

# Package ‘PRSPGx’

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**Type** Package

**Title** Construct PGx PRS

**Version** 0.1.0

**Maintainer** Song Zhai <zs violet1993@gmail.com>

**Description** Construct pharmacogenomics (PGx) polygenic risk score (PRS) with PRS-PGx-Unadj (unadjusted), PRS-PGx-CT (clumping and thresholding), PRS-PGx-L, -GL, -SGL (penalized regression), PRS-PGx-Bayes (Bayesian regression). Package is based on "Pharmacogenomics Polygenic Risk Score for Drug Response Prediction Using PRS-PGx Methods" by Zhai, S., Zhang, H., Mehrotra, D.V., and Shen, J., 2021 (submitted).

**License** GPL (>= 2)

**Depends** R (>= 4.0.0)

**Imports** gglasso (>= 1.5.0), SGL (>= 1.3.0), glmnet (>= 4.0.2), bigsnpr (>= 1.5.2), Matrix (>= 1.2.18), GIGrvg (>= 0.5.0), MCMCpack (>= 1.4.6), bdsmatrix (>= 1.3.4), bigsparser (>= 0.4.0), lmtest (>= 0.9.37), mvtnorm (>= 1.1.0), propagate (>= 1.0.6), bigparallelr (>= 0.2.3), methods (>= 3.6.3), bigstatsr (>= 1.2.3)

**Suggests** knitr, rmarkdown

**VignetteBuilder** knitr

**Encoding** UTF-8

**LazyData** true

**RoxygenNote** 7.1.1

**NeedsCompilation** yes

**Author** Song Zhai [aut, cre]

**Repository** CRAN

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PRSPGx.example	<i>Simulated example data</i>
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### Description

Simulated example data required by PRS-DIS and PRS-PGx functions.

### Usage

```
data(PRSPGx.example)
```

### Format

A list with 8 sublists:

**PGx\_GWAS** PGx GWAS including SNP ID, MAF, position,  $\beta$ ,  $\alpha$ , 2-df p-value, and N; SD(Y), and mean(T)

**DIS\_GWAS** disease GWAS including SNP ID, MAF, position,  $\beta$ ,  $SE(\beta)$ , p-value, and N

**G\_reference** simulated individual-level genotype from the reference panel matched with the simulated sample PGx genotype

**Y** simulated phenotype (continuous)

**T** simulated treatment assignment, 1 = treatment, 0 = placebo

**G** simulated sample PGx genotype with 100 SNPs and 4000 subjects

**beta** simulated prognostic effect sizes (i.e., the underlying true prognostic effect sizes)

**alpha** simulated predictive effect sizes (i.e., the underlying true predictive effect sizes)

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PRS_Dis_CT	<i>Construct disease PRS unadjusted or using clumping and thresholding</i>
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### Description

Shrink prognostic effect sizes by p-value cutoff (PRS-Dis-CT turns out to be PRS-Dis-Unadj when setting p-value cutoff = 1)

**Usage**

```
PRs_Dis_CT(  
  DIS_GWAS,  
  G_reference,  
  pcutoff = 1e-05,  
  clumping = TRUE,  
  p1 = 1e-04,  
  d1 = 250000,  
  r1 = 0.8  
)
```

**Arguments**

DIS_GWAS	a numeric matrix containing disease GWAS summary statistics, including SNP ID, position, $\beta$ , $SE(\beta)$ , p-value, N, and MAF
G_reference	a numeric matrix containing the individual-level genotype information from the reference panel (e.g., 1KG)
pcutoff	a numeric value indicating the p-value cutoff
clumping	a logical flag indicating should clumping be performed
p1	a numeric value indicating p-value threshold to decide flag SNPs in clumping
d1	a numeric value indicating window size in clumping
r1	a numeric value indicating correlation in clumping

**Details**

PRs-Dis-CT automatically sets predictive effect sizes equivalent to the prognostic effect sizes; and only need disease GWAS summary statistics

**Value**

A numeric list, the first sublist contains estimated prognostic effect sizes, the second sublist contains estimated predictive effect sizes

**Author(s)**

Song Zhai

**References**

- Euesden, J., Lewis, C.M. & O'Reilly, P.F. PRSice: Polygenic Risk Score software. *Bioinformatics* 564, 1466-1468 (2015).
- Zhai, S., Zhang, H., Mehrotra, D.V. & Shen, J. Paradigm Shift from Disease PRS to PGx PRS for Drug Response Prediction using PRS-PGx Methods (submitted).

