Package 'midasHLA'

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Title R package for immunogenomics data handling and association analysis

Version 1.16.0

Description MiDAS is a R package for immunogenetics data transformation and statistical analysis. MiDAS accepts input data in the form of HLA alleles and KIR types, and can transform it into biologically meaningful variables, enabling HLA amino acid fine mapping, analyses of HLA evolutionary divergence, KIR gene presence, as well as validated HLA-KIR interactions. Further, it allows comprehensive statistical association analysis workflows with phenotypes of diverse measurement scales. MiDAS closes a gap between the inference of immunogenetic variation and its efficient utilization to make relevant discoveries related to T cell, Natural Killer cell, and disease biology.

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`aaVariationToCounts` *Transform amino acid variation data frame into counts table*

Description

`aaVariationToCounts` convert amino acid variation data frame into counts table.

Usage

```
aaVariationToCounts(aa_variation)
```

Arguments

`aa_variation`	Amino acid variation data frame as returned by hlaToAAVariation.

Value

Amino acid counts data frame. First column holds samples ID's, further columns, corresponding to specific amino acid positions, give information on the number of their occurrences in each sample.

adjustPValues *Adjust P-values for Multiple Comparisons*

Description

Given a set of p-values, returns p-values adjusted using one of several methods.

Usage

```
adjustPValues(p, method, n = length(p))
```

Arguments

p	numeric vector of p-values (possibly with NAs). Any other R object is coerced by as.numeric.
method	correction method. Can be abbreviated.
n	number of comparisons, must be at least length(p); only set this (to non-default) when you know what you are doing! Note that for Bonferroni correction it is possible to specify number lower than length(p).

Details

This function modifies stats::p.adjust method such that for Bonferroni correction it is possible to specify n lower than length(p). This feature is useful in cases when knowledge about the biology or redundance of alleles reduces the need for correction.

See p.adjust for more details.

Value

A numeric vector of corrected p-values (of the same length as p, with names copied from p).

allele_frequencies *Alleles frequencies scraped from allelefrequencies.net*

Description

Accessed on 28.07.20

Usage

```
allele_frequencies
```

Format

A data frame with 2096 rows and 3 variables:

var allele number, character

population reference population name, character

frequency allele frequency in reference population, float

Details

A dataset containing allele frequencies across 5697 alleles For details visit the search results page in the allelefrequencies.net database website.

Source

www.allelefrequencies.net

---

analyzeAssociations *Association analysis*

Description

`analyzeAssociations` perform association analysis on a single variable level using a statistical model of choice.

Usage

```
analyzeAssociations(
  object,
  variables,
  placeholder = "term",
  correction = "bonferroni",
  n_correction = NULL,
  exponentiate = FALSE
)
```

Arguments

`object`	An existing fit from a model function such as lm, glm and many others.
`variables`	Character vector specifying variables to use in association tests.
`placeholder`	String specifying term in `object`'s formula which should be substituted with variables during analysis.
`correction`	String specifying multiple testing correction method. See details for further information.

n_correction — Integer specifying number of comparisons to consider during multiple testing correction calculations. For Bonferroni correction it is possible to specify a number lower than the number of comparisons being made. This is useful in cases when knowledge about the biology or redundance of alleles reduces the need for correction. For other methods it must be at least equal to the number of comparisons being made; only set this (to non-default) when you know what you are doing!

exponentiate — Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to tidy. This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to FALSE.

Details

correction specifies p-value adjustment method to use, common choice is Benjamini & Hochberg (1995) ("BH"). Internally this is passed to p.adjust.

Value

Tibble containing combined results for all variables. The first column "term" hold the names of variables. Further columns depends on the used model and are determined by associated tidy function. Generally they will include "estimate", "std.error", "statistic", "p.value", "conf.low", "conf.high", "p.adjusted".

Examples

```
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles")

# analyzeAssociations expects model data to be a data.frame
midas_data <- as.data.frame(midas)

# define base model
object <- lm(disease ~ term, data = midas_data)

# test for alleles associations
analyzeAssociations(object = object,
                    variables = c("B*14:02", "DRB1*11:01"))
```

---

analyzeConditionalAssociations

Stepwise conditional association analysis

Description

analyzeConditionalAssociations perform stepwise conditional testing adding the previous top-associated variable as covariate, until there are no more significant variables based on a self-defined threshold.

Usage

```
analyzeConditionalAssociations(
  object,
  variables,
  placeholder = "term",
  correction = "bonferroni",
  n_correction = NULL,
  th,
  th_adj = TRUE,
  keep = FALSE,
  rss_th = 1e-07,
  exponentiate = FALSE
)
```

Arguments

object	An existing fit from a model function such as lm, glm and many others.
variables	Character vector specifying variables to use in association tests.
placeholder	String specifying term to substitute with value from x. Ignored if set to NULL.
correction	String specifying multiple testing correction method. See details for further information.
n_correction	Integer specifying number of comparisons to consider during multiple testing correction calculations. For Bonferroni correction it is possible to specify a number lower than the number of comparisons being made. This is useful in cases when knowledge about the biology or redundance of alleles reduces the need for correction. For other methods it must be at least equal to the number of comparisons being made; only set this (to non-default) when you know what you are doing!
th	Number specifying threshold for a variable to be considered significant.
th_adj	Logical flag indicating if adjusted p-value should be used as threshold criteria, otherwise unadjusted p-value is used.
keep	Logical flag indicating if the output should be a list of results resulting from each selection step. Default is to return only the final result.
rss_th	Number specifying residual sum of squares threshold at which function should stop adding additional variables. As the residual sum of squares approaches 0 the perfect fit is obtained making further attempts at variable selection nonsense. This behavior can be controlled using rss_th.
exponentiate	Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to tidy. This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to FALSE.

Value

Tibble with stepwise conditional testing results or a list of tibbles, see keep argument. The first column "term" hold the names of variables. Further columns depends on the used model and are determined by associated tidy function. Generally they will include "estimate", "std.error", "statistic", "p.value", "conf.low", "conf.high", "p.adjusted".

Examples

```
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles")

# analyzeConditionalAssociations expects model data to be a data.frame
midas_data <- as.data.frame(midas)

# define base model
object <- lm(disease ~ term, data = midas_data)
analyzeConditionalAssociations(object,
                           variables = c("B*14:02", "DRB1*11:01"),
                           th = 0.05)
```

`applyInheritanceModel` *Apply inheritance model*

Description

Helper function transforming experiment counts to selected `inheritance_model`.

Usage

```
applyInheritanceModel(
  experiment,
  inheritance_model = c("dominant", "recessive", "additive", "overdominant")
)

## S3 method for class 'matrix'
applyInheritanceModel(
  experiment,
  inheritance_model = c("dominant", "recessive", "additive", "overdominant")
)

## S3 method for class 'SummarizedExperiment'
applyInheritanceModel(
  experiment,
  inheritance_model = c("dominant", "recessive", "additive", "overdominant")
)
```

Arguments

`experiment`	Matrix or SummarizedExperiment object.
`inheritance_model`	String specifying inheritance model to use. Available choices are `"dominant"`, `"recessive"`, `"additive"`.

