Package 'RRate'

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Title Estimating Replication Rate for Genome-Wide Association Studies

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Description Replication Rate (RR) is the probability of replicating a statistically significant association in genome-wide association studies. This R-package provide the estimation method for replication rate which makes use of the summary statistics from the primary study. We can use the estimated RR to determine the sample size of the replication study, and to check the consistency between the results of the primary study and those of the replication study.

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Description

Replication Rate (RR) is the probability of replicating a statistically significant association in genome-wide association studies. This R-package provide the estimation method for replication rate which makes use of the summary statistics from the primary study. We can use the estimated RR to determine the sample size of the replication study, and to check the consistency between the results of the primary study and those of the replication study.

Details

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The goal of genome-wide association studies (GWAS) is to discover genetic variants associated with diseases/traits. Replication is a common validation method in GWAS. We regard an association as true finding when it shows significance in both the primary and replication studies. A worth pondering question is: what is the probability of a primary association (i.e. statistically significant association in the primary study) being validated in the replication study?

We refer the Bayesian replication probability as the replication rate (RR). Here we implement the estimation method for RR which makes use of the summary statistics from the primary study. We can use the estimated RR to determine the sample size of the replication study, and to check the consistency between the results of the primary study and those of the replication study.

The principal component of RRate package is `repRateEst`. Also we implement sample size determination method (`repSampleSizeRR` and `repSampleSizeRR2`) and consistency checking method (Hosmer-Lemeshow test, `HLtest`).

1. To estimate the RR, we need obtain the summary statistics of each genotyped SNPs in the primary study. We have put a example summary statistics (smryStats1) in the package. You can use `data(smryStats1)` to load the example data. You can also obtain the ground-truth parameters (allele frequencies, odds ratios) of the example data using `data(param)`. We also put the corresponding summary statistics of the replicaition study in the package (smryStats2).

2. You can use `SEest` to estimate the standard error of the observed log-odds ratio.

`SEest(n0,n1,fU,fA)`

Details about the function can be seen using help(SEest).

3. You can use `repRateEst` to estimate the RR for each associations discovered from the primary study (i.e. primary associations).

`repRateEst(MUhat,SE, SE2,zalpha2,zalphaR2,boot=100,output=TRUE,idx=TRUE,dir='output',info=T)`

Details about the function can be seen using help(repRateEst).

4. You can use repSampleSizeRR and repSampleSizeRR2 to determine the sample size of the replication study.

repSampleSizeRR(RR, n, MUhat,SE,zalpha2,zalphaR2,idx=TRUE)

repSampleSizeRR2(RR,CCR2, MUhat,SE,fU,fA,zalpha2,zalphaR2, idx=TRUE)

Details about these functions can be seen using help(repSampleSizeRR) and help(repSampleSizeRR2).

5. You can use HLtest to check the consistency between the results of the primary study and those of the replication study.

HLtest(x,p,g=10,null='all',boot=1000,info=T,dir='.')

Details about the function can be seen using help(HLtest)

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References

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted*.

See Also

repRateEst, SEest, repSampleSizeRR, repSampleSizeRR2, HLtest

Examples

```
alpha<-5e-6              #Significance level in the primary study
alphaR<-5e-3             #Significance level in the replication study
zalpha2<-qnorm(1-alpha/2)
zalphaR2<-qnorm(1-alphaR/2)

##Load data
data('smryStats1')      #Example of summary statistics in 1st study
z1<-smryStats1$Z        #Z values in 1st study
n2.0<-2000              #Number of individuals in control group
n2.1<-2000              #Number of individuals in case group

SE2<-SEest(n2.0, n2.1, smryStats1$F_U, smryStats1$F_A) #SE in replication study
######  RR estimation  ######
RRresult<-repRateEst(log(smryStats1$OR),smryStats1$SE, SE2,zalpha2,zalphaR2, output=TRUE,dir='.')
RR<-RRresult$RR         #Estimated RR
```

HLtest	*Hosmer-Lemeshow test*

Description

Test whether each element of x is sampled with the probability specified by the corrsponding element in p.

Usage

```
HLtest(x, p, g = 10, null = "all", boot = 1000, info = T, dir = ".")
```

Arguments

x	A boolean vector.
p	A probability vector having the same length with x.
g	The group number used in the test.
null	a character in c('all', 'chi2','boot'). If null=='chi2', then we use (g-1) degree of freedom chi2 distribution to approximately compute p value. If null=='boot', then we use parametric bootstrap to compute p value. If null=='all', then both methods are used. This is the default option.
boot	The resampling times to compute p value. Only effective when null=='boot' or 'all'
info	Draw the null distribution of the test statistic.
dir	The directory to save the plot of the null distribution.

