

Package ‘RVS’

April 12, 2018

Type Package

Title Computes estimates of the probability of related individuals sharing a rare variant

Version 1.0.0

Date 2017-07-11

Author Alexandre Bureau, Ingo Ruczinski, Samuel Younkin, Thomas Sherman

Maintainer Thomas Sherman <tsherma4@jhu.edu>

Description Rare Variant Sharing (RVS) implements tests of association and linkage between rare genetic variant genotypes and a dichotomous phenotype, e.g. a disease status, in family samples. The tests are based on probabilities of rare variant sharing by relatives under the null hypothesis of absence of linkage and association between the rare variants and the phenotype and apply to single variants or multiple variants in a region (e.g. gene-based test).

License GPL-2

Depends R (>= 3.4.0)

Imports gRain, snpStats, kinship2, methods, stats, utils

Suggests knitr, testthat, rmarkdown, BiocStyle

VignetteBuilder knitr

RoxygenNote 5.0.1

biocViews Genetics, GenomeWideAssociation, VariantDetection, ExomeSeq, WholeGenome

Collate 'RVgene.R' 'pedigree-methods.R' 'RVsharing.R'
'documentation.R' 'grainNetworkHelper.R' 'monteCarloMethods.R'
'multipleFamilyCalculations.R' 'relatedFoundersCorrection.R'
'sharingProbabilityCalculations.R'

NeedsCompilation no

R topics documented:

ComputeKinshipPropCoef	2
ex.ped.mat	3
fam15157.vcf	3
fam28003.vcf	3
GeneDrop	4

get.psubset	4
multipleFamilyPValue	5
ped2trio	6
processPedigree	6
RVgene	7
RVS	9
RVsharing	9
samplePedigrees	11
snpMat	11
SnpMatrixToCount	11

Index 13

ComputeKinshipPropCoef

ratio of excess kinship among descendants over mean kinship among founders

Description

Computes, for each pair of final descendants in the pedigree structure contained in the pedigree object, the ratio of the difference between the inferred and expected kinship coefficient for the pair over the mean kinship among founders.

Usage

```
ComputeKinshipPropCoef(ped)
```

```
## S4 method for signature 'pedigree'
ComputeKinshipPropCoef(ped)
```

Arguments

ped pedigree object (S3)

Details

The ratio for each pair of final descendants is computed using equation (A1) of Bureau et al. Dividing the difference between the inferred and expected kinship coefficient for each pair by this ratio gives a pair-specific estimate of the mean kinship among founders, which can then be averaged over all pairs of final descendants from the same population to obtain a global estimate of the mean kinship among founders.

Value

a symmetric matrix of ratios for all pair of final descendants in the pedigree structure contained in the pedigree

References

Bureau, A., Younkin, S., Parker, M.M., Bailey-Wilson, J.E., Marazita, M.L., Murray, J.C., Mangold, E., Albacha-Hejazi, H., Beaty, T.H. and Ruczinski, I. (2014) Inferring rare disease risk variants based on exact probabilities of sharing by multiple affected relatives. *Bioinformatics*, 30(15): 2189-96, doi:10.1093/bioinformatics/btu198.

Examples

```
data(samplePedigrees)
ComputeKinshipPropCoef(samplePedigrees$firstCousinTriple)
```

ex.ped.mat	<i>matrix of pedigree information and genotype data from famVCF stored in the LINKAGE format</i>
------------	--

Description

matrix of pedigree information and genotype data from famVCF stored in the LINKAGE format

Usage

```
ex.ped.mat
```

fam15157.vcf	<i>VCF objects containing genotype data for two families: fam15157 and fam28003 (corresponding to the secondCousinTriple and firstAndSecondCousinsTriple families in samplePedigrees)</i>
--------------	---

Description

VCF objects containing genotype data for two families: fam15157 and fam28003 (corresponding to the secondCousinTriple and firstAndSecondCousinsTriple families in samplePedigrees)

