

# Package ‘snpsettest’

October 14, 2022

**Title** A Set-Based Association Test using GWAS Summary Statistics

**Version** 0.1.1

**Description** The goal of 'snpsettest' is to provide simple tools that perform set-based association tests (e.g., gene-based association tests) using GWAS (genome-wide association study) summary statistics. A set-based association test in this package is based on the statistical model described in VEGAS (versatile gene-based association study), which combines the effects of a set of SNPs accounting for linkage disequilibrium between markers. This package uses a different approach from the original VEGAS implementation to compute set-level p values more efficiently, as described in

<<https://github.com/HimesGroup/snpsettest/wiki/Statistical-test-in-snpsettest>>.

**License** GPL (>= 3)

**Depends** R (>= 3.1.0)

**Imports** gaston, data.table, Rcpp

**Suggests** tidyr, knitr, rmarkdown

**VignetteBuilder** knitr

**LinkingTo** Rcpp, RcppArmadillo

**Encoding** UTF-8

**LazyData** true

**RoxygenNote** 7.1.2

**URL** <https://github.com/HimesGroup/snpsettest>

**BugReports** <https://github.com/HimesGroup/snpsettest/issues>

**NeedsCompilation** yes

**Author** Jaehyun Joo [aut, cre],  
Blanca Himes [aut]

**Maintainer** Jaehyun Joo <jaehyunjoo@outlook.com>

**Repository** CRAN

**Date/Publication** 2022-01-18 03:40:02 UTC

## R topics documented:

exGWAS . . . . .	2
gene.curated.GRCh37 . . . . .	3
gene.curated.GRCh38 . . . . .	3
harmonize_sumstats . . . . .	4
map_snp_to_gene . . . . .	6
read_reference_bed . . . . .	7
snpset_test . . . . .	8

<b>Index</b>	<b>10</b>
--------------	-----------

---

exGWAS	<i>An example file of GWAS summary statistics</i>
--------	---

---

### Description

An example file of GWAS summary statistics

### Usage

exGWAS

### Format

Data frame with columns

**id** SNP ID.

**chr** chromosome.

**pos** base-pair position.

**A1, A2** allele codes.

**pvalue** p value.

### Examples

head(exGWAS)

---

gene.curated.GRCh37 *Human gene information from the GENCODE GRCh37 version*

---

### Description

Human gene information was extracted from the GENCODE release 19. This data only contains 'KNOWN' status genes with the following gene biotypes: protein-coding, Immunoglobulin (Ig) variable chain and T-cell receptor (TcR) genes.

### Usage

```
gene.curated.GRCh37
```

### Format

Data frame with columns

**gene.id** SNP ID.

**chr** chromosome.

**start** genomic start location (1-based).

**end** genomic end location.

**strand** genomic strand.

**gene.name** gene symbols mapped to the GENCODE genes.

**gene.type** gene biotypes in the GENCODE genes.

### Source

[https://www.encodegenes.org/human/release\\_19.html](https://www.encodegenes.org/human/release_19.html)

### Examples

```
head(gene.curated.GRCh37)
```

---

gene.curated.GRCh38 *Human gene information from the GENCODE GRCh38 version*

---

### Description

Human gene information was extracted from the GENCODE release 37. This data only contains genes with the following gene biotypes: protein-coding, Immunoglobulin (Ig) variable chain and T-cell receptor (TcR) genes.

### Usage

```
gene.curated.GRCh38
```

**Format**

Data frame with columns

**gene.id** SNP ID.

**chr** chromosome.

**start** genomic start location (1-based).

**end** genomic end location.

**strand** genomic strand.

**gene.name** gene symbols mapped to the GENCODE genes.

**gene.type** gene biotypes in the GENCODE genes.

**Source**

[https://www.encodegenes.org/human/release\\_37.html](https://www.encodegenes.org/human/release_37.html)

**Examples**

```
head(gene.curated.GRCh38)
```

---

harmonize\_sumstats      *Harmonizing GWAS summary to reference data*

---

**Description**

Finds an intersection of variants between GWAS summary and reference data.

**Usage**

```
harmonize_sumstats(  
  sumstats,  
  x,  
  match_by_id = TRUE,  
  check_strand_flip = FALSE,  
  return_indice = FALSE  
)
```

**Arguments**

**sumstats**      A data frame with two columns: "id" and "pvalue".

- id = SNP ID (e.g., rs numbers)
- pvalue = SNP-level p value

If `match_by_id = FALSE`, it requires additional columns: "chr", "pos", "A1" and "A2".