Details

Under "dominant" model homozygotes and heterozygotes are coded as 1. In "recessive" model homozygotes are coded as 1 and other as 0. In "additive" model homozygotes are coded as 2 and heterozygotes as 1. In "overdominant" homozygotes (both 0 and 2) are coded as 0 and heterozygotes as 1.

Value

experiment converted to specified inheritance model.

---

as.data.frame.MiDAS *Coerce MiDAS to Data Frame*

Description

Coerce MiDAS to Data Frame

Usage

```
## S3 method for class 'MiDAS'
as.data.frame(x, ...)
```

Arguments

x	any R object.
...	additional arguments to be passed to or from methods.

Value

Data frame representation of MiDAS object. Consecutive columns hold values of variables from MiDAS's experiments and colData. The metadata associated with experiments is not preserved.

---

backquote *Backquote character*

Description

backquote places backticks around elements of character vector

Usage

```
backquote(x)
```

Arguments

x	Character vector.

Details

backquote is useful when using HLA allele numbers in formulas, where '*' and ':' characters have special meanings.

Value

Character vector with its elements backticked.

---

characterMatches *Check if character matches one of possible values*

Description

characterMatches checks if all elements of a character vector matches values in choices.

Usage

```
characterMatches(x, choice)
```

Arguments

x	Character vector to test.
choice	Character vector with possible values for x.

Value

Logical indicating if x's elements matches any of the values in choice.

---

checkAlleleFormat *Check HLA allele format*

Description

checkAlleleFormat test if the input character follows HLA nomenclature specifications.

Usage

```
checkAlleleFormat(allele)
```

Arguments

allele	Character vector with HLA allele numbers.

Details

Correct HLA number should consist of HLA gene name followed by "*" and sets of digits separated with ":". Maximum number of sets of digits is 4 which is termed 8-digit resolution. Optionally HLA numbers can be supplemented with additional suffix indicating its expression status. See http://hla.alleles.org/nomenclature/naming.html for more details.

HLA alleles with identical sequences across exons encoding the peptide binding domains might be designated with G group allele numbers. Those numbers have additional G or GG suffix. See http://hla.alleles.org/alleles/g_groups.html for more details. They are interpreted as valid HLA alleles designations.

Value

Logical vector specifying if `allele` elements follows HLA alleles naming conventions.

Examples

```
allele <- c("A*01:01", "A*01:02")
checkAlleleFormat(allele)
```

`checkColDataFormat` *Assert colData data*

Description

`checkColDataFormat` asserts if the colData data frame has proper format.

Usage

```
checkColDataFormat(data_frame)
```

Arguments

`data_frame`	Data frame containing colData data used to construct `MiDAS` object.

Value

Logical indicating if `data_frame` is properly formatted. Otherwise raise an error.

checkHlaCallsFormat *Assert hla calls data frame format*

Description

checkHlaCallsFormat asserts if hla calls data frame have proper format.

Usage

```
checkHlaCallsFormat(hla_calls)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.

Value

Logical indicating if hla_calls follows hla calls data frame format. Otherwise raise an error.

checkKirCallsFormat *Assert KIR counts data frame format*

Description

checkKirCallsFormat asserts if KIR counts data frame have proper format.

Usage

```
checkKirCallsFormat(kir_calls)
```

Arguments

kir_calls	KIR calls data frame, as returned by readKirCalls function.

Value

Logical indicating if kir_calls follow KIR counts data frame format. Otherwise raise an error.

checkKirGenesFormat *Check KIR genes format*

Description

checkKirGenesFormat test if the input character follows KIR gene names naming conventions.

Usage

```
checkKirGenesFormat(genes)
```

Arguments

genes	Character vector with KIR gene names.

Details

KIR genes: "KIR3DL3", "KIR2DS2", "KIR2DL2", "KIR2DL3", "KIR2DP1", "KIR2DL1", "KIR3DP1", "KIR2DL1", "KIR3DP1", "KIR2DL4", "KIR3DL1", "KIR3DS1", "KIR2DL5", "KIR2DS3", "KIR2DS5", "KIR2DS4", "KIR2DS1", "KIR3DL2".

Value

Logical vector specifying if genes elements follow KIR genes naming conventions.

Examples

```
checkKirGenesFormat(c("KIR3DL3", "KIR2DS2", "KIR2DL2"))
```

checkStatisticalModel *Assert statistical model*

Description

checkStatisticalModel asserts if object is an existing fit from a model functions such as lm, glm and many others. Containing MiDAS object as its data atribute.

Usage

```
checkStatisticalModel(object)
```

Arguments

object	An existing fit from a model function such as lm, glm and many others.

Value

Logical indicating if `object` is an existing fit from a model functions such as lm, glm and many others. Containing MiDAS object as its data attribute. Otherwise raise an error.

`colnamesMatches` *Check column names*

Description

`colnamesMatches` check if data frame's columns are named as specified

Usage

```
colnamesMatches(x, cols)
```

Arguments

`x`	Data frame to test.
`cols`	Ordered character vector to test against `x`'s colnames.

Value

Logical indicating if `x`'s colnames equals `choice`.

`convertAlleleToVariable`
Convert allele numbers to additional variables

Description

`convertAlleleToVariable` converts input HLA allele numbers to additional variables based on the supplied dictionary.

Usage

```
convertAlleleToVariable(allele, dictionary)
```

Arguments

`allele`	Character vector with HLA allele numbers.
`dictionary`	Path to file containing HLA allele dictionary or a data frame.

Details

dictionary file should be a tsv format with header and two columns. First column should hold allele numbers, second additional variables (eg. expression level).

Type of the returned vector depends on the type of the additional variable.

Value

Vector containing HLA allele numbers converted to additional variables according to dictionary.

Examples

```
dictionary <- system.file("extdata", "Match_allele_HLA_supertype.txt", package = "midasHLA")
convertAlleleToVariable(c("A*01:01", "A*02:01"), dictionary = dictionary)
```

---

countsToVariables *Convert counts table to variables*

Description

countsToVariables converts counts table to additional variables.

Usage

```
countsToVariables(counts, dictionary, na.value = NA, nacols.rm = TRUE)
```

Arguments

counts	Data frame with counts, such as returned by hlaCallsToCounts function. First column should contain samples IDs, following columns should contain counts (natural numbers including zero).
dictionary	Path to file containing variables dictionary or data frame. See details for further explanations.
na.value	Vector of length one speciyfing value for variables with no matching entry in dictionary. Default is to use 0.
nacols.rm	Logical indicating if result columns that contain only NA should be removed.

Details

dictionary file should be a tsv format with header and two columns. First column should be named "Name" and hold variable name, second should be named "Expression" and hold expression used to identify variable (eg. "KIR2DL3 & ! KIR2DL2" will match all samples with KIR2DL3 and without KIR2DL2). Optionally a data frame formatted in the same manner can be passed instead.

Dictionaries shipped with the package:

kir_haplotypes KIR genes to KIR haplotypes dictionary.

Value

Data frame with variable number of columns. First column named "ID" corresponds to "ID" column in counts, further columns hold indicators for converted variables. 1 and 0 code presence and absence of a variable respectively.

Examples

