

Package ‘RVS’

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Type Package

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

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

Maintainer Thomas Sherman <tomsherman159@gmail.com>

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

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'multipleFamilyCalculations.R'
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R topics documented:

ComputeKinshipPropCoef	2
convertMatrix	3
enrichmentPValue	4
enrichmentPValue_R_Backend	5
ex.ped.mat	5
fam15157.vcf	6
fam28003.vcf	6
GeneDrop	6
get.psubset	7
multipleFamilyPValue	8
multipleFamilyPValue_R_Backend	9
multipleVariantPValue	10
multipleVariantPValue_R_Backend	11
ped2trio	11
processPedigree	12
RVgene	13
RVS	16
RVsharing	16
samplePedigrees	18
snpMat	19
SnpmatrixToCount	19
Index	20

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)

```

convertMatrix

convert snpMatrix to a list of vectors of sharing

Description

convert snpMatrix to a list of vectors of sharing

Usage

```

convertMatrix(snpMat, famIds, minorAllele)

```

Arguments

snpMat	SnpMatrix
famIds	family ids corresponding to rows of the snpMap
minorAllele	vector specifying the minor allele of each variant

Value

list of boolean vectors indicating sharing pattern for each variant

enrichmentPValue *enrichment p-value across multiple families and variants*

Description

Computes a p-value for all variants seen across all families

Usage

```
enrichmentPValue(snpMat, famInfo, sharingProbs, threshold = 0)
```

Arguments

snpMat	SnpMatrix
famInfo	data frame containing pedigree, member, father, mother, sex, affected fields for each sequenced subject
sharingProbs	vector of sharing probabilities, must be a named vector with famid's for each probability
threshold	minimum p-value threshold passed to multipleFamilyPValue

Details

For each variant, the families which have all sequenced subjects sharing the variant and the families which have some sequenced subjects sharing the variant are recorded. All unique (family, variant) pairs are accumulated into a single vector and passed to multipleFamilyPValue

Value

p-value

References

Fu, J., Beaty, T.H., Scott, A.F., Hetmanski, J., Parker, M.M., Bailey-Wilson, J.E., Marazita, M.L., et al. 2017. Whole Exome Association of Rare Deletions in Multiplex Oral Cleft Families. *Genetic Epidemiology* 41 (1): 61–69. doi:10.1002/gepi.22010.

enrichmentPValue_R_Backend
R backend for enrichmentPValue calculation

Description

R backend for enrichmentPValue calculation

Usage

```
enrichmentPValue_R_Backend(
  snpMat,
  famIds,
  sharingProbs,
  minorAllele,
  threshold = 0
)
```

Arguments

snpMat	SnpMatrix
famIds	family ids corresponding to rows of the snpMap
sharingProbs	vector of sharing probabilities, must be a named vector with famid's for each probability
minorAllele	which variant value to count as the minor allele
threshold	minimum p-value threshold passed to multipleFamilyPValue

Value

p-value

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	<i>deprecated function</i>
----------	----------------------------

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: `psshare`: vector of RV sharing probabilities `ped.tocompute.vec`: vector of names of the families whose sharing probability is contained in `psshare`. 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, minPValue = 0)
```

Arguments

sharingProbs	named vector of sharing probabilities, where names correspond to famid value of pedigree
observedSharing	boolean vector describing if all affected subjects in the family share the variant (TRUE if all share)
minPValue	the minimum p-value threshold, once the true p-value is determined to be less than this, the computation stops and minPValue is returned - this prevents extremely long computations for extremely small p-values

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

multipleFamilyPValue_R_Backend
R backend for multipleFamilyPValue calculation

Description

R backend for multipleFamilyPValue calculation

Usage

```
multipleFamilyPValue_R_Backend(sharingProbs, observedSharing, minPValue = 0)
```

Arguments

sharingProbs	named vector of sharing probabilities, where names correspond to famid value of pedigree
observedSharing	boolean vector describing if all affected subjects in the family share the variant (TRUE if all share)
minPValue	the minimum p-value threshold, once the true p-value is determined to be less than this, the computation stops and minPValue is returned - this prevents extremely long computations for extremely small p-values

Value

p-value

multipleVariantPValue *generalization of multipleFamilyPValue to multiple variants*

Description

Computes a p-value for each variant sharing pattern across families

Usage

```
multipleVariantPValue(  
  snpMat,  
  famInfo,  
  sharingProbs,  
  minorAllele = NULL,  
  filter = NULL,  
  alpha = 0  
)
```

