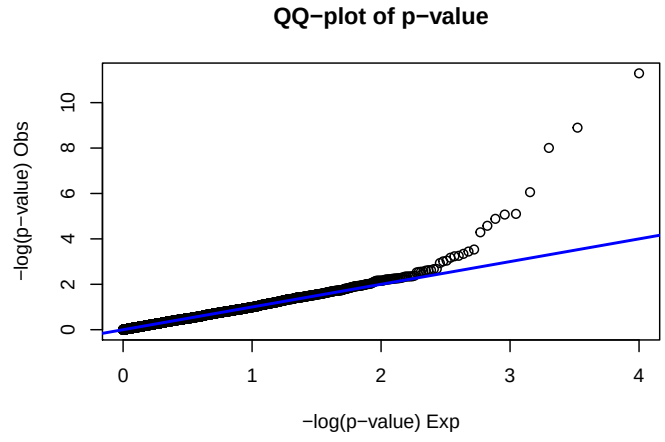
compare with no tagging ex.model

```
generate.sumstat.plot(ex.sumstat.noLD,ex.nsnp.noLD)
```









The true h^2 of our LD model should stay the same, because $\beta = 0$ for all the tagging SNPs.

GWAS-based estimates may be a different story!

Total and SNP h^2 of the ex.model

```
# the trait h2
V.G=sum(ex.sumstat[1:ex.nsnp.true,"beta"]^2*(2*ex.sumstat[1:ex.nsnp.true,"MAF"]*(1-ex.sumstat[1:ex.nsnp.tr
V.e=ex.sigma^2
round(V.G/(V.G+V.e),3)
```

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

```
# the causal ones
V.G.loci=ex.sumstat[1:ex.nsnp.true,"beta"]^2*(2*ex.sumstat[1:ex.nsnp.true,"MAF"]*(1-ex.sumstat[1:ex.nsnp.t
round(V.G.loci/(V.G+V.e),3)
```

```
##  [1] 0.023 0.009 0.032 0.031 0.019 0.021 0.029 0.022 0.030 0.028
```

```
# the tagging ones
V.G.loci=ex.sumstat[(ex.nsnp-sum(ex.ntag.T)+1):ex.nsnp,"beta"]^2*(2*ex.sumstat[(ex.nsnp-sum(ex.ntag.T)+1)
round(V.G.loci/(V.G+V.e),3)
```

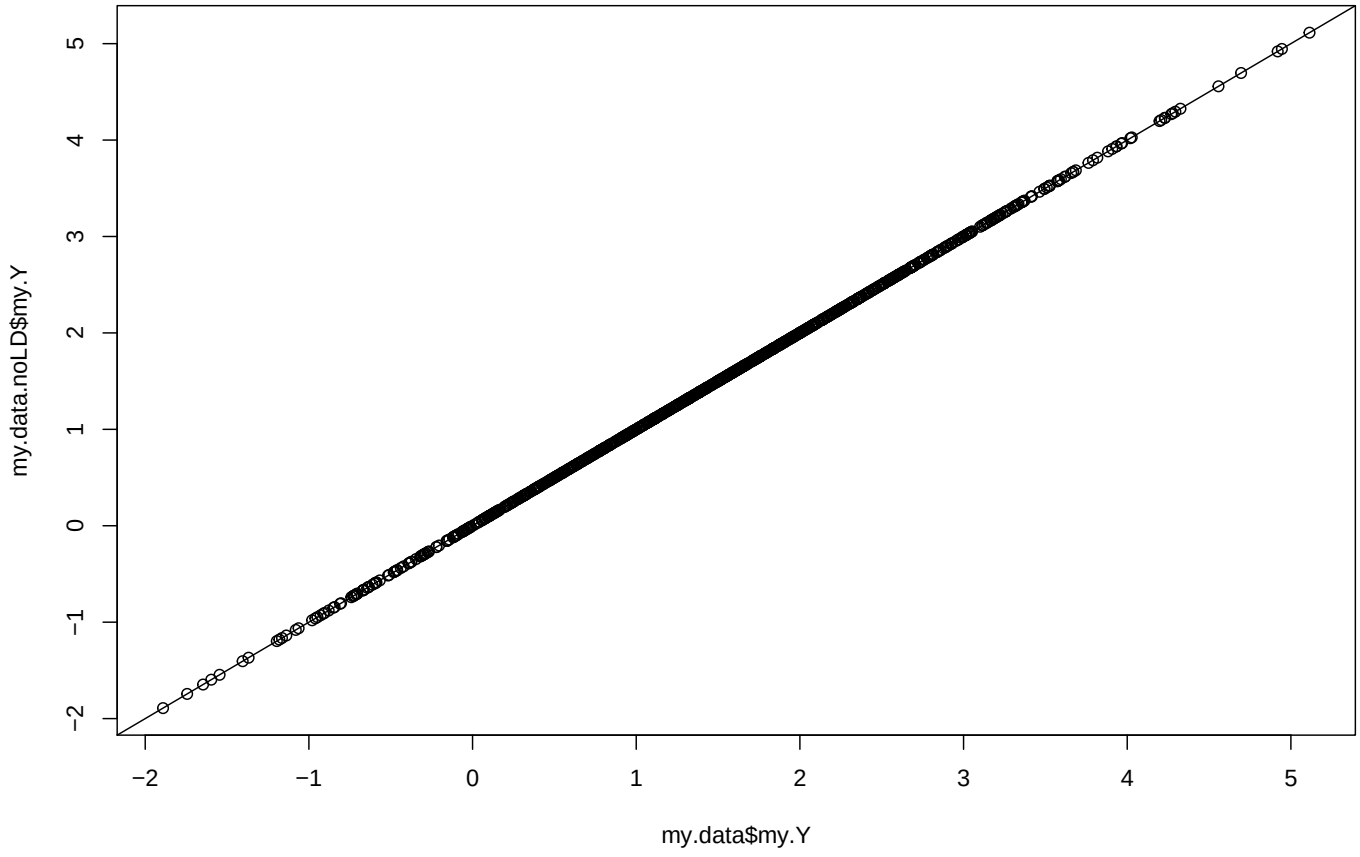
```
##  [1] 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

Move to my.data now