**Examples**

```
data(PRSPGx.example); attach(PRSPGx.example)
coef_est <- PRS_Dis_CT(DIS_GWAS, G_reference, pcutoff = 0.01, clumping = TRUE)
summary(coef_est$coef.G)
summary(coef_est$coef.TG)
```

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 PRS\_Dis\_LDpred2

*Construct disease PRS using LDpred2*


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**Description**

Using `snp_ldpred2_grid` function from `bigsnpr` function

**Usage**

```
PRS_Dis_LDpred2(DIS_GWAS, G_reference, pcausal, h2)
```

**Arguments**

DIS_GWAS	a numeric matrix containing disease GWAS summary statistics, including SNP ID, position, $\beta$ , $SE(\beta)$ , p-value, N, and MAF
G_reference	a numeric matrix containing the individual-level genotype information from the reference panel (e.g., 1KG)
pcausal	a numeric value indicating the hyper-parameter as the proportion of causal variants
h2	a numeric value indicating the estimated heritability

**Details**

PRS-Dis-LDpred2 automatically sets predictive effect sizes equivalent to the prognostic effect sizes; and only need disease GWAS summary statistics and external reference genotype

**Value**

A numeric list, the first sublist contains estimated prognostic effect sizes, the second sublist contains estimated predictive effect sizes

**Author(s)**

Song Zhai

**References**

Prive, F., Arbel, J. & Vilhjalmsson, B.J. LDpred2: better, faster, stronger. *Bioinformatics* 36, 5424-5431 (2020).

Zhai, S., Zhang, H., Mehrotra, D.V. & Shen, J. Paradigm Shift from Disease PRS to PGx PRS for Drug Response Prediction using PRS-PGx Methods (submitted).

**Examples**

```
data(PRSPGx.example); attach(PRSPGx.example)
coef_est <- PRS_Dis_LDpred2(DIS_GWAS, G_reference, pcausal = 0.1, h2 = 0.4)
summary(coef_est$coef.G)
summary(coef_est$coef.TG)
```

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PRSPGx\_Bayes

*Construct PGx PRS using Bayesian regression*


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**Description**

Flexibly shrink prognostic and predictive effect sizes simultaneously with global-local shrinkage parameters

**Usage**

```
PRS_PGx_Bayes(
  PGx_GWAS,
  G_reference,
  n.itr = 1000,
  n.burnin = 500,
  n.gap = 10,
  paras,
  standardize = TRUE
)
```

**Arguments**

PGx_GWAS	a numeric list containing PGx GWAS summary statistics (with SNP ID, position, $\beta$ , $\alpha$ , 2-df p-value, MAF and N), $SD(Y)$ , and $mean(T)$
G_reference	a numeric matrix containing the individual-level genotype information from the reference panel (e.g., 1KG)
n.itr	a numeric value indicating the total number of MCMC iteration
n.burnin	a numeric value indicating the number of burn in
n.gap	a numeric value indicating the MCMC gap
paras	a numeric vector containing hyper-parameters $(v, \phi)$
standardize	a logical flag indicating should phenotype and genotype be standardized

**Details**

PRS-PGx-Bayes only needs PGx summary statistics and external reference genotype

**Value**

A numeric list, the first sublist contains estimated prognostic effect sizes, the second sublist contains estimated predictive effect sizes

**Author(s)**

Song Zhai

**References**

Ge, T., Chen, CY., Ni, Y. et al. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* 10, 1776 (2019).

Zhai, S., Zhang, H., Mehrotra, D.V. & Shen, J. Paradigm Shift from Disease PRS to PGx PRS for Drug Response Prediction using PRS-PGx Methods (submitted).

