Package 'MultiPhen'

January 20, 2025

Type Package
Title A Package to Test for Multi-Trait Association
Version 2.0.3
Date 2020-02-06
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Depends MASS, abind, epitools, meta
Imports HardyWeinberg, RColorBrewer
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Description Performs genetic association tests between SNPs (one-at-a-time) and multiple phenotypes (separately or in joint model).
License GPL-2
LazyLoad yes
NeedsCompilation no

Repository CRAN

Date/Publication 2020-02-09 13:50:02 UTC

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MultiPhen-package MultiPhen, a package for the genetic association testing of multiple phenotypes

Description

MultiPhen is the package containing the function mPhen, which performs association testing between genetic variants (SNPs; CNVs to be added soon) and multiple phenotypes. The primary purpose is for modelling and testing multiple phenotypes jointly by performing an ordinal regression where SNPs are treated as the outcome and multiple phenotypes are predictors; this can have large increases in statistical power to detect genotype-phenotype associations over the univariate approach. However, mPhen can also be used to perform standard univariate linear regression (SNP as predictor) and univariate ordinal regression (SNP as outcome) on the phenotypes under study. mPhen can be applied to genotyped or imputed data. From version 0.4 the option "multiPhenTest" is now called "JointModel", and its default is now "TRUE"

Details

Package:	MultiPhen
Type:	Package
Version:	2.0.0
Date:	2013-12-09
License:	GPL-2
LazyLoad:	yes

Author(s)

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References

O'Reilly et al. 2012. MultiPhen: Joint model of multiple phenotypes can increase discovery in GWAS. http://dx.plos.org/10.1371/journal.pone.0034861

mPhen

Description

mPhen performs association testing between genetic variants (SNPs; CNVs) and multiple phenotypes. The primary purpose is for modelling and testing multiple phenotypes jointly by performing an ordinal regression where SNPs are treated as the outcome and multiple phenotypes are predictors; this can have large increases in statistical power to detect genotype-phenotype associations over the univariate approach (method described in O'Reilly et al. 2012, see below). However, mPhen can also be used to perform standard univariate linear regression (SNP as predictor) and univariate ordinal regression (SNP as outcome) on the phenotypes under study. mPhen can be applied to directly genotyped or imputed data.

Usage

genoData	Either a matrix (for directly measured genotypes) or 3 dimensional array (for imputed genotypes). The first dimension (rows) corresponds to individuals, and row.names are inidividual IDs. The second dimension corresponds to SNPS, with col.names equal to the snp identifiers. For directly measured genotypes, the value in each cell is a numeric genotype(i.e. $AA = 0$, $AB=1$, $BB = 2$). For imputed genotypes, the 3rd dimension corresponds to genotypes (with dimnames(genoData)[[3]]) equal to a numeric vector corresponding to genotype values. The values in these cells are the probability of each genotype multiplied by
	1000. For copy number genotypes the numeric values correspond to numbers of copies. An example provided by 'snps' and 'snps.imputed'
phenoData	Matrix containing phenotype data, where each row corresponds to an individ- ual and row.names are individual IDs. Each column contains data on a certain phenotype across the sample of individuals (can be quantitative, case/control or ordinal. Must be numeric); the column header provides the phenotype name. An example is provided by 'pheno'.
phenotypes	Vector of phenotype names, to be tested. If value is 'all' then all phenotypes are included after removing covariates and residuals.
covariates	Vector of phenotypes, from phenoData, to be considered as covariates to be controlled for in the regression (Default is no covariates).
resids	Vector of residuals, from phenoData, alternative way to adjust for covariates, which pre-calculates offset terms to use in the per SNP regression (Default is no residuals).
strats	Statification vector (i.e. cases/controls, exposed/not exposed, male/female etc), from phenoData (Default is no stratification).

mPhen

opts A list of options, which is obtained from mPhen.options(c("regression","pheno.input")). To get more information about these options, type mPhen.options(c("regression","pheno.input"),descr=TF

Value

Returns a list, with two items. The first item (Results) is a Results is a 4 dimensional matrix, with dimensions [strata, snps, phenotypes, result_type], where result_type includes beta, pvalue and Nobs. The second item is a vector of minor allele frequencies.