```
# my data

my.ntag.T=ex.ntag.T # SAME tagging; no heterogeneity between my. and ex.

my.nsnp.true=10; my.beta.true=0.3; my.maf=ex.sumstat[,"MAF"]
my.nsnp=(5000+sum(my.ntag.T)); my.nsample=1000; my.sigma=1; my.seed=102

my.data=generate.my.data.LD(my.seed,my.nsample,my.nsnp,my.nsnp.true,my.beta.true,my.sigma,my.maf,my.ntag.T
```

Checking our data: my.Y = my.Y.noLD (given the same seed etc.)

```
plot(my.data$my.Y,my.data.noLD$my.Y); abline(0,1)
```



Tagging SNPs have large GWAS Z and small p-values, but their true $\beta = 0$. Thus, they do not affect how we generate Y based on the true model.

(Multiple causal SNPs in LD is a different story!)

the LD

```
my.data$my.sumstat[c(1:12,4999:my.nsnp),]
```

```
##              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,] 0.37662575  0.3820  0.0 -0.02435158 0.05358273 -0.4544670 6.495915e-01
## [14,] 0.37629499  0.3780  0.0  0.01024406 0.05300796  0.1932551 8.467985e-01
## [15,] 0.21748927  0.3780  0.0  0.17164714 0.06066349  2.8294965 4.755586e-03
## [16,] 0.21748927  0.3780  0.0  0.17164714 0.06066349  2.8294965 4.755586e-03
## [17,] 0.06972117  0.3780  0.0  0.33447059 0.09604226  3.4825358 5.182232e-04
## [18,] 0.06972117  0.3780  0.0  0.33447059 0.09604226  3.4825358 5.182232e-04
## [19,] 0.36935781  