

# Package ‘generalize’

September 20, 2016

**Type** Package

**Title** Test generalization of association analysis from study1 to study2 and display results

**Version** 1.1

**Date** 2016-09-20

**Author** Tamar Sofer

**Maintainer** Tamar Sofer <tsofer.uw@gmail.com>

**Description** Given multiple SNP-trait testing results from two studies, when one is considered the discovery study (study1) and the other (study2) is the follow-up, calculate r-values to quantify the strength of association between each of the SNPs and the trait. If effect sizes are available results can be displayed in a figure.

**License** GPL-2

**LazyData** true

**Suggests** ggplot2, gridExtra, RColorBrewer

## R topics documented:

generalize-package . . . . .	1
dat . . . . .	3
matchEffectAllele . . . . .	4
prepareGenResFigure . . . . .	5
r.value . . . . .	7
testGeneralization . . . . .	8

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

---

generalize-package	<i>Test generalization of association analysis from study1 to study2 and display results</i>
--------------------	--

---

## Description

Given multiple SNP-trait testing results from two studies, when one is considered the discovery study (study1) and the other (study2) is the follow-up, calculate r-values to quantify the strength of association between each of the SNPs and the trait. If effect sizes are available results can be displayed in a figure.

## Details

The DESCRIPTION file: This package was not yet installed at build time.

Index: This package was not yet installed at build time.

Code used to perform generalization testing for a set of association from study 1 (the discovery study) to study 2 (the follow-up, generalization study).

## Author(s)

Tamar Sofer

Maintainer: Tamar Sofer <tsofer.uw@gmail.com>

## Examples

```
data(dat)
head(dat)
## first match effects on alleles:
dat.matched <- matchEffectAllele(dat$rsID, study2.effect = dat$study2.beta,
study1.alleleA = dat$study1.alleleA, study2.alleleA = dat$study2.alleleA,
study1.alleleB = dat$study1.alleleB, study2.alleleB = dat$study2.alleleB)

dat$study2.beta <- dat.matched$study2.effect

## test for generalization:

gen.res <- testGeneralization(dat$rsID, dat$study1.pval, dat$study2.pval,
dat$study1.n.test[1], study1.effect = dat$study1.beta,
study2.effect = dat$study2.beta, directional.control = TRUE,
control.measure = "FDR" )
head(gen.res)

require(ggplot2)
require(gridExtra)
require(RColorBrewer)

## prepare figure
prepareGenResFigure(dat$rsID, dat$study1.beta, dat$study1.se, dat$study2.beta,
dat$study2.se, gen.res$generalized, gen.res$gen.rvals, dat$study1.n.test[1],
output.file = paste0(getwd(), "/Generalization_example.pdf"),
study1.name = "Study1", study2.name = "Study2")

## marking genome-wide significant hits in study 2 with red stars
## (here nothing is genome-wide significant so there will be no difference!)
prepareGenResFigure(dat$rsID, dat$study1.beta, dat$study1.se, dat$study2.beta,
dat$study2.se, gen.res$generalized, gen.res$gen.rvals, dat$study1.n.test[1], plot.width = 10,
output.file = paste0(getwd(), "/Generalization_example.pdf"), study1.name = "Study1",
study2.name = "Study2", add.stars = 5e-8)
```

---

dat	<i>A data set of previously published SNP-platelet count associations in Gieger et al., 2011, and association results for the same SNPs in the HCHS/SOL.</i>
-----	--

---

## Description

A data set with SNP associations reported for platelet counts, in study1 being Gieger et al., 2011, study2 the HCHS/SOL.

## Usage

```
data("dat")
```

## Format

A data frame with 42 observations on the following 15 variables.

rsID SNP identifier

chromosome chromosome

position position in human build 37

study1.alleleA effect Allele in study 1

study1.alleleB other Allele in study 1

study1.beta estimated effect size is study 1

study1.se SE of beta in study 1

study1.pval two-sided p-value in study 1

study1.n.test number of tested SNPs in study 1

study2.alleleA effect Allele in study 2

study2.alleleB other Allele in study 2

study2.beta estimated effect size is study 2

study2.se SE of beta in study 2

study2.pval two-sided p-value in study 2

Ref Reference for the platelet GWAS paper from which the study1 results are taken - Gieger,2011.