```
countsToVariables(MiDAS_tut_KIR, "kir_haplotypes")
```

---

dfToExperimentMat *Helper transform data frame to experiment matrix*

Description

Function deletes 'ID' column from a df, then transpose it and sets the column names to values from deleted 'ID' column.

Usage

```
dfToExperimentMat(df)
```

Arguments

df	Data frame

Value

Matrix representation of df.

---

dict_dist_grantham *Grantham distance*

Description

Integer vector giving Grantham distance values between pairs of amino acid residues.

Usage

```
dict_dist_grantham
```

Format

Named integer vector of length 400.

distGrantham *Calculate Grantham distance between amino acid sequences*

Description

distGrantham calculates normalized Grantham distance between two amino acid sequences. For details on calculations see Grantham R. 1974..

Usage

```
distGrantham(aa1, aa2)
```

Arguments

aa1	Character vector giving amino acid sequence using one letter codings. Each element must correspond to single amino acid.
aa2	Character vector giving amino acid sequence using one letter codings. Each element must correspond to single amino acid.

Details

Distance between amino acid sequences is normalized by length of compared sequences.

Lengths of aa1 and aa2 must be equal.

Value

Numeric vector of normalized Grantham distance between aa1 and aa2.

experimentMatToDf *Helper transform experiment matrix to data frame*

Description

Function transpose mat and inserts column names of input mat as a 'ID' column.

Usage

```
experimentMatToDf(mat)
```

Arguments

mat	Matrix

Value

Data frame representation of mat.

`filterByFrequency` *Filter MiDAS object by frequency*

Description

Filter MiDAS object by frequency

Usage

```
filterByFrequency(
  object,
  experiment,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL,
  carrier_frequency = FALSE
)
```

Arguments

`object`	MiDAS object.
`experiment`	String specifying experiment.
`lower_frequency_cutoff`	Number giving lower frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
`upper_frequency_cutoff`	Number giving upper frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
`carrier_frequency`	Logical flag indicating if carrier frequency should be returned.

Value

Filtered MiDAS object.

Examples

```
filterByFrequency(object = MiDAS_tut_object,
                  experiment = "hla_alleles",
                  lower_frequency_cutoff = 0.05,
                  upper_frequency_cutoff = 0.95,
                  carrier_frequency = TRUE)
```

filterByOmnibusGroups *Filter MiDAS object by omnibus groups*

Description

Filter MiDAS object by omnibus groups

Usage

```
filterByOmnibusGroups(object, experiment, groups)
```

Arguments

object	MiDAS object.
experiment	String specifying experiment.
groups	Character vector specifying omnibus groups to select. See getOmnibusGroups for more details.

Value

Filtered MiDAS object.

Examples

```
filterByOmnibusGroups(object = MiDAS_tut_object,
                      experiment = "hla_aa",
                      groups = c("A_3", "A_6", "C_1"))
```

filterByVariables *Filter MiDAS object by features*

Description

Filter MiDAS object by features

Usage

```
filterByVariables(object, experiment, variables)
```

Arguments

object	MiDAS object.
experiment	String specifying experiment.
variables	Character vector specifying features to select.

Value

Filtered MiDAS object.

Examples

```
filterByVariables(object = MiDAS_tut_object,
                  experiment = "hla_alleles",
                  variables = c("A*25:01", "A*26:01", "B*07:02"))
```

`filterExperimentByFrequency` *Filter experiment by frequency*

Description

Helper function for experiments filtering

Usage

```
filterExperimentByFrequency(
  experiment,
  carrier_frequency = FALSE,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL
)

## S3 method for class 'matrix'
filterExperimentByFrequency(
  experiment,
  carrier_frequency = FALSE,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL
)

## S3 method for class 'SummarizedExperiment'
filterExperimentByFrequency(
  experiment,
  carrier_frequency = FALSE,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL
)
```

Arguments

`experiment`	Matrix or SummarizedExperiment object.
`carrier_frequency`	Logical flag indicating if carrier frequency should be returned.
`lower_frequency_cutoff`	Positive number or `NULL`. Numbers greater than 1 are interpreted as number of feature occurrences, numbers between 0 and 1 as fractions.
`upper_frequency_cutoff`	Positive number or `NULL`. Numbers greater than 1 are interpreted as number of feature occurrences, numbers between 0 and 1 as fractions.

Value

Filtered experiment matrix.

`filterExperimentByVariables` *Filter experiment by variable*

Description

Helper function for experiments filtering

Usage

```
filterExperimentByVariables(experiment, variables)

## S3 method for class 'matrix'
filterExperimentByVariables(experiment, variables)

## S3 method for class 'SummarizedExperiment'
filterExperimentByVariables(experiment, variables)
```

Arguments

`experiment`	Matrix or SummarizedExperiment object.
`variables`	Character vector specifying features to choose.

Value

Filtered `experiment` object.

filterListByElements *Filter list by elements*

Description

Filter two level list by its secondary elements and remove empty items

Usage

```
filterListByElements(list, elements)
```

Arguments

list	A list.
elements	Character vector of elements to keep.

Value

List filtered according to elements argument.

formatResults *Pretty format statistical analysis results helper*

Description

formatResults format statistical analysis results table to html or latex format.

Usage

```
formatResults(
  results,
  filter_by = "p.value <= 0.05",
  arrange_by = "p.value",
  select_cols = c("term", "estimate", "std.error", "p.value", "p.adjusted"),
  format = c("html", "latex"),
  header = NULL,
  scroll_box_height = "400px"
)
```

Arguments

results	Tibble as returned by runMiDAS.
filter_by	Character vector specifying conditional expression used to filter results, this is equivalent to ... argument passed to filter.
arrange_by	Character vector specifying variable names to use for sorting. Equivalent to ... argument passed to arrange.
select_cols	Character vector specifying variable names that should be included in the output table. Can be also used to rename selected variables, see examples.
format	String "latex" or "html".
header	String specifying header for result table. If NULL no header is added.
scroll_box_height	A character string indicating the height of the table.

Value

Character vector of formatted table source code.

Examples

```
## Not run:
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles")
object <- lm(disease ~ term, data = midas)
res <- runMiDAS(object,
                experiment = "hla_alleles",
                inheritance_model = "dominant")
formatResults(res,
              filter_by = c("p.value <= 0.05", "estimate > 0"),
              arrange_by = c("p.value * estimate"),
              select_cols = c("allele", "p-value" = "p.value"),
              format = "html",
              header = "HLA allelic associations")

## End(Not run)
```

---

getAAFrequencies *Calculate amino acid frequencies*

Description

getAAFrequencies calculates amino acid frequencies in amino acid data frame.

Usage

```
getAAFrequencies(aa_variation)
```

Arguments

aa_variation	Amino acid variation data frame as returned by hlaToAAVariation.

Details

Both gene copies are taken into consideration for frequencies calculation, `frequency = n / (2 * j)` where `n` is the number of amino acid occurrences and `j` is the number of samples in `aa_variation`.

Value

Data frame with each row holding specific amino acid position, it's count and frequency.

Examples