0.3780  0.0  0.32234988 0.05230483  6.1629085 1.034940e-09
## [20,] 0.36935781  0.3780  0.0  0.32234988 0.05230483  6.1629085 1.034940e-09
## [21,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [22,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [23,] 0.16243508  0.3780  0.0  0.32262395 0.06958963  4.6360925 4.021553e-06
## [24,] 0.16243508  0.3780  0.0  0.32262395 0.06958963  4.6360925 4.021553e-06
## [25,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [26,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [27,] 0.31318998  0.3780  0.0  0.36190034 0.05517189  6.5595060 8.652840e-11
## [28,] 0.31318998  0.3780  0.0  0.36190034 0.05517189  6.5595060 8.652840e-11
## [29,] 0.20006021  0.3780  0.0  0.35342514 0.06681630  5.2895046 1.507249e-07
## [30,] 0.20006021  0.3780  0.0  0.35342514 0.06681630  5.2895046 1.507249e-07
## [31,] 0.32990538  0.3780  0.0  0.31052039 0.05197947  5.9739043 3.218822e-09
## [32,] 0.32990538  0.3780  0.0  0.31052039 0.05197947  5.9739043 3.218822e-09
## [33,] 0.29562285  0.3780  0.0  0.33840898 0.05429097  6.2332464 6.731015e-10
```

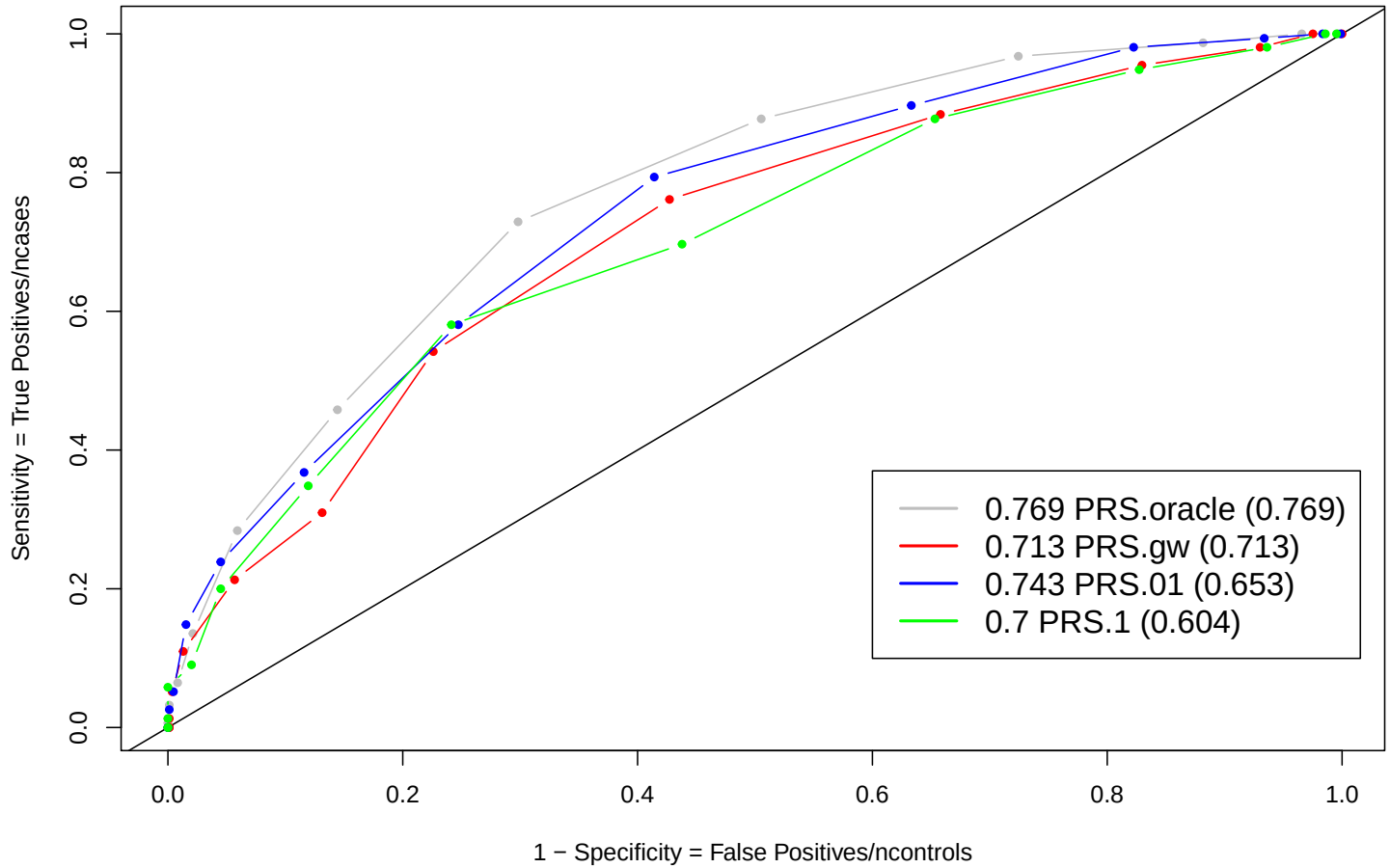
Move to PRS now

We can use the same PRS functions, as PRS construction only depend on ex.sumstat that, which were already generated and checked.