## Details

This data set provides the top results from a platelet GWAS reported in Gieger et al., 2011, and the association testing results for the same SNP in the HCHS/SOL study. These results will soon be published in the American Journal of Human Genetics (as of Dec 2015), by Schick et al.

## Source

Gieger, Christian, et al. "New gene functions in megakaryopoiesis and platelet formation." *Nature* 480.7376 (2011): 201-208, Schick, Ursula M., et al. "Genome-wide association study of platelet count identifies ancestry-specific loci in Hispanic/Latino Americans." *The American Journal of Human Genetics* 98.2 (2016): 229-242.

**Examples**

```
data(dat)
head(dat)
```

---

matchEffectAllele	<i>check and update signs of estimated effect sizes in study 2 by matching alleles between study 1 and study 2</i>
-------------------	--

---

**Description**

Compare effect alleles and other alleles and change the sign of the effect in study2 in cases where the effect alleles are different between studies.

**Usage**

```
matchEffectAllele(snpID, study2.effect, study1.alleleA, study2.alleleA,
  study1.alleleB = NULL, study2.alleleB = NULL)
```

**Arguments**

snpID	a vector of snp identifiers (e.g. rsIDs)
study2.effect	Numeric vector of the SNP effects from study2, or their directions given as 1, -1.
study1.alleleA	Character vector providing the effect alleles corresponding to snpID in study1.
study2.alleleA	Character vector providing the effect alleles corresponding to snpID in study2.
study1.alleleB	Character vector providing the non-effect (other) alleles corresponding to snpID in study1
study2.alleleB	Character vector providing the non-effect (other) alleles corresponding to snpID in study2.

**Details**

Returns a data frame matching each snpID with its estimated effect size in study2, after making sure that both studies use the same effect alleles for all given SNPs. If there is enough information, strand-ambiguous SNPs flag is also given.

**Value**

Returns a data frame with SNP identifiers, direction of effects of study2 after possibly flipping the directions of effects of study2 so the same effect allele is used in both studies. If effect estimates were given in study1.direction and study2.direction, then effect estimates are returned accordingly.

**Warning**

....

**Author(s)**

Tamar Sofer

## Examples

```
data(dat)
head(dat)
## match effects on alleles:

dat.matched <- matchEffectAllele(dat$rsID, study2.effect = dat$study2.beta,
  study1.alleleA = dat$study1.alleleA, study2.alleleA = dat$study2.alleleA,
  study1.alleleB = dat$study1.alleleB, study2.alleleB = dat$study2.alleleB)

head(dat.matched)
```

---

prepareGenResFigure	<i>Prepare a figure illustrating generalization testing results</i>
---------------------	---

---

## Description

The function takes vectors of effect sizes and standard errors from study1 and study2, and generalization testing results in the form of r-values and generalization status, corresponding to a set of SNPs selected for follow-up after association testing in study1. The function creates a figure to visualize these results, and the observed effect sizes and confidence intervals. The confidence intervals are scaled to control the false coverage rate (FCR) at the 95

## Usage

```
prepareGenResFigure(snpID, study1.beta, study1.se, study2.beta, study2.se,
  generalized, gen.rvals, study1.n.test, output.file, study1.name = "Study1",
  study2.name = "Study2", make.title = FALSE, legend.position = c(0.9, 0.9),
  CI.line.width = 1.7, x.ticks.size = 15, plot.width = 8, plot.height = 8,
  trait = NULL, plot.title = NULL, add.stars = NULL, alpha.level.follow = 0.05)
```

## Arguments

snpID	a vector of snp identifiers (e.g. rsIDs)
study1.beta	Numeric vector of the effect estimates from study1.
study1.se	Numeric vector of the SE of the effect estimates from study1.
study2.beta	Numeric vector of the effect estimates from study2.
study2.se	Numeric vector of the SE of the effect estimates from study2.
generalized	Generalization status, return by the function testGeneralization
gen.rvals	r-values from generalization testing. Returned by the function testGeneralization.
study1.n.test	Number of SNPs tested in study 1.
output.file	Name of file for the figure.
study1.name	A string, name of study1.
study2.name	A string, name of study2.
make.title	Should the plot have a title?
legend.position	Legend position.