```
aa_variation <- hlaToAAVariation(MiDAS_tut_HLA)
getAAFrequencies(aa_variation)
```

---

getAlleleResolution *Infer HLA allele resolution*

Description

`getAlleleResolution` returns the resolution of input HLA allele numbers.

Usage

```
getAlleleResolution(allele)
```

Arguments

allele	Character vector with HLA allele numbers.

Details

HLA allele resolution can take the following values: 2, 4, 6, 8. See http://hla.alleles.org/nomenclature/naming.html for more details.

`NA` values are accepted and returned as `NA`.

Value

Integer vector specifying allele resolutions.

Examples

```
allele <- c("A*01:01", "A*01:02")
getAlleleResolution(allele)
```

getAllelesForAA *Get HLA alleles for amino acid position*

Description

List HLA alleles and amino acid residues at a given position.

Usage

```
getAllelesForAA(object, aa_pos)
```

Arguments

object	MiDAS object.
aa_pos	String specifying gene and amino acid position, example "A_9".

Value

Data frame containing HLA alleles, their corresponding amino acid residues and frequencies at requested position.

Examples

```
getAllelesForAA(object = MiDAS_tut_object, aa_pos = "A_9")
```

getExperimentFrequencies *Calculate experiment's features frequencies*

Description

getExperimentFrequencies calculate features frequencies.

Usage

```
getExperimentFrequencies(
  experiment,
  pop_mul = NULL,
  carrier_frequency = FALSE,
  ref = NULL
)

## S3 method for class 'matrix'
getExperimentFrequencies(
  experiment,
```

```
  pop_mul = NULL,
  carrier_frequency = FALSE,
  ref = NULL
)

## S3 method for class 'SummarizedExperiment'
getExperimentFrequencies(
  experiment,
  pop_mul = NULL,
  carrier_frequency = FALSE,
  ref = NULL
)
```

Arguments

`experiment`	Matrix or SummarizedExperiment object.
`pop_mul`	Number by which number of samples should be multiplied to get the population size.
`carrier_frequency`	Logical flag indicating if carrier frequency should be returned.
`ref`	Wide format data frame with first column named "var" holding features matching `experiment` and specific populations frequencies in following columns. See `getReferenceFrequencies` for more details.

Value

Data frame with each row holding specific variable, it's count and frequency.

`getExperimentPopulationMultiplicator` *Get experiment's population multiplicator*

Description

`getExperimentPopulationMultiplicator` extracts population multiplicator from experiment's metadata.

Usage

```
getExperimentPopulationMultiplicator(experiment)

## S3 method for class 'matrix'
getExperimentPopulationMultiplicator(experiment)

## S3 method for class 'SummarizedExperiment'
getExperimentPopulationMultiplicator(experiment)
```

Arguments

experiment	Matrix or SummarizedExperiment object.

Value

Experiment's population multiplicator number.

---

getExperiments *Get available experiments in MiDAS object.*

Description

Get available experiments in MiDAS object.

Usage

```
getExperiments(object)
```

Arguments

object	MiDAS object.

Value

Character vector giving names of experiments in object.

Examples

```
getExperiments(object = MiDAS_tut_object)
```

---

getFrequencies *Calculate features frequencies for a given experiment in MiDAS object.*

Description

Calculate features frequencies for a given experiment in MiDAS object.

Usage

```
getFrequencies(
  object,
  experiment,
  carrier_frequency = FALSE,
  compare = FALSE,
 ref_pop = list(hla_alleles = c("USA NMDP African American pop 2", "USA NMDP Chinese",
   "USA NMDP European Caucasian", "USA NMDP Hispanic South or Central American",
    "USA NMDP Japanese", "USA NMDP North American Amerindian",
  "USA NMDP South Asian Indian"), kir_genes = c("USA California African American KIR",
    "USA California Asian American KIR", "USA California Caucasians KIR",
    "USA California Hispanic KIR")),
  ref = list(hla_alleles = allele_frequencies, kir_genes = kir_frequencies)
)
```

Arguments

object	MiDAS object.
experiment	Matrix or SummarizedExperiment object.
carrier_frequency	Logical flag indicating if carrier frequency should be returned.
compare	Logical flag indicating if hla_calls frequencies should be compared to reference frequencies given in ref.
ref_pop	Named list of character vectors giving names of reference populations in ref to compare with. Optionally vectors can be named, then those names will be used as population names. Each vector should correspond to a specific experiment.
ref	Named list of reference frequencies data frames. Each element should give reference for a specific experiment. See allele_frequencies for an example on how reference frequency data frame should be formatted.

Value

Data frame with features from selected experiment and their corresponding frequencies. Column "term" hold features names, "Counts" hold number of feature occurrences, "Freq" hold feature frequencies. If argument compare is set to TRUE, further columns will hold frequencies in reference populations.

Examples

```
# using default reference populations
getFrequencies(object = MiDAS_tut_object,
               experiment = "hla_alleles",
               compare = TRUE)

# using customized set of reference populations
getFrequencies(
  object = MiDAS_tut_object,
  experiment = "hla_alleles",
```

```
  compare = TRUE,
  ref_pop = list(
    hla_alleles = c("USA NMDP Chinese", "USA NMDP European Caucasian")
  ),
  ref = list(hla_alleles = allele_frequencies)
)
```

`getFrequencyMask` *Helper function for filtering frequency data frame*

Description

Helper function for filtering frequency data frame

Usage

```
getFrequencyMask(
  df,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL
)
```

Arguments

`df`	Data frame as returned by `getExperimentFrequencies`.
`lower_frequency_cutoff`	Positive number or `NULL`. Numbers greater than 1 are interpreted as number of feature occurrences, numbers between 0 and 1 as fractions.
`upper_frequency_cutoff`	Positive number or `NULL`. Numbers greater than 1 are interpreted as number of feature occurrences, numbers between 0 and 1 as fractions.

Value

Character vector containing names of variables after filtration.

getHlaCalls *Get HLA calls from MiDAS object.*

Description

Get HLA calls from MiDAS object.

Usage

```
getHlaCalls(object)
```

Arguments

object	MiDAS object.

Value

HLA calls data frame.

Examples

```
getHlaCalls(object = MiDAS_tut_object)
```

getHlaCallsGenes *Get HLA calls genes*

Description

getHlaCallsGenes get's genes found in HLA calls.

Usage

```
getHlaCallsGenes(hla_calls)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.

Value

Character vector of genes in hla_calls.

getHlaFrequencies *Calculate HLA allele frequencies*

Description

getHlaFrequencies calculates allele frequencies in HLA calls data frame.