Note

The user should remember that the genotype data file is always a matrix of at least a column, hence if taking a subset of 1 SNP in the non-imputed genotype data matrix, the option drop = FALSE should be used (see the example below)

Author(s)

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References

O'Reilly et al. 2012. MultiPhen: Joint model of multiple phenotypes can increase discovery in GWAS. http://dx.plos.org/10.1371/journal.pone.0034861

Examples

```
# for imputed data
```

mPhen.assoc

Description

This function is called by mPhen. If you are doing association on multiple batches of genotype data, it is more efficient to use this function, and to pre-prepare a 'phenoObject' object once and then use this function

Usage

```
mPhen.assoc(genoData, phenoObject,opts = mPhen.options("regression"),
subinds =1:(dim(genoData)[1]))
```

Arguments

phenoObject	A phenotype object prepared by mPhen.preparePheno
genoData	This can be obtained from mPhen.readGenoConnection()\$genoData. It is either a matrix (for directly measured genotypes) or 3 dimensional array (for imputed genotypes). The first dimension (rows) corresponds to individuals, and row.names are inidividual IDs. The second dimension corresponds to SNPS, with col.names equal to the snp identifiers. For directly measured genotypes, the value in each cell is a numeric genotype(i.e. AA = 0, AB=1, BB = 2). For imputed genotypes, the 3rd dimension corresponds to genotypes (with dimnames(genoData)[[3]]) equal to a numeric vector corresponding to genotype values. The values in these cells are the probability of each genotype multiplied by 1000. For copy number genotypes the numeric values correspond to numbers of copies. An example provided by 'snps'.
opts	A list of options, which is obtained from mPhen.options("regression"). To get more information about these options, type mPhen.options("regression",descr=TRUE)
subinds	This indicates the indices of individuals to include in the analysis. It is possible to have repeat indices (i.e. for bootstrap)

Value

Returns a list, with two items. The first item (Results) is a Results is a 4 dimensional matrix, with dimensions [strata, snps, phenotypes, result_type], where result_type includes beta, pvalue and Nobs. The second item is a vector of minor allele frequencies.

mPhen.cca

Description

Carries out a sparse canonical correlation analysis

Usage

Arguments

genoData	A 2 dimensional array. The first dimension (rows) corresponds to individuals, and row.names are inidividual IDs. The second dimension corresponds to SNPS, with col.names equal to the snp identifiers. The entries are either genotypes, or expected genotypes.
phenoObject	A phenotype object prepared by mPhen.preparePheno.
opts	A list of options, which is obtained from mPhen.options("regression"). To get more information about these options, type mPhen.options("regression",descr=TRUE).
vs.G	If true performs variable selection on genotypes. Is equal to opts\$mPhen.variable_selection by default
vs.P	If true performs variable selection on phenotypes. Is equal to opts\$mPhen.variable_selection by default
subinds	This indicates the indices of individuals to include in the analysis. It is possible to have repeat indices (i.e. for bootstrap)

Value

A list with following elements

betasp	Phenotype weights
betasg	Genotype weights
resultsGeno	Single (combined) phenotype analysis results against all genotypes
resultsPheno	Multiple phenotype analysis results against single (combined) genotype

mPhen.defineOptions Defines and modifies options.

Description

This reads options from the command-line, if provided. Also it can replace references to system variables in option values, such as '*' or \\$WORK, with fully qualified values. Also translates coordinates which use Gb, Mb, Kb to integer values. All defined options of the form mPhen.xxx are examined and modified.

Usage

```
mPhen.defineOptions(file = NULL, getOptionsFromCommandLine = TRUE)
```

Arguments file

specified if the options are in a script file and not set manually

getOptionsFromCommandLine

If running from a script using command Rscript, then this will read in command line options, such as \'-mPhen.logp=FALSE\'

Value

None

mPhen.options

Retrieves default mPhen options, and descriptions.

Description

This command is used to get options which can be modified to control the behaviour of MultiPhen commands. It provides a list of options which are relevant to a particular command. For example, mPhen.assoc() has its behaviour controlled by options in mPhen.options("regression"). In order to get a list of all options, you can type mPhen.options(descr=TRUE).

Usage

```
mPhen.options(type=c("regression", "plot", "geno.input",
"pheno.input","meta.analysis","misc"), descr = FALSE)
```

type	A value which can take any of the following values: "regression", "plot", "geno.input", "pheno.input", "meta
descr	If set to TRUE, then returns descriptions of all the options. If FALSE, then
	returns the values of all the options.