Details

Null Hypothesis: Each element of x is sampled with a probability which is the corresponding element of p. We group x to g groups according to p. Then we compare the success proportion with the mean value of p in each group.

Value

A list is returned:

H	The test statistic.
pval_chi2	The p value approximated by using chi2 distribution.
pval_boot	The p value computed by using parametric bootstrap.

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References

Hosmer, D. W., & Lemesbow, S. (1980). Goodness of fit tests for the multiple logistic regression model. *Communications in statistics-Theory and Methods*, 9(10), 1043-1069.

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted*.

See Also

RRate repRateEst, SEest, repSampleSizeRR, repSampleSizeRR2,

Examples

```
alpha<-5e-6              #Significance level in the primary study
alphaR<-5e-3             #Significance level in the replication study
zalpha2<-qnorm(1-alpha/2)
zalphaR2<-qnorm(1-alphaR/2)

##Load data
data('smryStats1')       #Example of summary statistics in 1st study
n2.0<-2000               #Number of individuals in control group
n2.1<-2000               #Number of individuals in case group

SE2<-SEest(n2.0, n2.1, smryStats1$F_U, smryStats1$F_A) #SE in replication study
######  RR estimation  ######
RRresult<-repRateEst(log(smryStats1$OR),smryStats1$SE, SE2,zalpha2,zalphaR2, output=TRUE,dir='.')

#### Hosmer-Lemeshow test  ####
data('smryStats2')       #Example of summary statistics in 2nd study
sigIdx<-(smryStats1$P<alpha)
repIdx<-(sign(smryStats1$Z[sigIdx])*smryStats2$Z[sigIdx]>zalphaR2)
groupNum<-10
HLresult<-HLtest(repIdx,RRresult$RR,g=groupNum,dir='.')
```

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repSampleSizeRR	*Sample size determination for the replication study based on RR*

Description

`repSampleSizeRR` and `repSampleSizeRR2` implement the RR-based sample size determination method for the replication study. If the replication study has the same control-to-case ratio with the primary study, then `repSampleSizeRR` can be used. Otherwise, `repSampleSize2` is more suitable.

Usage

```
repSampleSizeRR(GRR, n, MUhat, SE, zalpha2, zalphaR2, idx = TRUE)

repSampleSizeRR2(GRR,CCR2, MUhat,SE,fU,fA,zalpha2,zalphaR2, idx=TRUE)
```

Arguments

GRR	The desired global replication rate.
n	Sample size in the primary study.
MUhat	The observed effect size (log-odds ratio).
SE	The standard error of MUhat.
zalpha2	The critical value of z-values in the primary study, i.e. z_alpha/2.
zalphaR2	The critical value of z-values in the replication study, i.e. z_alphaR/2.
idx	The indexes of the SNPs having been further inverstigated in the replication study. We only calculate RR for primary associations with indexes in idx.
CCR2	The control-to-case ratio of the replication study.
fU	The allele frequency in the control group.
fA	The allele frequency in the case group.

Value

The determined sample size of the replication study is returned.

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References

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted*.

See Also

RRate repRateEst, SEest, HLtest

Examples

```
alpha<-5e-6              #Significance level in the primary study
alphaR<-5e-3             #Significance level in the replication study
zalpha2<-qnorm(1-alpha/2)
zalphaR2<-qnorm(1-alphaR/2)

##Load data
data('smryStats1')      #Example of summary statistics in 1st study
#### Sample size determination ###
n1<-4000                #Sample size of the primary study
n2_1<-repSampleSizeRR(0.8, n1, log(smryStats1$OR),smryStats1$SE,zalpha2,zalphaR2)

CCR2<-2                 #Control-to-case ration in the replication study
n2_2<-repSampleSizeRR2(0.8, CCR2, log(smryStats1$OR),smryStats1$SE,smryStats1$F_U,
smryStats1$F_A,zalpha2,zalphaR2)
```

RRate-functions | *Estimating Replication Rate for primary associations*

Description

`repRateEst` implements a replication rate estimation method. Two-component mixture prior is used in the estimation.

Usage

```
repRateEst(MUhat, SE, SE2, zalpha2, zalphaR2, boot = 100, output = TRUE,
idx = TRUE, dir = "output", info = TRUE)
```

Arguments

MUhat	The observed effect size (log-odds ratio) in the primary study.
SE	The standard error of the observed log-odds ratio in the primary study.
SE2	The standard error of the observed log-odds ratio in the replication study.
zalpha2	The critical value of z-values in the primary study, i.e. z_alpha/2.
zalphaR2	The critical value of z-values in the replication study, i.e. z_alphaR/2.
boot	The resampling number of bootstrop used for estimating the credible interval of the RR.
output	Bool value. To determine whether to output the estimated results in the dir or not.
idx	The indexes of the SNPs having been further inverstigated in the replication study. We only calculate RR for primary associations with indexes in `idx`.
dir	The directory to save the estimated results. It has effect when `output=T`
info	Bool value. To determine whether to show the parematers inference results in the terminal or not.