Usage

```
getHlaFrequencies(
  hla_calls,
  carrier_frequency = FALSE,
  compare = FALSE,
  ref_pop = c("USA NMDP African American pop 2", "USA NMDP Chinese",
   "USA NMDP European Caucasian", "USA NMDP Hispanic South or Central American",
    "USA NMDP Japanese", "USA NMDP North American Amerindian",
    "USA NMDP South Asian Indian"),
  ref = allele_frequencies
)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
carrier_frequency	Logical flag indicating if carrier frequency should be returned.
compare	Logical flag indicating if hla_calls frequencies should be compared to reference frequencies given in ref.
ref_pop	Character vector giving names of reference populations in ref to compare with. Optionally vector can be named, then those names will be used as population names.
ref	Data frame giving reference allele frequencies. See allele_frequencies for an example.

Details

Both gene copies are taken into consideration for frequencies calculation, frequency = n / (2 * j) where n is the number of allele occurrences and j is the number of samples in hla_calls.

Value

Data frame with each row holding HLA allele, it's count and frequency.

Examples

```
getHlaFrequencies(MiDAS_tut_HLA)
```

getHlaKirInteractions *Get HLA - KIR interactions*

Description

getHlaKirInteractions calculate presence-absence matrix of HLA - KIR interactions.

Usage

```
getHlaKirInteractions(
  hla_calls,
  kir_calls,
 interactions_dict = system.file("extdata", "Match_counts_hla_kir_interactions.txt",
    package = "midasHLA")
)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
kir_calls	KIR calls data frame, as returned by readKirCalls function.
interactions_dict	Path to HLA - KIR interactions dictionary.

Details

hla_calls are first reduced to all possible resolutions and converted to additional variables, such as G groups, using dictionaries shipped with the package.

interactions_dict file should be a tsv format with header and two columns. First column should be named "Name" and hold interactions names, second should be named "Expression" and hold expression used to identify interaction (eg. "C2 & KIR2DL1" will match all samples with C2 and KIR2DL1). The package is shipped with an interactions file based on Pende et al., 2019.

Value

Data frame with variable number of columns. First column named "ID" corresponds to "ID" column in counts, further columns hold indicators for HLA - KIR interactions. 1 and 0 code presence and absence of a variable respectively.

Examples

```
getHlaKirInteractions(
  hla_calls = MiDAS_tut_HLA,
  kir_calls = MiDAS_tut_KIR,
  interactions_dict = system.file(
    "extdata", "Match_counts_hla_kir_interactions.txt",
    package = "midasHLA")
)
```

getKirCalls *Get KIR calls from MiDAS object.*

Description

Get KIR calls from MiDAS object.

Usage

```
getKirCalls(object)
```

Arguments

object	MiDAS object.

Value

KIR calls data frame.

Examples

```
getKirCalls(object = MiDAS_tut_object)
```

getKIRFrequencies *Calculate KIR genes frequencies*

Description

getKIRFrequencies calculates KIR genes frequencies in KIR calls data frame.

Usage

```
getKIRFrequencies(kir_calls)
```

Arguments

kir_calls	KIR calls data frame, as returned by readKirCalls function.

Value

Data frame with each row holding KIR gene, it's count and frequency.

Examples

```
getKIRFrequencies(MiDAS_tut_KIR)
```

getObjectDetails *Get attributes of statistical model object*

Description

`getObjectDetails` extracts some of the statistical model object attributes that are needed for `runMiDAS` internal calculations.

Usage

```
getObjectDetails(object)
```

Arguments

`object`	An existing fit from a model function such as lm, glm and many others.

Value

List with following elements:

call Object's call

formula_vars Character containing names of variables in object formula

data MiDAS object associated with model

getOmnibusGroups *Get omnibus groups from MiDAS object.*

Description

Get omnibus groups from MiDAS object.

Usage

```
getOmnibusGroups(object, experiment)
```

Arguments

`object`	`MiDAS` object.
`experiment`	String specifying experiment.

Details

For some experiments features can be naturally divided into groups (here called omnibus groups). For example, in `"hla_aa"` experiment features can be grouped by amino acid position (`"B_46_E"`, `"B_46_A"`) can be grouped into `B_46` group). Such groups can be then used to perform omnibus test, see `runMiDAS` for more details.

Value

List of omnibus groups for a given experiment.

Examples

```
getOmnibusGroups(object = MiDAS_tut_object,
                 experiment = "hla_aa")
```

`getPlaceholder` *Get placeholder name from MiDAS object.*

Description

Get placeholder name from MiDAS object.

Usage

```
getPlaceholder(object)
```

Arguments

`object`	MiDAS object.

Value

String giving name of placeholder.

Examples

```
getPlaceholder(object = MiDAS_tut_object)
```

`getReferenceFrequencies`
Helper transforming reference frequencies

Description

Helper transforming reference frequencies

Usage

```
getReferenceFrequencies(ref, pop, carrier_frequency = FALSE)
```

Arguments

ref	Long format data frame with three columns "var", "population", "frequency".
pop	Character giving names of populations to include
carrier_frequency	Logical indicating if carrier frequency should be returned instead of frequency. Carrier frequency is calculated based on Hardy-Weinberg equilibrium model.

Value

Wide format data frame with population frequencies as columns.

---

getVariableAAPos *Find variable positions in sequence alignment*

Description

getVariableAAPos finds variable amino acid positions in protein sequence alignment.

Usage

```
getVariableAAPos(alignment, varchar = "[A-Z]")
```

Arguments

alignment	Matrix containing amino acid level alignment, as returned by readHlaAlignments,
varchar	Regex matching characters that should be considered when looking for variable amino acid positions. See details for further explanations.

Details

The variable amino acid positions in the alignment are those at which different amino acids can be found. As the alignments can also contain indels and unknown characters, the user choice might be to consider those positions as variable or not. This can be achieved by passing appropriate regular expression in varchar. Eg. when varchar = "[A-Z]" occurence of deletion/insertion (".") will not be treated as variability. In order to detect this kind of variability varchar = "[A-Z\\.]" should be used.

Value

Integer vector specifying which alignment columns are variable.

Examples

```
alignment <- readHlaAlignments(gene = "TAP1")
getVariableAAPos(alignment)
```

hasTidyMethod *Check if tidy method for class exist*

Description

hasTidyMethod check if there is a tidy method available for a given class.

Usage

```
hasTidyMethod(class)
```

Arguments

class	String giving object class.

Value

Logical indicating if there is a tidy method for a given class.

hlaAlignmentGrantham *Helper function returning alignment for Grantham distance calculations*

Description

Helper function returning alignment for Grantham distance calculations

Usage

```
hlaAlignmentGrantham(gene, aa_sel = 2:182)
```

Arguments

gene	Character vector specifying HLA gene.
aa_sel	Numeric vector specifying amino acids that should be extracted.

Value

HLA alignment processed for grantham distance calculation. Processing includes extracting specific amino acids, masking indels, gaps and stop codons.

`hlaCallsGranthamDistance` *Calculate Grantham distance between HLA alleles*

Description

`hlaCallsGranthamDistance` calculate Grantham distance between two HLA alleles of a given, using original formula by Grantham R. 1974..