- chr = chromosome

- pos = base-pair position (must be integer)
- A1, A2 = allele codes (allele order is not important)

x                    A bed.matrix object created using the reference data.

match\_by\_id        If TRUE, SNP matching will be performed by SNP IDs instead of genomic position and allele codes. Default is TRUE.

check\_strand\_flip

                    Only applies when match\_by\_id = FALSE. If TRUE, the function 1) removes ambiguous A/T and G/C SNPs for which the strand is not obvious, and 2) attempts to find additional matching entries by flipping allele codes (i.e., A->T, T->A, C->G, G->A). If the GWAS genotype data itself is used as the reference data, it would be safe to set FALSE. Default is FALSE.

return\_indice     Only applied when match\_by\_id = FALSE. If TRUE, the function provides an additional column indicating whether the match is with swapped alleles. If check\_strand\_flip = TRUE, the function also provides an additional column indicating whether the match is with flipped strand. Unnecessary for gene-based tests in this package, but may be useful for other purposes (e.g., harmonization for meta-analysis that needs to flip the sign of beta for a match with swapped alleles).

## Details

Pre-processing of GWAS summary data is required because the sets of variants available in a particular GWAS might be poorly matched to the variants in reference data. SNP matching can be performed either 1) by SNP ID or 2) by chromosome code, base-pair position, and allele codes, while taking into account possible strand flips and reference allele swap. For matched entries, the SNP IDs in GWAS summary data are replaced with the ones in the reference data.

## Value

A data frame with columns: "id", "chr", "pos", "A1", "A2" and "pvalue". If return\_indice = TRUE, the data frame includes additional columns key\_, swapped\_, and flipped\_. key\_ is "chr\_pos\_A1\_A2" in sumstat (the original input before harmonization). swapped\_ contains a logical vector indicating reference allele swap. flipped\_ contains a logical vector indicating strand flip.

## Examples

```
## GWAS summary statistics
head(exGWAS)

## Load reference genotype data
bfile <- system.file("extdata", "example.bed", package = "snpsettest")
x <- read_reference_bed(path = bfile)

## Harmonize by SNP IDs
hsumstats1 <- harmonize_sumstats(exGWAS, x)

## Harmonize by genomic position and allele codes
## Reference allele swap will be taken into account
```

```

hsumstats2 <- harmonize_sumstats(exGWAS, x, match_by_id = FALSE)

## Check matching entries by flipping allele codes
## Ambiguous SNPs will be excluded from harmonization
hsumstats3 <- harmonize_sumstats(exGWAS, x, match_by_id = FALSE,
                                check_strand_flip = TRUE)

```

---

map_snp_to_gene	<i>Map SNPs to genes</i>
-----------------	--------------------------

---

## Description

Annotate SNPs onto their neighboring genes (or arbitrary genomic regions) to perform set-based association tests.

## Usage

```

map_snp_to_gene(
  info_snp,
  info_gene,
  extend_start = 20L,
  extend_end = 20L,
  only_sets = FALSE
)

```

## Arguments

info_snp	A data frame with columns: "id", "chr", and "pos". <ul style="list-style-type: none"> <li>• id = SNP ID (e.g., rs numbers)</li> <li>• chr = chromosome</li> <li>• pos = base-pair position</li> </ul>
info_gene	A data frame with columns: "gene.id", "chr", "start", and "end". <ul style="list-style-type: none"> <li>• gene.id = gene ID (or identifier for genomic regions)</li> <li>• chr = chromosome (must be the same chromosome coding scheme in info_snp)</li> <li>• start = genomic start position</li> <li>• end = genomic end position</li> </ul> <p>If a gene has multiple intervals, SNPs mapped to any of them will be merged into a single set. Please assign unique IDs if you don't want this behavior.</p>
extend_start	A single non-negative integer, allowing for a certain kb window before the gene to be included. Default is 20 (= 20kb).
extend_end	A single non-negative integer, allowing for a certain kb window after the gene to be included. Default is 20 (= 20kb).
only_sets	If TRUE, only sets of SNPs for individual genes are returned. Otherwise, both sets and mapping information are returned. Default is FALSE.