Usage

```
fam15157.vcf
```

fam28003.vcf	<i>VCF objects containing genotype data for two families: fam15157 and fam28003 (corresponding to the secondCousinTriple and firstAndSecondCousinsTriple families in samplePedigrees)</i>
--------------	---

Description

VCF objects containing genotype data for two families: fam15157 and fam28003 (corresponding to the secondCousinTriple and firstAndSecondCousinsTriple families in samplePedigrees)

Usage

```
fam28003.vcf
```

GeneDrop *deprecated function*

Description

This function is deprecated with version ≥ 2.0 and should not be used, instead use RVsharing with nSim option

Usage

```
GeneDrop(...)

GeneDropSim.allsubsets.fn(...)

GeneDropSim.fn(...)

GeneDropSimExcessSharing.fn(...)
```

Arguments

... arguments to the old function

Value

none

Examples

```
tryCatch(GeneDrop(), error = function(e) message(e))
```

get.psubset *deprecated function*

Description

This function is deprecated with version ≥ 2.0 and should not be used, instead use multipleFamilyPValue

Usage

```
get.psubset(vec, not, pshare.data)
```

Arguments

vec a vector of names of all families where a variant is seen

not a vector of names of families where not all affected subjects share the rare variant

psshare.data a data frame with at least two of the following columns: pshare: vector of RV sharing probabilities ped.tocompute.vec: vector of names of the families whose sharing probability is contained in pshare. The names in the arguments vec and not must be found in ped.tocompute.vec

Value

P-value of the exact rare variant sharing test requiring sharing by all affected subjects.

Examples

```
data(samplePedigrees)
notSharedFams <- c(15159, 15053, 15157)
famids <- sapply(samplePedigrees, function(p) p$famid[1])
notShared <- famids %in% notSharedFams
probs <- sapply(samplePedigrees, RVsharing)
get.psubset(famids, notShared, data.frame(pshare=probs,
ped.tocompute.vec=famids))
```

multipleFamilyPValue *probability of sharing of rare variants in a subset of families*

Description

Computing probability of sharing of rare variants in a subset of families where rare variants are seen based on precomputed family-specific rare variant sharing probabilities.

Usage

```
multipleFamilyPValue(sharingProbs, observedSharing)
```

Arguments

sharingProbs sharing probabilities for all families
observedSharing boolean vector describing if all affected subjects in the family share the variant (TRUE if all share)

Details

All the subsets of families of size equal or inferior to the length of not are created, and the joint probability of each such subset not sharing a rare variant and the remaining families sharing a rare variant is obtained as the product of the family-specific rare variant sharing probabilities or its complement. The function then sums the pattern probabilities inferior or equal to the probability of the observed pattern of the not families not sharing a rare variant and the remaining families sharing a rare variant.

Value

P-value of the exact rare variant sharing test requiring sharing by all affected subjects

References

Bureau, A., Younkin, S., Parker, M.M., Bailey-Wilson, J.E., Marazita, M.L., Murray, J.C., Mangold, E., Albacha-Hejazi, H., Beaty, T.H. and Ruczinski, I. (2014) Inferring rare disease risk variants based on exact probabilities of sharing by multiple affected relatives. *Bioinformatics*, 30(15): 2189-96, doi:10.1093/bioinformatics/btu198.

Examples

```

data(samplePedigrees)
notSharedFams <- c(15159, 15053, 15157)
famids <- sapply(samplePedigrees, function(p) p$famid[1])
shared <- !famids %in% notSharedFams
probs <- sapply(samplePedigrees, RVsharing)
multipleFamilyPValue(probs, shared)

```

ped2trio

deprecated function

Description

This function is deprecated with version ≥ 2.0 and should not be used.

Usage

```
ped2trio(...)
```

Arguments

... arguments to the old function

Value

none

Examples

```
tryCatch(ped2trio(), error = function(e) message(e))
```

processPedigree

extract useful information from a pedigree

Description

Extract key information from a pedigree object, which makes subsequent computations much easier.