Value

A list of default option values. Note, the default value for opts = mPhen.options("regression"), has opts\$inverseRegress =TRUE, opts\$JointModel = TRUE and opts\$geno.link = "ordinal", which is the standard multiPhen model.

mPhen.plotCorrelation Plots correlation between phenotype values conditional on genotype

Description

Plots the correlation between phenotype values, with different genotypes coloured differently. Note that this will plot (dim(pheno_to_plot)[2] -1)* dim(geno)[2] plots

Usage

```
mPhen.plotCorrelation(pheno_to_plot,geno,title="",cex=0.25, cols =c(1, 2, 3))
```

Arguments

pheno_to_plot	the phenotype to plot
geno	Genotypes to use for stratifying samples
title	Title of plots
cex	Scaling of points
cols	thre colours to be used in the plot

Value

None

mPhen.preparePheno Prepare phenotype data for analysis

Description

This harmonises the phenotype data with genotype data, and also extract the relevant columns from a larger phenotype matrix, and also pre-calculates stratification indices and residuals. This is called by mPhen function, but quicker to do this just once for batched genotype data.

Usage

```
mPhen.preparePheno(phenoData,
pcs = NULL, indiv = if (is.null(pcs)) rownames(phenoData) else rownames(pcs),
    opts = mPhen.options("regression"))
```

Arguments

phenoData	This is typically the output of mPhen.readPhenoFiles() or mPhen.simulate(). It is a list containing the elements phenoData\$pheno and phenoData\$limit. The element phenoData\$pheno is a matrix containing phenotype data, where each row corresponds to an individual and row.names are individual IDs. Each col- umn contains data on a certain phenotype across the sample of individuals (can be quantitative, case/control or ordinal. Must be numeric); the column header provides the phenotype name. An example is provided by 'pheno'. The ele- ment phenoData\$limit is a list which specifies which of the phenotypes to use as covariates, variables to associate, etc, in the following way:
	limit\$phenotypes - vector of phenotypes to be tested. If set to 'all' then all phe- notypes are used. limit\$covariates - vector of phenotypes to be considered as co- variates to be controlled for in the regression, limit\$resids - vector of phenotypes to be considered as residuals, which is an alternative way to adjust for covariates, which pre-calculates offset terms to use in the per SNP regression limit\$strats - statification vector (i.e. cases/controls, exposed/not exposed, male/female etc). limit\$excls - Exclusion vector, ie. names of phenotypes which should be used as exclusion criteria respectively. Rows will be excluded if the value in any of exclusion columns is NA or 1
	Alternatively, phenoData can simply be a matrix containing phenotype data, in which case, the default value of limit used is limit = list(phenotypes="all")
pcs	This is the genotype pcs which should be used in the analysis. If specified it should be in the same sample order as 'inidv'. The user still needs to specify in the phenoData\$limit\$covariate or phenoData\$limit\$resids the names of the PCs they wish to include (i.e. covariate = $c("PC1","PC2")$). These would typically be obtained from mPhen.readGenotypes.
indiv	individuals to be used. If unspecified the fucntion defaults to using all individuals
opts	A list of options, which is obtained from mPhen.options("regression"). To get more information about these options, type mPhen.options("regression",descr=TRUE)

Value

A list object, which can then be used in mPhen.assoc.

mPhen.readGenotypes Open, and read from a read connection to a genotype file

Description

Opens a read connection to a list of files which have a VCF-like format. Can read a .gz file. Also supports plink bed format. Also supports cnvPipe format. Also supports a .zip file format used by cnvHap.

Usage

mPhen.readGenotypes(genoConnection, indiv = NULL,opts =mPhen.options("geno.input"))

Arguments

genoConnection	A list of paths to genotype files. Each file might represent a different cohort with overlapping snp set. These files can be .vcf .vcf.gz and .zip files. They can also be plink bed files. In the case that bed files are used, the root name of the file should be given (i.e. hapmap2 instead of hapmap2.bed).
	Alternatively, this can also be the object returned by mPhen.readGenotypes(). This means that the connection only has to be established once, and can be read from multiple times in batches.
indiv	A list of individual ids. If provided the results will be in this order. If not provided the results will be in the order given by the genotype file
opts	A list of options, which is obtained from mPhen.options("geno.input"). To get more information about these options, type mPhen.options("geno.input",descr=TRUE)