Arguments

snpMat	SnpMatrix
famInfo	data frame containing pedigree, member, father, mother, sex, affected fields for each sequenced subject
sharingProbs	vector of sharing probabilities, must be a named vector with famid's for each probability
minorAllele	vector specifying the minor allele of each variant
filter	criteria for filtering p-values
alpha	parameter for filter

Details

For each variant, the families which have all sequenced subjects sharing the variant and the families which have some sequenced subjects sharing the variant are recorded. These values are passed to multipleFamilyPValue

Value

list containing p-values and potential p-values for each variant

```
multipleVariantPValue_R_Backend
R backend for multipleVariantPValue calculation
```

Description

R backend for multipleVariantPValue calculation

Usage

```
multipleVariantPValue_R_Backend(
  snpMat,
  famIds,
  sharingProbs,
  minorAllele,
  filter = NULL,
  alpha = 0
)
```

Arguments

snpMat	SnpMatrix
famIds	family ids corresponding to rows of the snpMap
sharingProbs	vector of sharing probabilities, must be a named vector with famid's for each probability
minorAllele	vector specifying the minor allele of each variant
filter	criteria for filtering p-values
alpha	parameter for filter

Value

list of p-values and potential p-values

```
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	<i>extract useful information from a pedigree</i>
-----------------	---

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,
  ...
)
```

Arguments

data	A list of <code>SnpMatrix</code> objects corresponding to each pedigree object in <code>ped.listfams</code> , or a <code>data.frame</code> 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]). From the pedigree information, only the family ID in the first column, the subject ID in the second column and the affection status in the sixth column are used (columns 3 to 5 are ignored). Also, family members without genotype data do not need to appear in this object. The genotype of each variant can be coded in two ways, each corresponding to a different value of the <code>type</code> option: a minor allele count on one column with missing values coded NA, (<code>type="count"</code>) or the identity of the two alleles on two consecutive columns, with missing values coded 0 corresponding to the standard LINKAGE ped format (<code>type="alleles"</code>). If you provide a <code>SnpMatrix</code> object then the genotype should be coded as the minor allele count + 1, i.e. 01 is the homozygous genotype for the common allele.
ped.listfams	a list of pedigree objects, one object for each pedigree for which genotype data are included in <code>data</code> .
sites	a vector of the column indices of the variant sites to test in <code>data</code> . If the argument <code>fams</code> 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 data 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 data
pattern.prob.list	a list of precomputed rare variant sharing probabilities for all possible sharing patterns in the families in data and ped.listfams
nequiv.list	an optional vector of the number of configurations of rare variant sharing by the affected subjects corresponding to the same pattern and probability in pattern.prob.list. Default is a vector of 1s
N.list	a vector of the number of affected subjects sharing a rare variant in the corresponding pattern in pattern.prob.list
type	an optional character string taking value "alleles" or "count". Default is "alleles"
minor.allele.vec	an optional vector of the minor alleles at each site in the sites vector. It is not needed if type="count". If it is missing and type="alleles", the minor allele is assumed to take the value 2
precomputed.prob	an optional list of vectors precomputed rare variant sharing probabilities for families in data and ped.listfams. 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 N.list for the corresponding family (one probability per value of N.list)
maxdim	upper bound on the dimension of the array containing the joint distribution of the sharing patterns for all families in fams (to avoid running out of memory)
partial.sharing	logical indicating whether the test allowing for sharing by a subset of affected subjects should be performed. If FALSE, only the test requiring sharing by all affected subjects is computed. Default is TRUE
...	other arguments to be passed to RVsharing

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

Bureau, A., Begum, F., Taub, M.A., Hetmanski, J., Parker, M.M., Albacha-Hejazi, H., Scott, A.F., et al. (2019) Inferring Disease Risk Genes from Sequencing Data in Multiplex Pedigrees Through Sharing of Rare Variants. *Genet Epidemiol.* 43(1):37-49. doi: 10.1002/gepi.22155.

