

# Package ‘hierGWAS’

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**Title** Assessing statistical significance in predictive GWA studies

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**Description** Testing individual SNPs, as well as arbitrarily large groups of SNPs in GWA studies, using a joint model of all SNPs. The method controls the FWER, and provides an automatic, data-driven refinement of the SNP clusters to smaller groups or single markers.

**Depends** R (>= 3.2.0)

**License** GPL-3

**LazyData** true

**Imports** fastcluster,glmnet, fmsb

**Suggests** BiocGenerics, RUnit, MASS

**biocViews** SNP, LinkageDisequilibrium, Clustering

**Collate** 'cluster.snp.R' 'lasso.select.R' 'multisplit.R' 'MEL.R'  
'test.snp.R' 'adj.pval.R' 'comp.cluster.pval.R'  
'iterative.DFS.R' 'test.hierarchy.R' 'return.r2.R'  
'compute.r2.R'

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cluster.snp	<i>Hierarchical Clustering of SNP Data</i>
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**Description**

Clusters SNPs hierachically.

**Usage**

```
cluster.snp(x = NULL, d = NULL, method = "average", SNP_index = NULL)
```

**Arguments**

x	The SNP data matrix of size nobs x nvar. Default value is NULL
d	NULL or a dissimilarity matrix. See the 'Details' section.
method	The agglomeration method to be used. This should be (an unambiguous abbreviation of) one of "ward.D", "ward.D2", "single", "complete", "average" (= UPGMA), "mcquitty" (= WPGMA), "median" (= WPGMC) or "centroid" (= UPGMC). See <a href="#">hclust</a> for details.
SNP_index	NULL or the index vector of SNPs to be clustered. See the 'Details' section.

**Details**

The SNPs are clustered using [hclust](#), which performs a hierarchical cluster analysis using a set of dissimilarities for the nvar objects being clustered. There are 3 possible scenarios.

If d = NULL, x is used to compute the dissimilarity matrix. The dissimilarity measure between two SNPs is 1 - LD (Linkage Disequilibrium), where LD is defined as the square of the Pearson correlation coefficient. If SNP\_index = NULL, all nvar SNPs will be clustered; otherwise only the SNPs with indices specified by SNP\_index will be considered.

If the user wishes to use a different dissimilarity measure, d needs to be provided. d must be either a square matrix of size nvar x nvar, or an object of class [dist](#). If d is provided, x and SNP\_index will be ignored.

**Value**

An object of class [dendrogram](#) which describes the tree produced by the clustering algorithm [hclust](#).

**Examples**

```
library(MASS)
x <- mvrnorm(60,mu = rep(0,60), Sigma = diag(60))
clust.1 <- cluster.snp(x = x, method = "average")
SNP_index <- seq(1,10)
clust.2 <- cluster.snp(x = x, method = "average", SNP_index = SNP_index)
d <- dist(x)
clust.3 <- cluster.snp(d = d, method = "single")
```

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compute.r2	<i>R2 computation</i>
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**Description**

Calculates the R2 of a cluster of SNPs.

**Usage**

```
compute.r2(x, y, res.multisplit, covar = NULL, SNP_index = NULL)
```

**Arguments**

x	The input matrix, of dimension nob <sub>s</sub> x nvar. Each row represents a subject, each column a SNP.
y	The response vector. It can be continuous or discrete.
res.multisplit	The output of multisplit.
covar	NULL or the matrix of covariates one wishes to control for, of size nob <sub>s</sub> x ncov <sub>ar</sub> .
SNP_index	NULL or the index vector of the cluster of SNPs whose R2 will be computed. See the 'Details' section.

**Details**

The R2 of a cluster of SNPs is computed on the second half-samples. The cluster members, are intersected with the SNPs selected by the lasso, and the R2 of this model is calculated. Thus, we obtain B R2 values. Finally, the mean of these values is taken. If the value of SNP\_index is NULL, the R2 of the full model with all the SNPs will be computed.

**Value**

The R2 value of the SNP cluster

**References**

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies. (unpublished)

**Examples**

```
library(MASS)
x <- mvrnorm(60, mu = rep(0, 60), Sigma = diag(60))
beta <- rep(0, 60)
beta[c(5, 9, 3)] <- 1
y <- x %*% beta + rnorm(60)
SNP_index <- c(5, 9, 3)
res.multisplit <- multisplit(x, y)
r2 <- compute.r2(x, y, res.multisplit, SNP_index = SNP_index)
```

hierGWAS

*Assessing statistical significance in predictive GWA studies*

---

**Description**

Testing individual SNPs, as well as arbitrarily large groups of SNPs in GWA studies, using a joint model of all SNPs. The method controls the FWER, and provides an automatic, data-driven refinement of the SNP clusters to smaller groups or single markers.

**Details**

hierGWAS is a package designed to assess statistical significance in GWA studies, using a hierarchical approach.