Value

Returns a list object which can be used by subsequent calls to readGenotypes(..). This list also includes a value genoData, which contains the genotypes which have been read. This includes a connection to the underlying file (conn), a list of sample ids, and a flag indicating whether the file is zipped. It also includes 'pcs', which is a matrix of genotype pcs. These are only calculated is opts\$mPhen.numGenoPCs>0, and are only calculated once all batches have been read (but will include all genotypes which have been read previously using the same connection).

mPhen.readPhenoFiles Read and merge phenotype files

Description

This helper function merges multiple phenotype files into a single phenotype matrix, and applies missing value and exclusion criteria

Usage

```
mPhen.readPhenoFiles(phenoFiles,
limitFile = getOption("mPhen.limitFile","./limit.txt"),
excludeFile =getOption("mPhen.excludeFile","./exclude.txt"),
opts = mPhen.options("pheno.input"),
indiv = NULL)
```

Arguments

phenoFiles	A list of paths to phenotype files (can be more than 1)
excludeFile	A path to a file which lists ids to exclude from further analysis, or alternatively is a two column file, with the first column of ids and a second column of num- berical values which are used in conjunction with opts\$quantileThresh
limitFile	As an alternative to specifying covariates, resids, strats and excl in mPhen.preparePheno(), you can also specify this information via a limitfile, which is tab delimited file in which the first column specifies the type of variable to set (pheno, covar, resid, strat, excl), the second column specifies the phenotype name, and the third column option-ally specifies a transformation Different lines can then be used for different values. The transformation syntax includes 'quantile' and 'factor', and also 'thresh_x_y' in which values less than x are coded 0 and greater than y are coded 1; and also 'toptail_x_y' where values less than x percentile are coded 0 and greater than y percentile are coded 1.
opts	A list of options, which is obtained from mPhen.options("pheno.input"). To get more information about these options, type mPhen.options("pheno.input",descr=TRUE)
indiv	A list of individual ids. If provided the phenotype matrix will be re-ordered to match

Value

An object consisting of a single merged phenotype matrix, and also a 'limit' object which specifies phenotypes to include in analyses. The limit is a list with the following entries. phenotypes - vector of phenotypes to be tested. If set to 'all' then all phenotypes are used. covariates - vector of phenotypes to be considered as covariates to be controlled for in the regression, resids - vector of phenotypes to be considered as residuals, which is an alternative way to adjust for covariates, which pre-calculates offset terms to use in the per SNP regression strats - statification vector (i.e. cases/controls, exposed/not exposed, male/female etc).

excls - Exclusion vector, ie. names of phenotypes which should be used as exclusion criteria respectively. Rows will be excluded if the value in any of exclusion columns is NA or 1

mPhen.sampleCovar Generates a covariance matrix.

Description

This function can be use to sample covariance matrices. This is useful when simulating data to test Multiphenotype based association strategies. This function lets the user decide on the orthoganality within 'blocks' and between 'blocks' of correlated variables/

Usage

```
mPhen.sampleCovar(noPhenos,blockSize, orthogAll = c(0.9,0.5),
dirichletScale = 50, resample = FALSE,
sd = rgamma(noPhenos,shape=10,rate = 10))
```

Arguments

noPhenos	The number of phenotypes to simulate
blockSize	The number of phenotypes per covariance block
orthogAll	The orthogonality relationships between and within blocks expressed as a number on the interval $(0,1)$. A number closer to one indicates closer to orthogonality, whereas 0 indicates non-orthogonality. First number is orthogonality between blocks, second is orthogonality within blocks.
dirichletScale	When sampling off diagonal elements of the cholesky decomposition, how much deviation from uniform to allow. Should be a number in interval (0,+Inf). Smaller value leads to greater variation
resample	Whether to randomly shuffle phenotype columns after sampling.
sd	Standard deviation for each phenotype

Value

Simulated covariance matrix

mPhen.sampleGeno Sample genotypes

Description

...