```
# Even the ex.nsnp is slightly bigger now, use the same alpha due to LD
alpha.level=c(0.00001,0.01,0.1)
l.threshold=1
```

the LD my.model, ntag.T=2

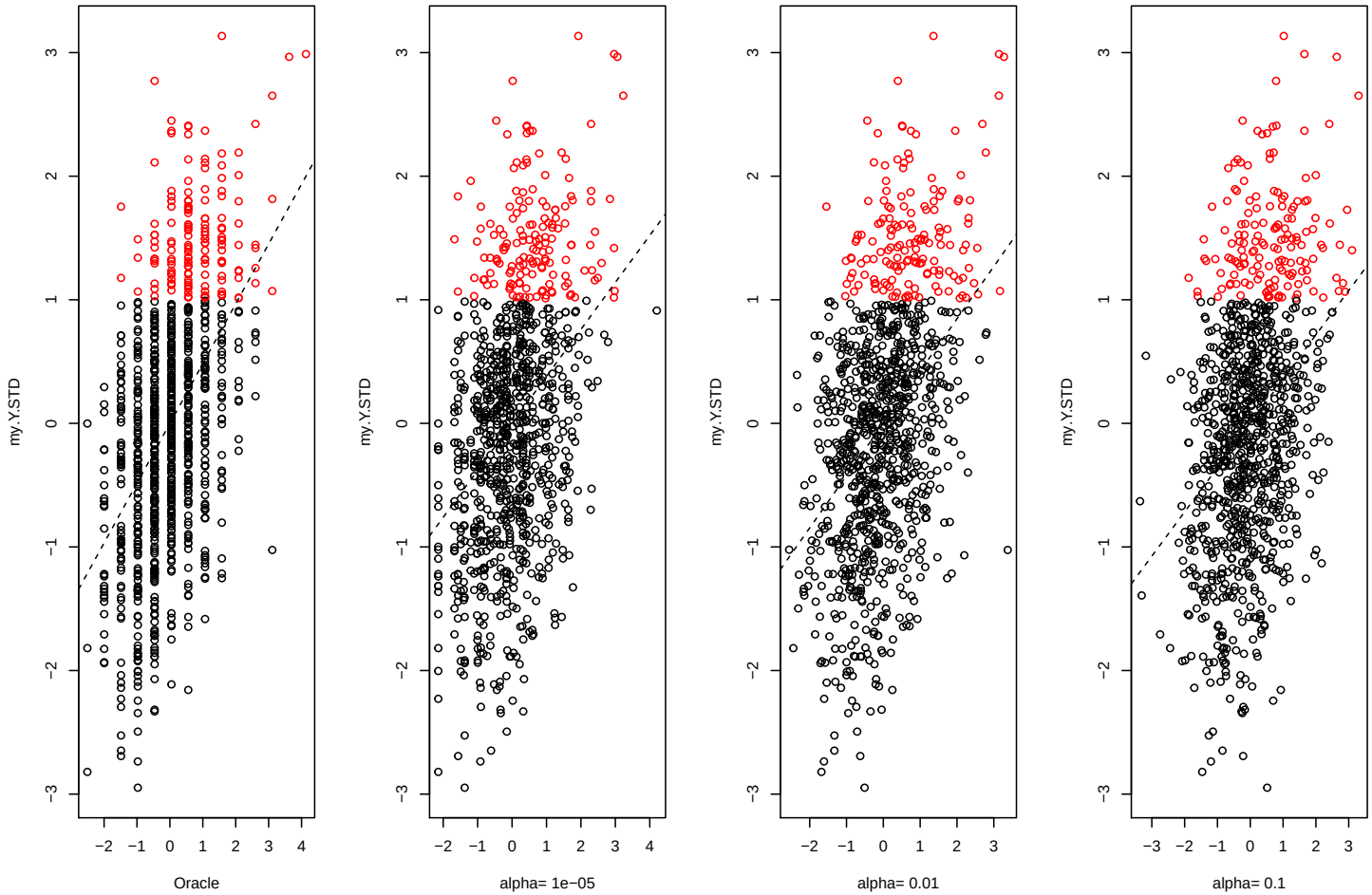
```
# generate the ROC plots
my.PRS.output=generate.my.PRS.output(ex.sumstat,my.data,alpha.level,l.threshold)
generate.ROC.plot(my.PRS.output)
```




```
##       alpha   J TP  FP
## [1,] 1e-05  18  6  12
## [2,] 1e-02  86 10  76
## [3,] 1e-01 512 10 502
```

the LD my.model, ntag.T=2