Usage

```
processPedigree(ped, carriers = NULL)
```

```
## S4 method for signature 'pedigree'
processPedigree(ped, carriers = NULL)
```

Arguments

ped pedigree object (S3)

carriers subjects in which the rare variant is seen

Value

list containing relevant pedigree info

Examples

```
data(samplePedigrees)
processPedigree(samplePedigrees$firstCousinPair)
```

RVgene

Probability of sharing of rare variants in a family sample within a gene

Description

Computing probability of sharing of rare variants in a family sample within a genomic region such as a gene.

Usage

```
RVgene(data, ped.listfams, sites, fams, pattern.prob.list, nequiv.list, N.list,
        type = "alleles", minor.allele.vec, precomputed.prob = list(0),
        maxdim = 1e+09, partial.sharing = TRUE, useAffected = TRUE)
```

Arguments

data	A list of SnpMatrix objects corresponding to each pedigree object in ped.listfams, alternatively a data.frame or matrix encoding the pedigree information and genotype data in the standard LINKAGE ped format or the PLINK raw format with additive component only (see PLINK web site [1]). In fact, only the family ID in the first column, the subject ID in the second column, the affection status in the sixth column and the genotype data starting in the seventh column are used (columns 3 to 5 are ignored). Also, family members without genotype data do not need to appear in this matrix. The genotype of each variant can be coded in two ways, each corresponding to a different value of the type option: a minor allele count on one column with missing values coded NA, obtained for example by converting a SnpMatrix object (type="count") or the identity of the two alleles on two consecutive columns, with missing values coded 0 corresponding to the standard LINKAGE ped format (type="alleles")
ped.listfams	a list of pedigree objects, one object for each pedigree in ped.mat.
sites	a vector of the column indices of the variant sites to test in ped.mat. If the argument fams is provided, the variant sites are tested in each corresponding family in the fams vector (a variant present in multiple families must then be repeated for every families where it appears).
fams	an optional character vector of the names of families in ped.mat and ped.listfams carrying the variants listed in the corresponding position in sites. If missing, the names of the families carrying the minor allele at each position in sites are extracted from ped.mat
pattern.prob.list	a list of precomputed rare variant sharing probabilities for all possible sharing patterns in the families in ped.mat and ped.listfams

<code>nequiv.list</code>	an optional vector of the number of configurations of rare variant sharing by the affected subjects corresponding to the same pattern and probability in <code>pattern.prob.list</code> . Default is a vector of 1s
<code>N.list</code>	a vector of the number of affected subjects sharing a rare variant in the corresponding pattern in <code>pattern.prob.list</code>
<code>type</code>	an optional character string taking value "alleles" or "count". Default is "alleles"
<code>minor.allele.vec</code>	an optional vector of the minor alleles at each site in the <code>sites</code> vector. It is not needed if <code>type="count"</code> . If it is missing and <code>type="alleles"</code> , the minor allele is assumed to take the value 2
<code>precomputed.prob</code>	an optional list of vectors precomputed rare variant sharing probabilities for families in <code>ped.mat</code> and <code>ped.listfams</code> . If the vectors are named, the names must be strings formed by the concatenation of the sorted carrier names separated by semi-columns. If the vectors are not named, the vectors must represent probabilities for all the possible values of <code>N.list</code> for the corresponding family (one probability per value of <code>N.list</code>)
<code>maxdim</code>	upper bound on the dimension of the array containing the joint distribution of the sharing patterns for all families in <code>fams</code> (to avoid running out of memory)
<code>partial.sharing</code>	logical indicating whether the test allowing for sharing by a subset of affected subjects should be performed. If <code>FALSE</code> , only the test requiring sharing by all affected subjects is computed. Default is <code>TRUE</code>
<code>useAffected</code>	allows the user to condition on seeing the variant among the affected subjects instead of the final descendants. Default is <code>TRUE</code>