Details

The RR estimation is based on the following two-component mixture model: mu=pi_0 delta_0+(1-pi_0) N(0, sigma_0^2).

Details can be seen the following reference paper.

Value

`repRateEst` returns the RR, lfdr, prediction power and infered parameters. The returened value is a LIST:

idx	The index of the SNPs which RR are estimated.
pi0	The proportion of nonassociated SNPs.
sigma02	The variance of the associated SNPs' effect sizes

RR	Estimated replication rate.
RRlow	The lower limit of the 95% CI for RR.
RRhigh	The upper limit of the 95% CI for RR.
lfdr	Estimated local false discovery rate of the primary study
lfdrLow	The lower limit of the 95% CI for lfdr.
lfdrHigh	The upper limit of the 95% CI for lfdr.
predPower	The Bayesian predictive power of the replication study.
predPowerLow	The lower limit of the 95% CI for predPower.
perdPowerHigh	The upper limit of the 95% CI for predPower.
GRR	The Global Replication Rate (Mean value of RR)
GRRlow	The lower limit of the 95% CI for GRR.
GRRhigh	The upper limit of the 95% CI for GRR.

Author(s)

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References

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted*.

See Also

[RRate](#), [SEest](#), [repSampleSizeRR](#), [repSampleSizeRR2](#), [HLtest](#)

Examples

```
alpha<-5e-6              #Significance level in the primary study
alphaR<-5e-3             #Significance level in the replication study
zalpha2<-qnorm(1-alpha/2)
zalphaR2<-qnorm(1-alphaR/2)

##Load data
data('smryStats1')       #Example of summary statistics in 1st study
n2.0<-2000               #Number of individuals in control group
n2.1<-2000               #Number of individuals in case group

SE2<-SEest(n2.0, n2.1, smryStats1$F_U, smryStats1$F_A) #SE in replication study
######  RR estimation  ######
RRresult<-repRateEst(log(smryStats1$OR),smryStats1$SE, SE2,zalpha2,zalphaR2, output=TRUE,dir='.')
RR<-RRresult$RR          #Estimated RR
```

SEest | *Estimating standard error of the observed log-odds ratio*

Description

SEest implements the Woolf's method to estimate the standard error of the observed log-odds ratio.

Usage

```
SEest(n0,n1,fU,fA)
```

Arguments

n0   Sample size in the control group.

n1   Sample size in the case group.

fU   Allele frequency in the control group.

fA   Allele frequency in the case group.

Details

The Woolf's method to estimate the standard error of log(OR) is based on the following formula:

se(log(OR))=sqrt(1/(n0 fU(1-fU))+1/(n1 fA(1-fA))).

Value

The estimated standard error is returned.

Author(s)

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References

Woolf, B. (1955). On estimating the relation between blood group and disease. *Ann Hum Genet*, 19(4), 251-253.

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted*.

See Also

RRate, repRateEst, repSampleSizeRR, repSampleSizeRR2, HLtest

Examples

```
##Load data
data('smryStats1')        #Example of summary statistics in 1st study
n2.0<-2000                #Number of individuals in control group
n2.1<-2000                #Number of individuals in case group

SE2<-SEest(n2.0, n2.1, smryStats1$F_U, smryStats1$F_A) #SE in replication study
```

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smryStats   *Example summary statistics*

Description

Example summary statistics from the primary and replication studies in GWAS. These summary statistics are generated from a simulated study. The primary study (smryStats1) has 2000 cases and 2000 controls. The replication study (smryStats2) has 1000 cases and 1000 controls. The SNP number is 10,000. The disease pravalence is 1%. Minor allele frequencies are from U(0.05, 0.5), and log-odds ratio are from 0.95N(0,1)+0.05N(0, 0.04). The ground-truth parameters for each SNP are in param.

Usage

```
data(smryStats1)

data(smryStats2)

data(param)
```

Details

The data sets are described as

SNP: SNP ID

F_A: Allele frequency in case group

F_U: Allele frequency in control group

Z: Z value from log-odds ratio test

P: P value

OR: Odds ratio

SE: Standard error of log(OR)

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References

Jiang, W., Xue, J-H, and Yu, W. What is the probability of replicating a statistically significant association in genome-wide association studies?. *Submitted.*

See Also

RRate repRateEst, SEest, repSampleSizeRR, repSampleSizeRR2, HLtest

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