```
generate.association.plot(my.PRS.output)
```




```
##      [,1]                [,2]        [,3]         [,4]         [,5]
## [1,] "slope.hat"         "0.484"     "0.38"       "0.423"      "0.358"
## [2,] "Z.value"           "17.467"    "12.983"     "14.748"     "12.116"
## [3,] "p.value"           "8.131e-60" "1.001e-35" "1.111e-44" "1.27e-31"
## [4,] "n, case, control" "1000"      "155"        "845"        " "
```

Did we make a mistake?! Recall

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

When $r^2 = 1$ and $ntag.T = 2$ for all the causal SNPS:

$$PRS_i^{my.LD} = \sum_{j=1}^{J_{LD}} \hat{\beta}_j^{ex.LD} G_{ij}^{my.LD}$$

$$= 3 \times \sum_{j=1;TP}^{J_{noLD}} \hat{\beta}_j^{ex.noLD} G_{ij}^{my.noLD} + \sum_{j=1;FP}^{J_{noLD}} \hat{\beta}_j^{ex.noLD} G_{ij}^{my.noLD}$$

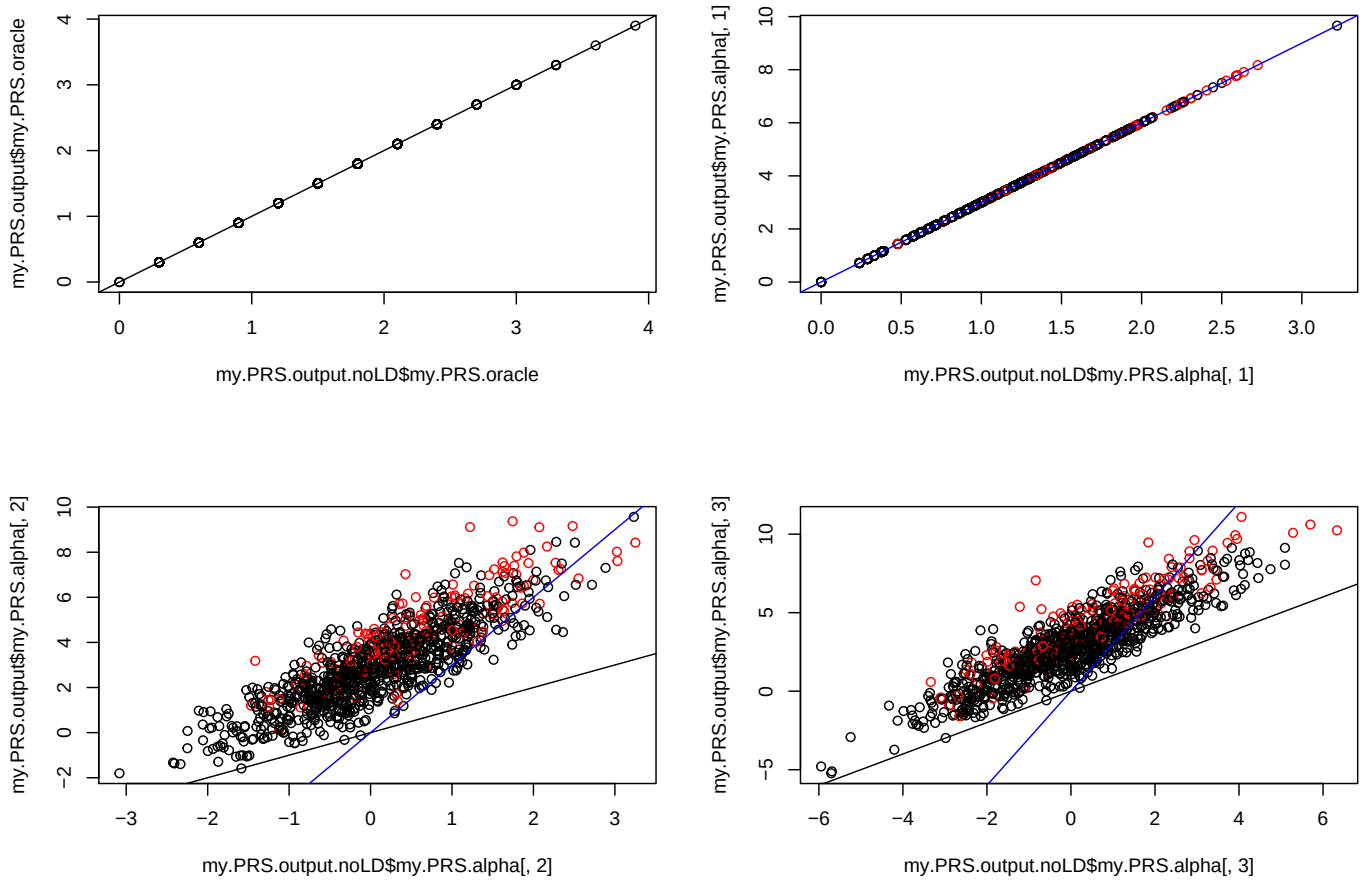
When FP=0

$$PRS_i^{my.LD} = 3 \times PRS_i^{my.noLD}$$

PRS.oracle should stay the same

$$PRS_{i,oracle}^{my.LD} = \sum_{j=1}^{J=10} \beta_j \cdot G_{ij}^{my.LD} = \sum_{j=1}^{J=10} \beta_j \cdot G_{ij}^{my.noLD} = PRS_{i,oracle}^{my.noLD}, \text{ where } \beta_j = 0.3$$

Check the NON-STD PRS data



In this simplest setting ($r^2 = 1$ and only causal SNPs are tagged), NOT adjusting LD '=' leveraging LD to improve performance!

Could consider different types of ntag.T, e.g.