Details

The function extracts the carriers of the minor allele at each entry in `sites` in each family where it is present in `ped.mat` (or in the families specified in `fams` if that argument is specified). It then computes exact rare variant sharing probabilities in each family for each variant by calling `RVsharing`. If multiple rare variants are seen in the same family, the smallest sharing probability among all rare variants is retained. The joint rare variant sharing probability over all families is obtained as the product of the family-specific probabilities. The p-value of the test allowing for sharing by a subset of affected subjects over the rare variants in the genomic region is then computed as the sum of the probabilities of the possible combinations of sharing patterns among all families with a probability less than or equal to the observed joint probability and a total number of carriers greater than or equal to the sum of the number of carriers in all families, using the values in `pattern.prob.list`, `nequiv.list` and `N.list`. The families where all affected subjects share a rare variant are determined by verifying if the length of the carrier vector equals the maximum value of `N.list` for that family. The p-value of the test requiring sharing by all affected subjects is computed by calling `multipleFamilyPValue`.

Value

A list with items: `p` P-value of the exact rare variant sharing test allowing for sharing by a subset of affected subjects. `pall` P-value of the exact rare variant sharing test requiring sharing by all affected subjects. `potentialp` Minimum achievable p-value if all affected subjects were carriers of a rare variant.

References

<http://www.cog-genomics.org/plink2/formats>

Bureau, A., Younkin, S., Parker, M.M., Bailey-Wilson, J.E., Marazita, M.L., Murray, J.C., Mangold, E., Albacha-Hejazi, H., Beaty, T.H. and Ruczinski, I. (2014) Inferring rare disease risk variants based on exact probabilities of sharing by multiple affected relatives. *Bioinformatics*, 30(15): 2189-96, doi:10.1093/bioinformatics/btu198.

Examples

```
data(samplePedigrees)
data(ex.ped.mat)
fam15157 <- samplePedigrees$secondCousinTriple
fam15157.pattern.prob = c(RVsharing(fam15157,carriers=c(15,16,17)),
  RVsharing(fam15157,carriers=c(15,16)),
  RVsharing(fam15157,carriers=c(15)))
fam15157.nequiv = c(1,3,3)
# check that distribution sums to 1
sum(fam15157.pattern.prob*fam15157.nequiv)
fam15157.N = 3:1
# Creating lists
ex.pattern.prob.list = list("15157"=fam15157.pattern.prob)
ex.nequiv.list = list("15157"=fam15157.nequiv)
ex.N.list = list("15157"=fam15157.N)
ex.ped.obj = list(fam15157)
names(ex.ped.obj) = c("15157")
sites = c(92,119)
minor.allele.vec=c(1,4)
RVgene(ex.ped.mat[1:17,],ex.ped.obj,sites,
  pattern.prob.list=ex.pattern.prob.list,
  nequiv.list=ex.nequiv.list,N.list=ex.N.list,
  minor.allele.vec=minor.allele.vec)
# calling with a SnpMatrix
data(snpMat)
RVgene(list(snpMat),ex.ped.obj,sites,
  pattern.prob.list=ex.pattern.prob.list, nequiv.list=ex.nequiv.list,
  N.list=ex.N.list,minor.allele.vec=minor.allele.vec)
```

RVS

RVS

Description

RVS

RVsharing

probability of sharing a rare variant among relatives

Description

computing probability that a rare variant is shared by a set of subjects in a pedigree using the gRain package

Usage

```
RVsharing(ped, carriers = NULL, alleleFreq = NA, kinshipCoeff = NA,
  nSim = NA, founderDist = NULL, useAffected = FALSE, kinshipOrder = 5,
  ...)

## S4 method for signature 'pedigree'
RVsharing(ped, carriers = NULL, alleleFreq = NA,
  kinshipCoeff = NA, nSim = NA, founderDist = NULL, useAffected = FALSE,
  kinshipOrder = 5, ...)

## S4 method for signature 'list'
RVsharing(ped, carriers = NULL, alleleFreq = NA,
  kinshipCoeff = NA, nSim = NA, founderDist = NULL, useAffected = FALSE,
  kinshipOrder = 5, ...)
```