**Examples**

```
data(PRSPGx.example); attach(PRSPGx.example)
paras = c(3, 5)
coef_est <- PRS_PGx_Bayes(PGx_GWAS, G_reference, paras = paras)
summary(coef_est$coef.G)
summary(coef_est$coef.TG)
```

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PRS\_PGx\_CT

*Construct PGx PRS unadjusted or using clumping and thresholding*

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**Description**

Shrink prognostic and predictive effect sizes simultaneously by 2-df (main and interaction) p-value cutoff (PRS-PGx-CT turns out to be PRS-PGx-Unadj when setting p-value cutoff = 1)

**Usage**

```
PRS_PGx_CT(
  PGx_GWAS,
  G_reference,
  pcutoff = 1e-04,
  clumping = TRUE,
  p1 = 1e-04,
  d1 = 250000,
  r1 = 0.8
)
```

**Arguments**

PGx_GWAS	a numeric matrix containing PGx GWAS summary statistics, including SNP ID, MAF, position, $\beta$ , $\alpha$ , 2-df p-value, and N
G_reference	a numeric matrix containing the individual-level genotype information from the reference panel (e.g., 1KG)
pcutoff	a numeric value indicating the p-value cutoff
clumping	a logical flag indicating should clumping be performed
p1	a numeric value indicating p-value threshold to decide flag SNPs in clumping
d1	a numeric value indicating window size in clumping
r1	a numeric value indicating correlation in clumping

**Details**

PRS-PGx-CT only needs PGx summary statistics

**Value**

A numeric list, the first sublist contains estimated prognostic effect sizes, the second sublist contains estimated predictive effect sizes, the third sublist contains 2-df p-values

**Author(s)**

Song Zhai

**References**

Zhai, S., Zhang, H., Mehrotra, D.V. & Shen, J. Paradigm Shift from Disease PRS to PGx PRS for Drug Response Prediction using PRS-PGx Methods (submitted).

**Examples**

```
data(PRSPGx.example); attach(PRSPGx.example)
coef_est <- PRSPGx_CT(PGx_GWAS, G_reference, pcutoff = 0.01, clumping = TRUE)
summary(coef_est$coef.G)
summary(coef_est$coef.TG)
```

**Description**

Shrink prognostic and predictive effect sizes simultaneously via the penalized term. With different assumptions on the relationship between the two effects, can be PRS-PGx-L (Lasso), PRS-PGx-GL (Group Lasso), and PRS-PGx-SGL (Sparse Group Lasso)

**Usage**

```
PRS_PGx_Lasso(Y, Tr, G, intercept = TRUE, lambda, method, alpha = 0.5)
```

**Arguments**

Y	a numeric vector containing the quantitative trait
Tr	a numeric vector containing the treatment assignment
G	a numeric matrix containing genotype information
intercept	a logical flag indicating should intercept be fitted (default=TRUE) or set to be FALSE
lambda	a numeric value indicating the penalty
method	a logical flag for different penalized regression methods: 1 = PRS-PGx-L, 2 = PRS-PGx-GL, 3 = PRS-PGx-SGL
alpha	a numeric value indicating the mixing parameter (only used when method = 3). alpha = 1 is the lasso penalty. alpha = 0 is the group lasso penalty

**Details**

PRS-PGx-Lasso requires individual-level data

**Value**

A numeric list, the first sublist contains estimated prognostic effect sizes, the second sublist contains estimated predictive effect sizes

**Author(s)**

Song Zhai

**References**

Yang, Y. & Zou, H. A fast unified algorithm for solving group-lasso penalize learning problems. *Statistics and Computing* 25, 1129-1141 (2015).

Simon, N., Friedman, J., Hastie, T. & Tibshirani, R. Fit a GLM (or cox model) with a combination of lasso and group lasso regularization. *R package version, 1* (2015).

Zhai, S., Zhang, H., Mehrotra, D.V. & Shen, J. Paradigm Shift from Disease PRS to PGx PRS for Drug Response Prediction using PRS-PGx Methods (submitted).

**Examples**

```
data(PRSPGx.example); attach(PRSPGx.example)
coef_est <- PRS_PGx_Lasso(Y, Tr, G, lambda = 1, method = 1)
summary(coef_est$coef.G)
summary(coef_est$coef.TG)
```



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