```
# only one tagging SNP
# ex.ntag.T=rep(1,ex.nsnp.true)

# heterogeneity in the number of tagging SNPs
# ex.ntag.T=c(1,2,3,4,5,6,7,8,9,10)
# ex.ntag.T=c(10,9,8,7,6,5,4,3,2,1)
# ex.ntag.T=c(2,2,1,4,3,10,2,3,7,5)

# my.ntag.T=ex.ntag.T # SAME tagging; no heterogeneity between my. and ex.
```

Results are not drastically different, as expected, e.g.

```
# external data
ex.nsnp.true=10; ex.beta.true=0.3
# specify the ntag.T for each of the nsnp.true
ex.ntag.T=c(2,2,1,4,3,10,2,3,7,5)
ex.nsnp=(5000+sum(ex.ntag.T)); ex.nsample=1000; ex.sigma=1; ex.seed=101
ex.sumstat=generate.ex.sumstat.LD(ex.seed,ex.nsample,ex.nsnp,ex.nsnp.true,ex.beta.true,ex.sigma,ex.ntag.T)

# my data
my.ntag.T=ex.ntag.T # SAME tagging; no heterogeneity between my. and ex.
my.nsnp.true=10; my.beta.true=0.3; my.maf=ex.sumstat[,"MAF"]
my.nsnp=(5000+sum(my.ntag.T)); my.nsample=1000; my.sigma=1; my.seed=102
my.data=generate.my.data.LD(my.seed,my.nsample,my.nsnp,my.nsnp.true,my.beta.true,my.sigma,my.maf,my.ntag.T
```

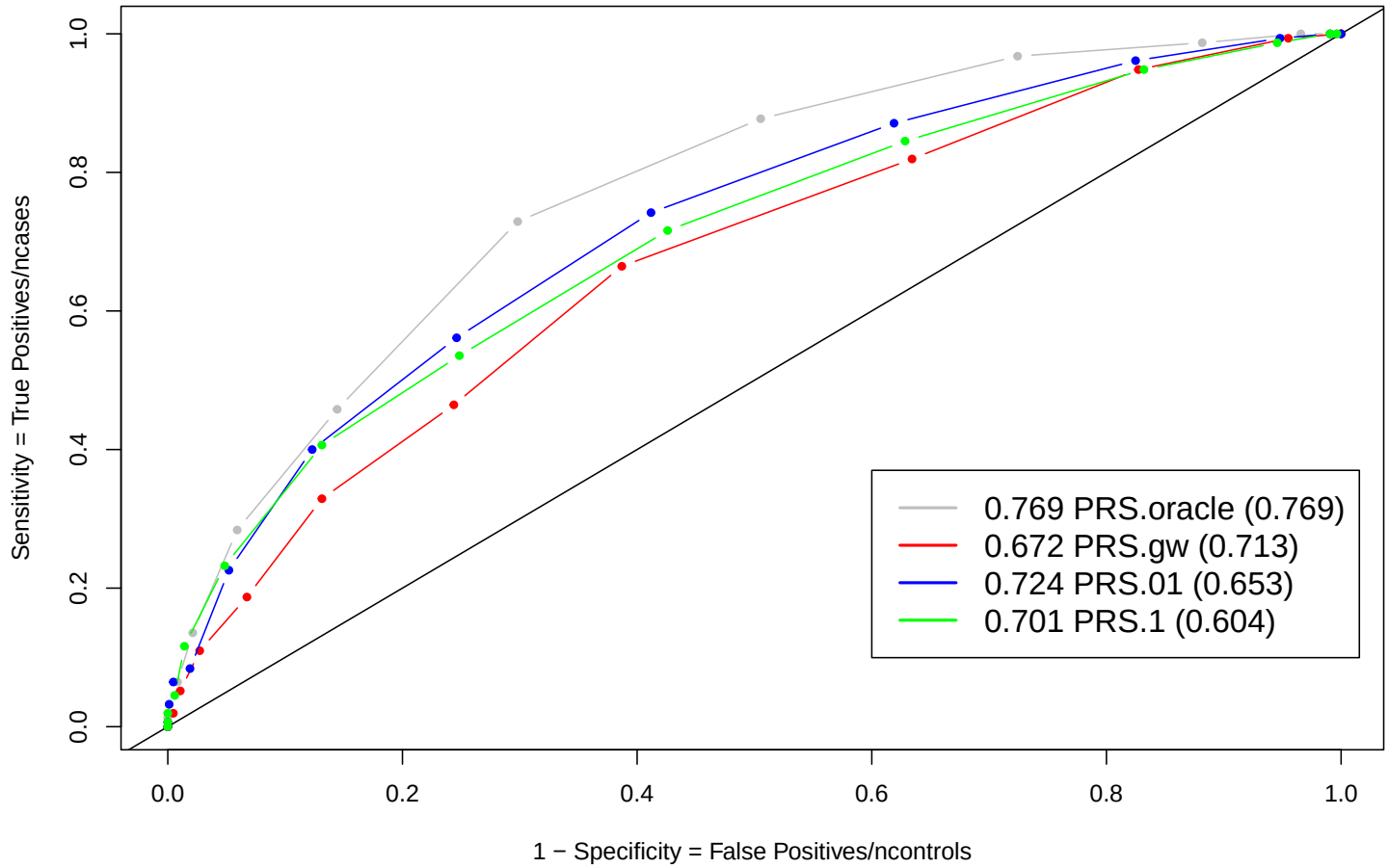
the LD