Arguments

ped	S3 pedigree object or a list of pedigree objects
carriers	subjects in pedigree that have the variant, if ped is a list, then this will also be a list of vectors specifying the carriers in each pedigree
alleleFreq	allele frequency among the founders
kinshipCoeff	mean kinship coefficient among the founders
nSim	number of simulations used in monte carlo calculation
founderDist	custom distribution among founders - only used when simulating probability with nSim
useAffected	allows the user to condition on seeing the variant among the affected subjects instead of the final descendants
kinshipOrder	order of the polynomial approximation to the distribution of the number of distinct alleles in the founders (d in Bureau et al.). Must be ≤ 5
...	allows for arguments in the style of v1.7

Details

the function RVsharing computes the probability that all subjects identified as carriers of a rare variant in the vector carriers (or all final descendants in the pedigree if carriers == NULL) share that rare variant AND the final descendants not included in carriers do not carry it, given that the rare variant has been detected in any subject in the union of the carriers and the final descendants of the pedigree. A final descendant is defined as a subject without descendant in the pedigree, it is not necessarily in the youngest generation. If carriers enumerates a subset of pedigree members, the function will then compute the probability these carriers share the rare variant AND the final descendants not included in carriers do not carry it based on the above terms. To obtain the probability that a set of pedigree members carry a rare variant given it was seen in any of the set members (ignoring the carrier status of final descendants not in the set), the pedigree must be trimmed of the other final descendants before calling RVsharing.

Value

sharing probability between all carriers in pedigree

References

Bureau, A., Younkin, S., Parker, M.M., Bailey-Wilson, J.E., Marazita, M.L., Murray, J.C., Mangold, E., Albacha-Hejazi, H., Beaty, T.H. and Ruczinski, I. (2014) Inferring rare disease risk variants based on exact probabilities of sharing by multiple affected relatives. *Bioinformatics*, 30(15): 2189-96, doi:10.1093/bioinformatics/btu198.

Examples

```
data("samplePedigrees")
RVsharing(samplePedigrees$firstCousinPair)
```

samplePedigrees	<i>list of 8 sample pedigree objects</i>
-----------------	--

Description

list of 8 sample pedigree objects

Usage

```
samplePedigrees
```

snpMat	<i>SnpMatrix with genotype information from famVCF for fam15157</i>
--------	---

Description

SnpMatrix with genotype information from famVCF for fam15157

Usage

```
snpMat
```

SnpMatrixToCount	<i>convert a list of SnpMatrices to a single matrix in a similar format as LINKAGE except with minor allele counts</i>
------------------	--

Description

creates a matrix in LINKAGE format using pedigree information from a list of pedigree objects and genotype information from a list of SnpMatrices

Usage

```
SnpMatrixToCount(matList, pedList)
```

Arguments

<code>matList</code>	list of SnpMatrices
<code>pedList</code>	list of pedigrees

Value

matrix in LINKAGE format

Examples

```
data(samplePedigrees)
data(snpMat)
ped <- samplePedigrees$secondCousinTriple
ex.ped.mat <- SnpMatrixToCount(list(snpMat), list(ped))
```

Index

ComputeKinshipPropCoef
 (ComputeKinshipPropCoef), 2
ComputeKinshipPropCoef, 2
ComputeKinshipPropCoef, pedigree-method
 (ComputeKinshipPropCoef), 2

ex.ped.mat, 3

fam15157.vcf, 3
fam28003.vcf, 3

GeneDrop, 4
GeneDropSim.allsubsets.fn (GeneDrop), 4
GeneDropSim.fn (GeneDrop), 4
GeneDropSimExcessSharing.fn (GeneDrop),
 4
get.psubset, 4

multipleFamilyPValue, 5

ped2trio, 6
processPedigree, 6
processPedigree, pedigree-method
 (processPedigree), 6

RVgene, 7
RVS, 9
RVS-package (RVS), 9
RVsharing, 9
RVsharing, list-method (RVsharing), 9
RVsharing, pedigree-method (RVsharing), 9

samplePedigrees, 11
snpMat, 11
SnpMatrixToCount, 11