Usage

```
hlaCallsGranthamDistance(
  hla_calls,
  genes = c("A", "B", "C"),
  aa_selection = "binding_groove"
)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`genes`	Character vector specifying genes for which allelic distance should be calculated.
`aa_selection`	String specifying variable region in peptide binding groove which should be considered for Grantham distance calculation. Valid choices includes: `"binding_groove"`, `"B_pocket"`, `"F_pocket"`. See details for more information.

Details

Grantham distance is calculated only for class I HLA alleles. First exons forming the variable region in the peptide binding groove are selected. Here we provide option to choose either `"binding_groove"` - exon 2 and 3 (positions 1-182 in IMGT/HLA alignments, however here we take 2-182 as many 1st positions are missing), `"B_pocket"` - residues 7, 9, 24, 25, 34, 45, 63, 66, 67, 70, 99 and `"F_pocket"` - residues 77, 80, 81, 84, 95, 116, 123, 143, 146, 147. Then all the alleles containing gaps, stop codons or indels are discarded. Finally distance is calculated for each pair.

See Robinson J. 2017. for more details on the choice of exons 2 and 3.

Value

Data frame of normalized Grantham distances between pairs of alleles for each specified HLA gene. First column (`ID`) is the same as in `hla_calls`, further columns are named as given by `genes`.

Examples

```
hlaCallsGranthamDistance(MiDAS_tut_HLA, genes = "A")
```

hlaCallsToCounts *Transform HLA calls to counts table*

Description

`hlaCallsToCounts` converts HLA calls data frame into a counts table.

Usage

```
hlaCallsToCounts(hla_calls, check_hla_format = TRUE)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`check_hla_format`	Logical indicating if `hla_calls` format should be checked. This is useful if one wants to use `hlaCallsToCounts` with input not adhering to HLA nomenclature standards. See examples.

Value

HLA allele counts data frame. First column holds samples ID's, further columns, corresponding to specific alleles, give information on the number of their occurrences in each sample.

hlaToAAVariation *Generate amino acid variation matrix*

Description

`hlaToAAVariation` convert HLA calls data frame to a matrix of variable amino acid positions.

Usage

```
hlaToAAVariation(hla_calls, indels = TRUE, unkchar = FALSE, as_df = TRUE)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`indels`	Logical indicating whether indels should be considered when checking variability.
`unkchar`	Logical indicating whether unknown characters in the alignment should be considered when checking variability.
`as_df`	Logical indicating if data frame should be returned. Otherwise a matrix is returned.

Details

Variable amino acid positions are found by comparing elements of the alignment column wise. Some of the values in alignment can be treated specially using `indels` and `unkchar` arguments. Function processes alignments for all HLA genes found in `hla_calls`.

Variable amino acid position uses protein alignments from EBI database.

Value

Matrix or data frame containing variable amino acid positions. Rownames corresponds to ID column in `hla_calls`, and colnames to alignment positions. If no variation is found one column matrix filled with `NA`'s is returned.

Examples

```
hlaToAAVariation(MiDAS_tut_HLA)
```

`hlaToVariable` *Convert HLA calls to variables*

Description

`hlaToVariable` converts HLA calls data frame to additional variables.

Usage

```
hlaToVariable(
  hla_calls,
  dictionary,
  reduce = TRUE,
  na.value = 0,
  nacols.rm = TRUE
)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`dictionary`	Path to file containing HLA allele dictionary or a data frame.
`reduce`	Logical indicating if function should try to reduce allele resolution when no matching entry in the dictionary is found. See details.
`na.value`	Vector of length one speciyfing value for alleles with no matching entry in `dictionary`. Default is to use `0`.
`nacols.rm`	Logical indicating if result columns that contain only `NA` should be removed.

Details

`dictionary` file should be a tsv format with header and two columns. First column should hold allele numbers and second corresponding additional variables. Optionally a data frame formatted in the same manner can be passed instead.

`dictionary` can be also used to access dictionaries shipped with the package. They can be referred to by using one of the following strings:

`"allele_HLA_Bw"` Translates HLA-B alleles together with A*23, A*24 and A*32 into Bw4 and Bw6 allele groups. In some cases HLA alleles containing Bw4 epitope, on nucleotide level actually carries a premature stop codon. Meaning that although on nucleotide level the allele would encode a Bw4 epitope it's not really there and it is assigned to Bw6 group. However in 4-digit resolution these alleles can not be distinguished from other Bw4 groups. Since alleles with premature stop codons are rare, Bw4 group is assigned.

`"allele_HLA-B_only_Bw"` Translates HLA-B alleles (without A*23, A*24 and A*32) into Bw4 and Bw6 allele groups.

`"allele_HLA-C_C1-2"` Translates HLA-C alleles into C1 and C2 allele groups.

`"allele_HLA_supertype"` Translates HLA-A and HLA-B alleles into supertypes, a classification that group HLA alleles based on peptide binding specificities.

`"allele_HLA_Ggroup"` Translates HLA alleles into G groups, which defines amino acid identity only in the exons relevant for peptide binding. Note that alleles DRB1*01:01:01 and DRB1*01:16 match more than one G group, here this ambiguity was removed by deleting matching with DRB5*01:01:01G group.

`reduce` control if conversion should happen in a greedy way, such that if some HLA number cannot be converted, it's resolution is reduced by 2 and another attempt is taken. This process stops when alleles cannot be further reduced or all have been successfully converted.

Value

Data frame with variable number of columns. First column named `"ID"` corresponds to `"ID"` column in `hla_calls`, further columns holds converted HLA variables.

Examples

```
hlaToVariable(MiDAS_tut_HLA, dictionary = "allele_HLA_supertype")
```

HWETest *Test for Hardy Weinberg equilibrium*

Description

Test experiment features for Hardy Weinberg equilibrium.

Usage

```
HWETest(
  object,
  experiment = c("hla_alleles", "hla_aa", "hla_g_groups", "hla_supertypes",
    "hla_NK_ligands"),
  HWE_group = NULL,
  HWE_cutoff = NULL,
  as.MiDAS = FALSE
)
```

Arguments

object	MiDAS object.
experiment	String specifying experiment to test. Valid values includes "hla_alleles", "hla_aa", "hla_g_groups", "hla_supertypes", "hla_NK_ligands".
HWE_group	Expression defining samples grouping to test for Hardy Weinberg equilibrium. By default samples are not grouped.
HWE_cutoff	Number specifying p-value threshold. When HWE_group is specified both groups are thresholded.
as.MiDAS	Logical flag indicating if MiDAS object should be returned.

Details

Setting as.MiDAS to TRUE will filter MiDAS object based on p-value cut-off given by HWE_cutoff.

Value

Data frame with Hardy Weinberg Equilibrium test results or a filtered MiDAS object.

Examples

```
# create MiDAS object
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles"
)

# get HWE p-values as data frame
HWETest(midas, experiment = "hla_alleles")

# get HWE in groups defined by disease status
# grouping by `disease == 1` will divide samples into two groups:
# `disease == 1` and `not disease == 1`
HWETest(midas, experiment = "hla_alleles", HWE_group = disease == 1)

# filter MiDAS object by HWE test p-value
HWETest(midas, experiment = "hla_alleles", HWE_cutoff = 0.05, as.MiDAS = TRUE)
```

isCharacterOrNULL *Check if object is character vector or NULL*

Description

isCharacterOrNULL checks if the object is a character vector or NULL.

Usage

```
isCharacterOrNULL(x)
```

Arguments

x	object to test.