```
my.data$my.sumstat[c(1:12,4999:my.nsnp),]
```

```
##              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,] 0.37662575  0.3820  0.0 -0.02435158 0.05358273 -0.4544670 6.495915e-01
## [14,] 0.37629499  0.3780  0.0  0.01024406 0.05300796  0.1932551 8.467985e-01
## [15,] 0.21748927  0.3780  0.0  0.17164714 0.06066349  2.8294965 4.755586e-03
## [16,] 0.21748927  0.3780  0.0  0.17164714 0.06066349  2.8294965 4.755586e-03
## [17,] 0.06972117  0.3780  0.0  0.33447059 0.09604226  3.4825358 5.182232e-04
## [18,] 0.06972117  0.3780  0.0  0.33447059 0.09604226  3.4825358 5.182232e-04
## [19,] 0.36935781  0.3780  0.0  0.32234988 0.05230483  6.1629085 1.034940e-09
## [20,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [21,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [22,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [23,] 0.34596068  0.3780  0.0  0.25019642 0.05335395  4.6893703 3.121234e-06
## [24,] 0.16243508  0.3780  0.0  0.32262395 0.06958963  4.6360925 4.021553e-06
## [25,] 0.16243508  0.3780  0.0  0.32262395 0.06958963  4.6360925 4.021553e-06
## [26,] 0.16243508  0.3780  0.0  0.32262395 0.06958963  4.6360925 4.021553e-06
## [27,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [28,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [29,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [30,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [31,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [32,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
## [33,] 0.18502467  0.3780  0.0  0.28017270 0.06679596  4.1944557 2.978552e-05
```

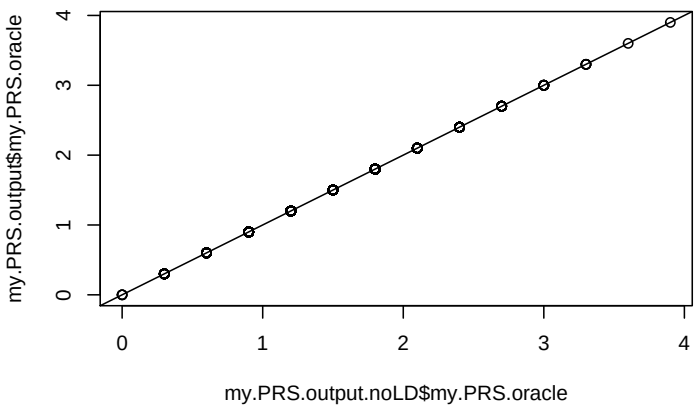
the LD my.model, ntag.T=c(2,2,1,4,3,10,2,3,7,5)

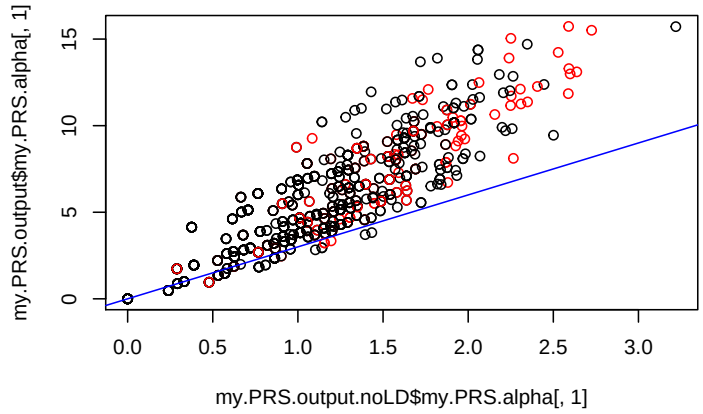
```
# generate the ROC plots
my.PRS.output=generate.my.PRS.output(ex.sumstat,my.data,alpha.level,l.threshold)
generate.ROC.plot(my.PRS.output)
```

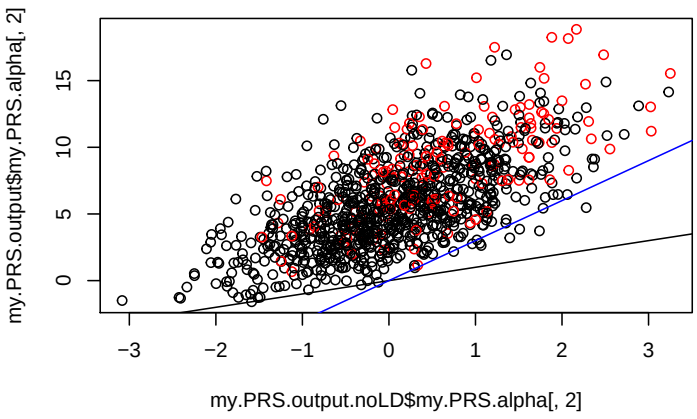


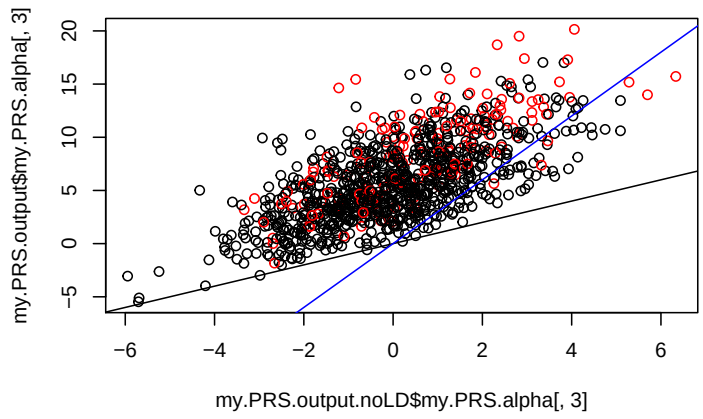