**Value**

A nested list containing following components:

- sets: a named list where each index represents a separate set of SNPs
- map: a data frame containing SNP mapping information

**Examples**

```
## GWAS summary statistics
head(exGWAS)

## Gene information data
head(gene.curated.GRCh37)

## Map SNPs to genes
snp_sets <- map_snp_to_gene(exGWAS, gene.curated.GRCh37)

## Better to use harmonized GWAS data for gene mapping
bfile <- system.file("extdata", "example.bed", package = "snpsettest")
x <- read_reference_bed(path = bfile)
hsumstats <- harmonize_sumstats(exGWAS, x)
snp_sets <- map_snp_to_gene(hsumstats, gene.curated.GRCh37)
```

---

read\_reference\_bed      *Read a PLINK bed file for reference data*

---

**Description**

Create a `bed.matrix` object from a `.bed` file. The function expects `.fam` and `.bim` files under the same directory. See [gaston::read.bed.matrix](#) for more details.

**Usage**

```
read_reference_bed(path, ...)
```

**Arguments**

path                    A path to the `.bed` file

...                      Further arguments used in [gaston::read.bed.matrix](#)

**Value**

A [gaston::bed.matrix](#) object with a Z-standardized genotype matrix

## Examples

```
## Get a path to the example .bed file
bfile <- system.file("extdata", "example.bed", package = "snpsettest")

## Read a .bed file
x <- read_reference_bed(path = bfile)
```

---

snpset\_test

*Set-based association tests*


---

## Description

Perform set-based association tests between multiple sets of SNPs and a phenotype using GWAS summary statistics. If the function encounters missing genotypes in the reference data, they will be imputed with genotype means.

## Usage

```
snpset_test(hsumstats, x, snp_sets, method = c("saddle", "davies"))
```

## Arguments

hsumstats	A data frame processed by <a href="#">harmonize_sumstats</a> .
x	A <code>bed.matrix</code> object created from the reference data.
snp_sets	A named list where each index represents a separate set of SNPs.
method	A method to compute a set-level p value. "saddle" uses Kuonen's saddlepoint approximation (1999) and "davies" uses the algorithm of Davies (1980). When "davies" method failed to produce a meaningful result, "saddle" method is used as a fallback. Default is "saddle".

## Value

A `data.table` with columns: "set.id", "pvalue", "n.snp", "top.snp.id" and "top.snp.pvalue"

- set.id = a name of SNP set
- tstat = a test statistic
- pvalue = a set-level p value
- n.snp = the number of SNPs used in a test
- top.snp.id = SNP ID with the smallest p-value within a set of SNPs
- top.snp.pvalue = The smallest p-value within a set of SNPs

## References

Kuonen, D. Saddlepoint Approximations for Distributions of Quadratic Forms in Normal Variables. *Biometrika* 86, 929–935 (1999).

Davies, R. B. Algorithm AS 155: The Distribution of a Linear Combination of Chi-Square Random Variables. *Journal of the Royal Statistical Society. Series C (Applied Statistics)* 29, 323–333 (1980).



**Examples**

```
## GWAS summary statistics
head(exGWAS)

## Load reference genotype data
bfile <- system.file("extdata", "example.bed", package = "snpsettest")
x <- read_reference_bed(path = bfile)

## GWAS harmonization with reference data
hsumstats <- harmonize_sumstats(exGWAS, x)

## Perform a set-based test with an arbitrary SNP set
snpset_test(hsumstats, x, list(test = c("SNP_880", "SNP_1533", "SNP_4189")))

## Gene information data
head(gene.curated.GRCh37)

## Map SNPs to genes
snp_sets <- map_snp_to_gene(hsumstats, gene.curated.GRCh37)

## Perform gene-based association tests
out <- snpset_test(hsumstats, x, snp_sets$sets)
```

# Index

## \* datasets

exGWAS, [2](#)

gene.curated.GRCh37, [3](#)

gene.curated.GRCh38, [3](#)

exGWAS, [2](#)

gaston::bed.matrix, [7](#)

gaston::read.bed.matrix, [7](#)

gene.curated.GRCh37, [3](#)

gene.curated.GRCh38, [3](#)

harmonize\_sumstats, [4](#), [8](#)

map\_snp\_to\_gene, [6](#)

read\_reference\_bed, [7](#)

snpset\_test, [8](#)