Value

Logical indicating if object is character vector or NULL

isClass *Check if object is of class x*

Description

isClassOrNULL checks if object is an instance of a specified class or is null.

Usage

```
isClass(x, class)
```

Arguments

x	object to test.
class	String specifying class to test.

Value

Logical indicating if x is an instance of class.

isClassOrNULL *Check if object is of class x or null*

Description

`isClassOrNULL` checks if object is an instance of a specified class or is null.

Usage

```
isClassOrNULL(x, class)
```

Arguments

`x`	object to test.
`class`	String specifying class to test.

Value

Logical indicating if `x` is an instance of `class`.

isCountOrNULL *Check if object is count or NULL*

Description

`isCountOrNULL` check if object is a count (a single positive integer) or NULL.

Usage

```
isCountOrNULL(x)
```

Arguments

`x`	object to test.

Value

Logical indicating if object is count or NULL

isCountsOrZeros *Check if vector contains only counts or zeros*

Description

`isCountsOrZeros` checks if vector contains only positive integers or zeros.

Usage

```
isCountsOrZeros(x, na.rm = TRUE)
```

Arguments

`x`	Numeric vector or object that can be `unlist` to numeric vector.
`na.rm`	Logical indicating if `NA` values should be accepted.

Value

Logical indicating if provided vector contains only positive integers or zeros.

isExperimentCountsOrZeros *Check if frequencies can be calculated for an experiment*

Description

`isExperimentCountsOrZeros` checks if experiment contains only positive integers or zeros.

Usage

```
isExperimentCountsOrZeros(x, na.rm = TRUE)
```

Arguments

`x`	Matrix or SummarizedExperiment object.
`na.rm`	Logical indicating if `NA` values should be accepted.

Value

Logical indicating if `x` contains only positive integers or zeros.

isExperimentInheritanceModelApplicable *Check if experiment is inheritance model applicable*

Description

`isExperimentInheritanceModelApplicable` check experiment's metadata for presence of `"inheritance_model_applica` flag, indicating if inheritance model can be applied.

Usage

```
isExperimentInheritanceModelApplicable(experiment)

## S3 method for class 'matrix'
isExperimentInheritanceModelApplicable(experiment)

## S3 method for class 'SummarizedExperiment'
isExperimentInheritanceModelApplicable(experiment)
```

Arguments

`experiment`	Matrix or SummarizedExperiment object.

Value

Logical flag.

isFlagOrNULL *Check if object is flag or NULL*

Description

`isFlagOrNULL` checks if object is flag (a length one logical vector) or NULL.

Usage

```
isFlagOrNULL(x)
```

Arguments

`x`	object to test.

Value

Logical indicating if object is flag or NULL

isNumberOrNULL *Check if object is number or NULL*

Description

isNumberOrNULL checks if object is number (a length one numeric vector) or NULL.

Usage

```
isNumberOrNULL(x)
```

Arguments

x	object to test.

Value

Logical indicating if object is number or NULL

isStringOrNULL *Check if object is string or NULL*

Description

isStringOrNULL checks if object is string (a length one character vector) or NULL.

Usage

```
isStringOrNULL(x)
```

Arguments

x	object to test.

Value

Logical indicating if object is string or NULL

isTRUEorFALSE *Check if object is TRUE or FALSE flag*

Description

isTRUEorFALSE check if object is a flag (a length one logical vector) except NA.

Usage

```
isTRUEorFALSE(x)
```

Arguments

x	object to test.

Value

Logical indicating if object is TRUE or FALSE flag

iterativeLRT *Iterative likelihood ratio test*

Description

iterativeLRT performs likelihood ratio test in an iterative manner over groups of variables given in omnibus_groups.

Usage

```
iterativeLRT(object, placeholder, omnibus_groups)
```

Arguments

object	An existing fit from a model function such as lm, glm and many others.
placeholder	String specifying term to substitute with value from x. Ignored if set to NULL.
omnibus_groups	List of character vectors giving sets of variables for which omnibus test should be applied.

Value

Data frame containing summarised likelihood ratio test results.

iterativeModel *Iteratively evaluate model for different variables*

Description

Information about variable statistic from each model is extracted using `tidy` function.

Usage

```
iterativeModel(object, placeholder, variables, exponentiate = FALSE)
```

Arguments

`object`	An existing fit from a model function such as lm, glm and many others.
`placeholder`	String specifying term to substitute with value from `x`. Ignored if set to `NULL`.
`variables`	Character vector specifying variables to use in association tests.
`exponentiate`	Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to `tidy`. This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to FALSE.

Value

Tibble containing per variable summarised model statistics. The exact output format is model dependent and controlled by model's dedicated `tidy` function.

kableResults *Create association analysis results table in HTML or LaTeX*

Description

`kableResults` convert results table (`runMiDAS` output) to HTML or LaTeX format.

Usage

```
kableResults(
  results,
  colnames = NULL,
  header = "MiDAS analysis results",
  pvalue_cutoff = NULL,
  format = getOption("knitr.table.format"),
  scroll_box_height = "400px"
)
```

Arguments

results	Tibble as returned by runMiDAS.
colnames	Character vector of form c("new_name" = "old_name"), used to rename results colnames.
header	String specifying results table header.
pvalue_cutoff	Number specifying p-value cutoff for results to be included in output. If NULL no filtering is done.
format	String "latex" or "html".
scroll_box_height	A character string indicating the height of the table.

Value

Association analysis results table in HTML or LaTeX.

Examples

```
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles")
object <- lm(disease ~ term, data = midas)
res <- runMiDAS(object, experiment = "hla_alleles", inheritance_model = "additive")
kableResults(results = res,
             colnames = c("HLA allele" = "allele"))
```

---

kir_frequencies *KIR genes frequencies scraped from allelefrequencies.net*

Description

Accessed on 28.08.20

Usage

```
kir_frequencies
```

Format

A data frame with 3744 rows and 3 variables:

var allele number, character

population reference population name, character

frequency KIR genes carrier frequency in reference population, float

Details

A dataset containing KIR genes frequencies across 16 genes. For details visit the search results page in the allelefrequencies.net database website.

Source

www.allelefrequencies.net

`lapply_tryCatch` *lapply with tryCatch routine*

Description

Used to run function iteratively over list, while using tryCatch to catch warnings and errors to finally present a summary of issues rather than error on each and every one. Used in `iterativeLRT` and `iterativeModel`.

Usage

```
lapply_tryCatch(X, FUN, err_res, ...)
```

Arguments

`X`	a vector (atomic or list) or an `expression` object. Other objects (including classed objects) will be coerced by `base::as.list`.
`FUN`	the function to be applied to each element of `X`: see 'Details'. In the case of functions like `+`, `%*%`, the function name must be backquoted or quoted.
`err_res`	Function creating a result that should be output in case of error.
`...`	optional arguments to `FUN`.

Value

List of elements as returned by `FUN`.

listMiDASDictionaries *List HLA alleles dictionaries*

Description

listMiDASDictionaries lists dictionaries shipped with the MiDAS package. See hlaToVariable for more details on dictionaries.