<code>CI.line.width</code>	the width of the line of the confidence intervals.
<code>x.ticks.size</code>	The size of the snp identifiers strings given at the bottom of the figure (at the X-axis).
<code>plot.width</code>	Figure width.
<code>plot.height</code>	Figure height.
<code>trait</code>	An optional string with the name of the trait associated (or not) with the SNPs. Used in the figure title if given.
<code>plot.title</code>	An optional string of a specific title
<code>add.stars</code>	An optional numerical value, corresponding to a p-value threshold. If a SNP from study2 has a two-sided p-value that is smaller than this threshold, then a star is plotted next to the estimated effect of the appropriate SNP.
<code>alpha.level.follow</code>	Significance level for plotting confidence interval. Default level is 0.05 (plots 95% confidence intervals)

## Details

A figure is created in `output.file`.

## Examples

```
data(dat)
head(dat)

## first match effects on alleles:
dat.matched <- matchEffectAllele(dat$rsID, study2.effect = dat$study2.beta,
study1.alleleA = dat$study1.alleleA, study2.alleleA = dat$study2.alleleA,
study1.alleleB = dat$study1.alleleB, study2.alleleB = dat$study2.alleleB)

head(dat.matched)

dat$study2.beta <- dat.matched$study2.effect

## test for generalization:

gen.res <- testGeneralization(dat$rsID, dat$study1.pval, dat$study2.pval,
dat$study1.n.test[1], study1.effect = dat$study1.beta,
study2.effect = dat$study2.beta, directional.control = TRUE,
control.measure = "FDR" )

## prepare figure
require(ggplot2)
require(gridExtra)
require(RColorBrewer)

## prepare figure
prepareGenResFigure(dat$rsID, dat$study1.beta, dat$study1.se, dat$study2.beta,
dat$study2.se, gen.res$generalized, gen.res$gen.rvals, dat$study1.n.test[1],
output.file = paste0(getwd(), "/Generalization_example.pdf"),
study1.name = "Study1", study2.name = "Study2")

## marking genome-wide significant hits in study 2 with red stars
## (here nothing is genome-wide significant so there will be no difference!)
prepareGenResFigure(dat$rsID, dat$study1.beta, dat$study1.se, dat$study2.beta,
```

```
dat$study2.se, gen.res$generalized, gen.res$gen.rvals, dat$study1.n.test[1],
output.file = paste0(getwd(), "/Generalization_example.pdf"),
study1.name = "Study1", study2.name = "Study2", add.stars = 5e-8)
```

---

r.value	<i>r-value computation</i>
---------	----------------------------

---

## Description

The function computes r-values given two vectors of p-values from primary and follow-up studies. r-values assess the False Discovery Rate (FDR) of replicability claims across the primary and follow-up studies. This is a function from Ruth Heller, adapted to compute FWER r-values in addition to FDR r-values.

## Usage

```
r.value(p1, p2, m, c2 = 0.5, control.measure = "FDR", l00 = 0.8 )
```

## Arguments

p1	Numeric vector of the p-values from study 1
p2	Numeric vector of the p-values from study 2
m	Number of features examined in the primary study.
c2	Parameter for relative boost to the p-values from the primary study. 0.5 (default) is recommended, since was observed in simulations to yield similar power to procedure with the optimal value (which is unknown for real data).
control.measure	A sting, either FDR or FWER, depending on the desired measure of control on false generalizations.
l00	Lower bound of the fraction of features (out of m) with true null hypotheses in both studies. For example, for GWAS on the whole genome, the choice of 0.8 is conservative in typical applications.
variation	When 'use.m.star' is selected $m^*$ is used. $m^*$ is defined as follows: $m^* = m \sum_{i=1}^m \frac{1}{i}$ . When 'use.t' is selected c1 is computed given the threshold tt. Both variations guarantee that the procedure that declares all r-values below q as replicability claims, controls the FDR at level q, for any type of dependency of the p-values in the primary study. default is 'none'.
tt	The selection rule threshold for p-values from the primary study. must be supplied when variation 'use.t' is selected.
Q	The level of false generalization (e.g. control FDR at the q level or FWER at the q level).

## Author(s)

Ruth Heller, Shay Yaacoby (shay66@gmail.com), small adaptation by Tamar Sofer.