Examples

```
data(samplePedigrees)
data(ex.ped.mat)
fam15157 <- samplePedigrees$secondCousinTriple
fam15157.pattern.prob = c(RVsharing(fam15157,carriers=c(15,16,17)),
  RVsharing(fam15157,carriers=c(15,16)),
  RVsharing(fam15157,carriers=c(15)))
fam15157.nequiv = c(1,3,3)
# check that distribution sums to 1
sum(fam15157.pattern.prob*fam15157.nequiv)
fam15157.N = 3:1
fam28003 <- samplePedigrees$firstAndSecondCousinsTriple
fam28003.pattern.prob = c(RVsharing(fam28003,carriers=c(36,104,110)),
  RVsharing(fam28003,carriers=c(36,104)),
  RVsharing(fam28003,carriers=c(104,110)),
  RVsharing(fam28003,carriers=c(36)),
  RVsharing(fam28003,carriers=c(104)))
fam28003.N = c(3,2,2,1,1)
fam28003.nequiv = c(1,2,1,1,2)
# check that distribution sums to 1
sum(fam28003.pattern.prob*fam28003.nequiv)
# Creating lists
ex.pattern.prob.list = list("15157"=fam15157.pattern.prob,"28003"=fam28003.pattern.prob)
ex.nequiv.list = list("15157"=fam15157.nequiv,"28003"=fam28003.nequiv)
ex.N.list = list("15157"=fam15157.N,"28003"=fam28003.N)
ex.ped.obj = list(fam15157,fam28003)
names(ex.ped.obj) = c("15157","28003")
sites = c(92,119)
minor.allele.vec=c(1,4)
RVgene(ex.ped.mat,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 list
data(famVCF)
fam15157.snp = suppressWarnings(VariantAnnotation::genotypeToSnpMatrix(fam15157.vcf))
fam28003.snp = suppressWarnings(VariantAnnotation::genotypeToSnpMatrix(fam28003.vcf))
ex.SnpMatrix.list = list(fam15157=fam15157.snp$genotypes, fam28003=fam28003.snp$genotypes)
RVgene(ex.SnpMatrix.list, 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

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).

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,
  splitPed = FALSE,
  useFounderCouples = TRUE,
  ...
)

## S4 method for signature 'pedigree'
RVsharing(
```



```

    ped,
    carriers = NULL,
    alleleFreq = NA,
    kinshipCoeff = NA,
    nSim = NA,
    founderDist = NULL,
    useAffected = FALSE,
    kinshipOrder = 5,
    splitPed = FALSE,
    useFounderCouples = TRUE,
    ...
)

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

```

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	a logical value indicating whether 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
splitPed	a logical value indicating whether to split the pedigree in subpedigrees below each founder to enable computations in pedigrees too large to be stored in a single Bayesian network

```

useFounderCouples      a logical value indicating whether to exploit the interchangeability of the mother
                        and father from founder couples to save computations. Warning! This works
                        only when all founders have only one spouse. Set to FALSE if at least one
                        founder has two or more spouses. Only used when splitPed = TRUE
...                    allows for additional arguments

```

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, or if `splitPed = TRUE`, a vector of sharing probabilities for all subsets of the carriers

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.

Sherman, T., Fu, J., Scharpf, R., Bureau, A., and Ruczinski, I. (2018) Detection of rare disease variants in extended pedigrees using RVS. *Bioinformatics*, 1-3, doi: 10.1093/bioinformatics/bty976

Examples

```

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

```

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

Description

list of 8 sample pedigree objects

Usage

```
samplePedigrees
```

```
snpMat
```

```
SnpMatrix with genotype information from famVCF for fam15157
```

Description

SnpMatrix with genotype information from famVCF for fam15157

Usage

```
snpMat
```

```
SnpMatrixToCount
```

```
convert a list of SnpMatrices to a single matrix in a similiar format as LINKAGE except with minor allele counts
```

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

```
matList      list of SnpMatrices
pedList      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
convertMatrix, 3

enrichmentPValue, 4
enrichmentPValue_R_Backend, 5
ex.ped.mat, 5

fam15157.vcf, 6
fam28003.vcf, 6

GeneDrop, 6
GeneDropSim.allsubsets.fn (GeneDrop), 6
GeneDropSim.fn (GeneDrop), 6
GeneDropSimExcessSharing.fn (GeneDrop),
 6
get.psubset, 7

multipleFamilyPValue, 8
multipleFamilyPValue_R_Backend, 9
multipleVariantPValue, 10
multipleVariantPValue_R_Backend, 11

ped2trio, 11
processPedigree, 12
processPedigree, pedigree-method
 (processPedigree), 12

RVgene, 13
RVS, 16
RVsharing, 16
RVsharing, list-method (RVsharing), 16
RVsharing, pedigree-method (RVsharing),
 16

samplePedigrees, 18
snpMat, 19
SnpMatrixToCount, 19