Usage

```
mPhen.sampleGeno(n = 100, sampSize = 100, chr="0",pos = 1:n,
snpids = paste(chr,pos,sep="_"),meanAlleleFreq=0.2, mu = 10,
samples =paste("id",1:sampSize,sep="_"),imputed = FALSE, dirichlet = 1)
```

n	Number of genotypes to sample
sampSize	Number of individuals to sample
chr	Name of chromosome
pos	Positions of genotypes on chromosome
snpids	Ids of genotypes
meanAlleleFreq	The mean allele frequency to simulate
mu	A weight parameter which controls how close to the meanAlleleFreq the allele frequencies are sampled, via a beta distribution. A higher number implies allele frequencies stay closer to mean
samples	The sample ids
imputed	Whether to simulate imputed data
dirichlet	The weight of a dirichlet distribution used to simulated imputed data

mPhen.simulate

Value

Returns matrix of genotypes, with individuals by rows, and snps by column, or a 3 dimensional array if imputed is TRUE

mPhen.simulate Simulates phenotypes according to a correlation structure.

Description

This function simulates phenotypes based on a pre-defined correlation structure (which can also be obtained from mPhen.sampleCovar), and a genetic effect x. The function works by sampling a phenotype from a correlation matrix in a linearly transformed space such that the genetic effect direction is only in the direction of the x-axis, then transforming back into the original space. If inverse is TRUE, then the phenotypes are sampled first with no genetic effect, then the genotype is sampled according to the effect direction.

Usage

```
mPhen.simulate(x,sample_names, covar,effDir,
varexp,inverse=FALSE, geno.link="gaussian",
effDirInReverseEigenspace=FALSE, freq = 0.1)
```

x	A vector of genotype effect. If a single SNP has an effect, this will just be genotypes at this SNP	
sample_names	Vector of sample names, should have same length as x	
covar	Covariance of phenotypes, should be an n by n matrix, where n is the number of phenotypes to simulate.	
effDir	Direction in phenotype space in which to simulate the effect	
varexp	The proportion of variance of phenotype variation in the target direction ex- plained by the genotypic effect overall.	
inverse	If TRUE, then simulates correlated phenotypes, and then simulates genotypes from phenotypes in specified direction. Otherwise, simulates correlated pheno- types with direction of effect based on input genotypes.	
geno.link	Only applicable if inverse = TRUE, in which case it specifies a link function for genotypes. Can be binomial, gaussian or ordinal.	
effDirInReverseEigenspace		
	If TRUE, then effDir is interpreted as eigenvector weights, ordered from eigenvector with smallest eigenvalue to eigenvector with biggest eigenvector (i.e. in reverse direction). This is useful if you want to simulate directs which are in the least variable axis of variation.	
freq	If inverse = TRUE, then this is target allele frequency.	

Value

Returns a list of three elements: pheno - a matrix of phenotype values, with phenotypes in columns and samples in rows; and geno- a vector genotypes, either sampled if inverse=TRUE, or the original genetic effect x; and limit - this is a default list of phenotypes to include in subsequent association analysis, as well as covariates (empty) and residuals (empty). This object can then be used by mPhen.preparePheno

mPhen.writeOutput Prepares output files and plots from MultiPhen results

Description

Writes output to files defined in mPhen.openOutputConnection, and extracts pvalues and betas for further plots.

Usage

```
mPhen.writeOutput(results,
output = getOption("mPhen.resultsName","resultsDir/"),geno = NULL,
towrite = list(long.txt = getOption("mPhen.writeLong",TRUE),
qc.txt = getOption("mPhen.writeQC",FALSE),
wide.txt = getOption("mPhen.writeWide",TRUE)),
toplot = list(.manh = TRUE, .qq = TRUE,.heatm = TRUE,
```

```
.fprint = !is.null(geno)),
opts = mPhen.options("plot"))
```

Arguments

results	Output of mPhen.assoc
output	Directory to write results, or object returned by mPhen.writeOutput()
towrite	List specifying which formats to write output - long.txt and wide.txt for standard results; qc.txt for per-sample qc output.
toplot	List specifying which formats to plot outputqq for qq plot, .manh for manhat- tan; .heatm for pvalue heatmap; .fprint for fingerprint plot
geno	Genotype matrix. Note that attr(geno,"closeConnection") controls whether plots are produced, as this indicates whether all batches of genotype data have been analysed
opts	A list of options, which is obtained from mPhen.options("plot"). To get more information about these options, type mPhen.options("plot",descr=TRUE)

Value

Returns an outputConnection, which can be used to write further results.

pheno

pheno

A dummy phenotype dataset that provides an example of the input phenotype data used by the package

Description

A dummy dataset of 5 phenotypes measured in 150 individuals. The data has been generated to yield significant results for SNP1 and SNP2 of the snps dataset. The first two columns have been generated as alpha + beta1*snp + beta2*snp2 + error (with different alphas, betas and errors for each phenotype), the third has been generated as alpha + beta1*testPheno2 + beta2*snp3 + error, the fourth column is the results of sample of a binomial distributioni correlated with testPheno3, and the final column is the 1st PC of the principal component analysis of the snps matrix.