There are 4 functions provided: `cluster.snp`, `multisplit`, `test.hierarchy` and `compute.r2`. `cluster.snp` performs the hierarchical clustering of the SNPs, while `multisplit` runs multiple penalized regressions on repeated random subsamples. These 2 functions need to be executed before `test.hierarchy`, which does the hierarchical testing, though the order in which the 2 functions are executed does not matter. `test.hierarchy` provides the final output of the method: a list of SNP groups or individual SNPs, along with their corresponding p-values. Finally, `compute.r2` computes the explained variance of an arbitrary group of SNPs, of any size. This group can encompass all SNPs, SNPs belonging to a certain chromosome, or an individual SNP.

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**References**

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies (unpublished)

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multisplit

*Variable Selection on Random Sample Splits.*

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**Description**

Performs repeated variable selection via the lasso on random sample splits.

**Usage**

```
multisplit(x, y, covar = NULL, B = 50)
```

**Arguments**

x	The SNP data matrix, of size nobs x nvar. Each row represents a subject, each column a SNP.
y	The response vector. It can be continuous or discrete.
covar	NULL or the matrix of covariates one wishes to control for, of size nobs x ncovar.
B	The number of random splits. Default value is 50.

**Details**

The samples are divided into two random splits of approximately equal size. The first subsample is used for variable selection, which is implemented using [glmnet](#). The first  $\lfloor \text{nobs}/6 \rfloor$  variables which enter the lasso path are selected. The procedure is repeated B times.

If one or more covariates are specified, these will be added unpenalized to the regression.

**Value**

A data frame with 2 components. A matrix of size  $B \times \lfloor \text{nobs}/2 \rfloor$  containing the second subsample of each split, and a matrix of size  $B \times \lfloor \text{nobs}/6 \rfloor$  containing the selected variables in each split.

**References**

Meinshausen, N., Meier, L. and Bühlmann, P. (2009), P-values for high-dimensional regression, *Journal of the American Statistical Association* 104, 1671-1681.

**Examples**

```
library(MASS)
x <- mvrnorm(60, mu = rep(0, 200), Sigma = diag(200))
beta <- rep(1, 200)
beta[c(5, 9, 3)] <- 3
y <- x %*% beta + rnorm(60)
res.multisplit <- multisplit(x, y)
```

---

simGWAS

*Simulated GWAS data*


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**Description**

This data set was simulated using PLINK. Please refer to the vignette for more details.

**Usage**

```
simGWAS
```

**Format**

The dataset contains the following components:

SNP.1 The first SNP, of dimension  $500 \times 1$ . Each row represents a subject.

...

SNP.1000 The last SNP, of dimension  $500 \times 1$ . Each row represents a subject.

y The response vector. It can be continuous or discrete.

sex The first covariate, representing the sex of the subjects: 0 for men and 1 for women.

age The second covariate, representing the age of the subjects.

**Value**

data.frame

**Examples**

```
data(simGWAS)
```

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test.hierarchy

*Hierarchical Testing of SNPs*

---

**Description**

Performs hierarchical testing of SNPs.

**Usage**

```
test.hierarchy(x, y, dendr, res.multisplit, covar = NULL, SNP_index = NULL,
  alpha = 0.05, global.test = TRUE, verbose = TRUE)
```

**Arguments**

x	The input matrix, of dimension $nobs \times nvar$ . Each row represents a subject, each column a SNP.
y	The response vector. It can be continuous or discrete.
dendr	The cluster tree obtained by hierchically clustering the SNPs using <code>cluster.snp</code> .
res.multisplit	The output of <code>multisplit</code> .
covar	NULL or the matrix of covariates one wishes to control for, of size $nobs \times ncover$ .
SNP_index	NULL or the index vector of SNP to be tested. See the 'Details' section.
alpha	The significance level at which the FWER is controlled. Default value is 0.05.
global.test	Specifies wether the global null hypothesis should be tested. Default value is TRUE. See the 'Details' section.
verbose	Report information on progress. Default value is TRUE

## Details

The testing is performed on the cluster tree given by `dendr`. If the SNP data matrix was divided (e.g. by chromosome), and clustered separately, the user must provide the argument `SNP_index`, to specify which part of the data is being tested.

Testing starts at the highest level, which includes all variables specified by `SNP_index`, and moves down the cluster tree. It stops when a cluster's null hypothesis cannot be rejected anymore. The smallest, still significant clusters will be returned.

By default the parameter `global.test = TRUE`, which means that first the global null hypothesis is tested. If the data is divided (e.g. by chromosome), and clustered separately, this parameter can be set to `FALSE` once the global null has been rejected. This helps save time.

## Value

A list of significant SNP groups with the following components:

<code>SNP_index</code>	The indices of the SNPs in the group
<code>pval</code>	The p-value of the SNP group

## References

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies

## Examples

```
library(MASS)
x <- mvrnorm(60, mu = rep(0, 60), Sigma = diag(60))
beta <- rep(0, 60)
beta[c(5, 9, 3)] <- 1
y <- x %*% beta + rnorm(60)
dendr <- cluster.snp(x = x, method = "average")
res.multisplit <- multisplit(x, y)
sign.clusters <- test.hierarchy(x, y, dendr, res.multisplit)
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