## Examples

```
# General example from Ruth Heller's website:
pv <- read.csv("http://www.math.tau.ac.il/~ruheller/Software/CrohnExample.csv")
rv <- r.value(p1=pv$p1,p2=pv$p2,m=635547,c2=0.5,l00=0.8)
rv2 <- r.value(p1=pv$p1,p2=pv$p2,m=635547,c2=0.5,l00=0.8,variation="use.t",tt=1e-5)

#### in this package, the function is called by testGeneralization.
```

---

testGeneralization	<i>Test for generalization of associations from study1 to study2</i>
--------------------	--

---

## Description

The function calls another function that computes r-values given two vectors of p-values from primary (study1) and follow-up (study2) studies and determine generalization (TRUE/FALSE) for each of the associations. The computes either FDR or FWER r-values. Directional control is applied by default, so that one-sided p-values are computed and used. only and associations with the same sign in the two studies are generalized.

## Usage

```
testGeneralization(snpID, study1.pval, study2.pval, study1.n.test,
  study1.effect = NULL, study2.effect = NULL, directional.control = TRUE,
  control.measure = "FDR", q = 0.05, l00 = 0.8, c2 = 0.5,
  variation = c("none", "use.m.star", "use.t"), tt = NULL, verbose = FALSE)
```

## Arguments

snpID	a vector of snp identifiers (e.g. rsIDs)
study1.pval	Numeric vector of the two sided p-values from study1.
study2.pval	Numeric vector of the two sided p-values from study2.
study1.n.test	Number of SNPs tested in study 1.
study1.effect	An optional numeric vector of SNP effects from study1, or their directions as 1, -1. \ Required for directional control using 1-sided p-values.
study2.effect	An optional numeric vector of SNP effects from study2, or their directions as 1, -1. \ Required for directional control using 1-sided p-values.
directional.control	should directional controlled by applied? i.e., a SNP could be generalized only if it has the same direction of association in both study1 and study2.
control.measure	Either "FDR" or "FWER", according to the desired control of false generalizations.
q	The level or false generalization (e.g. control FDR at the q level or FWER at the q level).
l00	Lower bound of the fraction of features (out of m) with true null hypotheses in both studies. For example, for GWAS on the whole genome, the choice of 0.8 is conservative effect in typical applications.



c2	Parameter for relative boost to the p-values from the primary study. 0.5 (default) is recommended, since was observed in simulations to yield similar power to procedure with the optimal value (which is unknown for real data).
variation	When 'use.m.star' is selected $m^*$ is used. $m^*$ is defined as follows: $m^* = m \sum_{i=1}^m \frac{1}{i}$ . When 'use.t' is selected c1 is computed given the threshold tt. Both variations guarantee that the procedure that declares all r-values below q as replicability claims, controls the FDR at level q, for any type of dependency of the p-values in the primary study. default is 'none'.
tt	The selection rule threshold for p-values from the primary study. must be supplied when variation 'use.t' is selected.
verbose	

### Details

Returns a data frame matching each snpID with its computed r-value and generalization status.

### Value

a data frame matching each snpID with its computed r-value and generalization status.

### Author(s)

Tamar Sofer

### Examples

```
data(dat)
head(dat)
## first match effects on alleles:

dat.matched <- matchEffectAllele(dat$rsID, study2.effect = dat$study2.beta,
study1.alleleA = dat$study1.alleleA, study2.alleleA = dat$study2.alleleA,
study1.alleleB = dat$study1.alleleB, study2.alleleB = dat$study2.alleleB)

head(dat.matched)

dat$study2.beta <- dat.matched$study2.effect

## test for generalization:

gen.res <- testGeneralization(dat$rsID, dat$study1.pval, dat$study2.pval, dat$study1.n.test[1],
study1.effect = dat$study1.beta, study2.effect = dat$study2.beta,
directional.control = TRUE, control.measure = "FDR" )
```

# Index

\*Topic **datasets**

dat, [3](#)

dat, [3](#)

generalize (generalize-package), [1](#)

generalize-package, [1](#)

matchEffectAllele, [4](#)

prepareGenResFigure, [5](#)

r.value, [7](#)

testGeneralization, [8](#)