Format

A matrix with 150 phenotype observations.

testPheno1 a numeric vector testPheno2 a numeric vector testPheno3 a numeric vector testPheno4 a numeric vector testPheno5 a numeric vector

Details

Please note the following IMPORTANT issue: the 'pheno' matrix has both column names and row names! the column names MUST be the names of the phenotypes and the row names MUST be the codes representing each individual in the pheno matrix, one individual for each row. Both row names and column names are extracted by the main function and are therefore mandatory

Examples

```
data(pheno)
head(pheno)
dimnames(pheno)[[1]] # the row names
dimnames(pheno)[[2]] # the column names
```

read.plink

Description

read.plink is a convenience function designed to read PLINK binary files (i.e. files that end with the suffix ".bed") in a R session. Please be aware that binary PLINK files are binary for a reason, i.e. to store genotype data in a compact way. Once they are imported in R they exist in R in a un "unpacked" form, and can therefore be very big. If the .bed file is big, or very big, the result will be that R will run out of memory and crash, or make the whole system slow or unresponsive. It is MANDATORY that in the directory containing the binary file also reside two accesory files, with the same name as the binary file but with extensions .fam and .bim, both produced by PLINK.

Usage

```
read.plink(root,indiv = NULL, opts = mPhen.options("geno.input"))
```

Arguments

root	filename of the dataset in PLINK binary format, WITHOUT the .bed extension.
indiv	List of individuals, results will be in this order
opts	List of options, use mPhen.options("geno.input",descr=TRUE) for more details
	of each option.

Details

Please note that, if the binary file is listed a "mydata.bed", the filename is "mydata", and the extension is ".bed". In this case "mydata" would be used as root value.

Value

A matrix of dimesions n by m, with n rows corresponding to the n individuals in the dataset, and m columns corresponding to the m markers. The colnames are retrived from the .fam file, and (should) correspond to the markers' names.

Note

Please do note that the concept of a "big" binary file, or a binary file that is "too big" is purely dependent on the computer on which the code is running. A computer with 512MB of RAM will stop being able to read in a whole binary file well before a 16GB RAM machine.

Author(s)

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References

The plink homepage is at: https://www.cog-genomics.org/plink2

snps

snps

A dummy snp dataset that provides an example of the input snp data used by the package

Description

A dummy dataset of three SNPs, as a matrix of 3 column and 150 rows. The genotypes are in 0/1/2 format (0 for "AA", 1 for "Aa" and 2 for "aa", where A and a correspond, arbitrarily, to the two alleles). The data has been randomly generated, for instructional purposes only, and do not yield a significant association with any of the example phenotypes.

Usage

data(snps)

Format

A data frame with 150 genotype observations.

rsID1 a numeric vector

rsID2 a numeric vector

rsID3 a numeric vector

Details

The 150 genotypes in 'snp' correspond to the phenotype data on 150 individuals in 'pheno', i.e. one individual for each line. Please note the following important points: genotype data must be in matrix format, with one row for each individual and as many columns for each SNP. In the case of one single genotype the data must still conform to this format, as a matrix of as many rows as individuals and one single column for the one genotype present. A second important point is that the column names must be the rsID of the SNP for genotypes in the 0/1/2 format. Further options of genotype format (incorporating raw genotype data, and CNV genotypes) will be available and documented in future releases.

Examples

data(snps)
dim(snps)
colnames(snps)

snps.imputed

Description

A toy dataset of three imputed SNP, for 150 individuals. For each individuals, and for each SNP, the first column is the probability of a minor allele homozygote genotype (genotype "0"), the second column is the probability of an heterozygote genotype (genotype "1") and the third and last column is the probability of a major allele homozygote (genotype "2").

Usage

data(snps.imputed)

Format

A matrix of 150 rows and nine columns.

Examples

data(snps.imputed)

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