```
##      alpha   J TP  FP
## [1,] 1e-05  30  6  24
## [2,] 1e-02 105 10  95
## [3,] 1e-01 531 10 521
```

the LD my.model, ntag.T=c(2,2,1,4,3,10,2,3,7,5)









The effect of adding ntag.F for null SNPs?

To do... Educated guess:

- AUC stays the same if ntag.T $=$ ntag.F
- AUC drops if ntag.T $\neq$ ntag.F
- AUC drops more significantly if ntag.T $<$ ntag.F
- AUC drops more significantly for less stringent alpha

Some models/methods not discussed

- GxG and GxE interactions
- Bayesian methods
- Rare variants
- The X chromosome
- Pitfalls of standardization (how do we define a case in practice?)
- Many more...

Recap of the learning goal: a **deeper** understanding of

1. **PRS foundation: GWAS, h2 and prediction**
   - the multiple hypothesis testing issue inherent in GWAS
   - the (high) variability inherent in the h2 estimates
   - h2 as a function of both genetic effect beta and MAF
   - the 'genetic effect size' of a SNP as a function of beta and MAF
   - a conceptual PRS construction based on the ground truth, PRS.oracle
   - DIY ROC plotting and AUC calculation for a PRS-based prediction

2. **PRS basic: PRS calculation and performance evaluation**
   - the complexity of constructing a good PRS even under the simplest setting without LD or any heterogeneities; 10 out 5000 independent SNPs are truly associated with the same effect size of 0.3 but varying MAFs.
   - 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 'genome-wide' significant SNPs vs. 66 SNPs significant at 0.01.
   - the various over-fitting or selection biases, and winner's curse in beta estimates for both false positives and true positives.

Learning goal Cont'd, a **deeper** understanding of

3. **PRS basic-plus: some obvious or not so obvious follow-up Qs**
   - 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?

4. **PRS heterogeneity and transportability**
   - First, why reference allele (genome build) matching is so consequential
   - Then, population and locus heterogeneity including
     my.maf $\neq$ ex.maf
     my.beta.true $\neq$ ex.beta.true
     my.nsnp.true $\neq$ ex.nsnp.true

5. **PRS LD consideration**
   - Some basic understanding of our **limited understanding of LD**.

End of the (hopefully fun) ride!