Usage

```
listMiDASDictionaries(pattern = "allele", file.names = FALSE)
```

Arguments

pattern	String used to match dictionary names, it can be a regular expression. By default all names are matched.
file.names	Logical value. If FALSE, only the names of dictionaries are returned. If TRUE their paths are returned.

Value

Character vector giving names of available HLA alleles dictionaries.

LRTest *Likelihood ratio test*

Description

LRTest carry out an asymptotic likelihood ratio test for two models.

Usage

```
LRTest(mod0, mod1)
```

Arguments

mod0	An existing fit from a model function such as lm, glm and many others.
mod1	Object of the same class as mod0 with extra terms included.

Details

mod0 have to be a reduced version of mod1. See examples.

Value

Data frame with the results of likelihood ratio test of the supplied models.

Column `term` holds new variables appearing in `mod1`, `df` difference in degrees of freedom between models, `logLik` difference in log likelihoods, `statistic` `Chisq` statistic and `p.value` corresponding p-value.

`MiDAS-class` *MiDAS class*

Description

The `MiDAS` class is a `MultiAssayExperiment` object containing data and metadata required for MiDAS analysis.

Valid `MiDAS` object must have unique features names across all experiments and colData. It's metadata list needs to have a `placeholder` element, which is a string specifying name of column in colData used when defining statistical model for downstream analyses (see `runMiDAS` for more details). Optionally the object's metadata can also store `'hla_calls'` and `'kir_calls'` data frames (see `prepareMiDAS` for more details).

Usage

```
## S4 method for signature 'MiDAS'
getExperiments(object)

## S4 method for signature 'MiDAS'
getHlaCalls(object)

## S4 method for signature 'MiDAS'
getKirCalls(object)

## S4 method for signature 'MiDAS'
getPlaceholder(object)

## S4 method for signature 'MiDAS'
getOmnibusGroups(object, experiment)

## S4 method for signature 'MiDAS'
getFrequencies(
  object,
  experiment,
  carrier_frequency = FALSE,
  compare = FALSE,
 ref_pop = list(hla_alleles = c("USA NMDP African American pop 2", "USA NMDP Chinese",
   "USA NMDP European Caucasian", "USA NMDP Hispanic South or Central American",
    "USA NMDP Japanese", "USA NMDP North American Amerindian",
  "USA NMDP South Asian Indian"), kir_genes = c("USA California African American KIR",
```

```
    "USA California Asian American KIR", "USA California Caucasians KIR",
    "USA California Hispanic KIR")),
  ref = list(hla_alleles = allele_frequencies, kir_genes = kir_frequencies)
)

## S4 method for signature 'MiDAS'
filterByFrequency(
  object,
  experiment,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL,
  carrier_frequency = FALSE
)

## S4 method for signature 'MiDAS'
filterByOmnibusGroups(object, experiment, groups)

## S4 method for signature 'MiDAS'
filterByVariables(object, experiment, variables)

## S4 method for signature 'MiDAS'
getAllelesForAA(object, aa_pos)
```

Arguments

object	MiDAS object.
experiment	String specifying experiment.
carrier_frequency	Logical flag indicating if carrier frequency should be returned.
compare	Logical flag indicating if hla_calls frequencies should be compared to reference frequencies given in ref.
ref_pop	Named list of character vectors giving names of reference populations in ref to compare with. Optionally vectors can be named, then those names will be used as population names. Each vector should correspond to a specific experiment.
ref	Named list of reference frequencies data frames. Each element should give reference for a specific experiment. See allele_frequencies for an example on how reference frequency data frame should be formatted.
lower_frequency_cutoff	Number giving lower frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
upper_frequency_cutoff	Number giving upper frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
groups	Character vector specifying omnibus groups to select. See getOmnibusGroups for more details.

variables	Character vector specifying features to select.
aa_pos	String specifying gene and amino acid position, example "A_9".

Value

Instance of class MiDAS

`midasToWide` *Transform MiDAS to wide format data.frame*

Description

Transform MiDAS to wide format data.frame

Usage

```
midasToWide(object, experiment)
```

Arguments

object	Object of class MiDAS
experiment	Character specifying experiments to include

Value

Data frame representation of MiDAS object. Consecutive columns holds values of variables from MiDAS's experiments and colData. The metadata associated with experiments is not preserved.

`MiDAS_tut_HLA` *MiDAS tutorial HLA data*

Description

Example HLA calls data used in MiDAS tutorial

Usage

```
MiDAS_tut_HLA
```

Format

Data frame with 1000 rows and 19 columns. First column holds samples ID's, following columns holds HLA alleles calls for different genes.

ID Character sample ID

A_1 Character

A_2 Character

B_1 Character

B_2 Character

C_1 Character

C_2 Character

DPA1_1 Character

DPA1_2 Character

DPB1_1 Character

DPB1_2 Character

DQA1_1 Character

DQA1_2 Character

DQB1_1 Character

DQB1_2 Character

DRA_1 Character

DRA_2 Character

DRB1_1 Character

DRB1_2 Character

`MiDAS_tut_KIR` *MiDAS tutorial KIR data*

Description

Example KIRR presence/absence data used in MiDAS tutorial

Usage

```
MiDAS_tut_KIR
```

Format

Data frame with 1000 rows and 17 columns. First column holds samples ID's, following columns holds presence/absence indicators for different KIR genes.

ID Character sample ID

KIR3DL3 Integer

KIR2DS2 Integer

KIR2DL2 Integer

KIR2DL3 Integer

KIR2DP1 Integer

KIR2DL1 Integer

KIR3DP1 Integer

KIR2DL4 Integer

KIR3DL1 Integer

KIR3DS1 Integer

KIR2DL5 Integer

KIR2DS3 Integer

KIR2DS5 Integer

KIR2DS4 Integer

KIR2DS1 Integer

KIR3DL2 Integer

MiDAS_tut_object *MiDAS tutorial MiDAS object*

Description

Example MiDAS object created with data used in MiDAS tutorial: `MiDAS_tut_HLA`, `MiDAS_tut_KIR`, `MiDAS_tut_pheno`. Used in code examlpes and unit tests.

Usage

```
MiDAS_tut_object
```

Format

MiDAS object with following experiments defined:

hla_alleles SummarizedExperiment with 447 rows and 1000 columns

hla_aa SummarizedExperiment with 1223 rows and 1000 columns

hla_g_groups SummarizedExperiment with 46 rows and 1000 columns

hla_supertypes SummarizedExperiment with 12 rows and 1000 columns
hla_NK_ligands SummarizedExperiment with 5 rows and 1000 columns
kir_genes SummarizedExperiment with 16 rows and 1000 columns
kir_haplotypes SummarizedExperiment with 6 rows and 1000 columns
hla_kir_interactions SummarizedExperiment with 29 rows and 1000 columns
hla_divergence matrix with 4 rows and 1000 columns
hla_het SummarizedExperiment with 9 rows and 1000 columns

`MiDAS_tut_pheno` *MiDAS tutorial phenotype data*

Description

Example phenotype data used in MiDAS tutorial

Usage

```
MiDAS_tut_pheno
```

Format

Data frame with 1000 rows and 4 columns.

ID Character sample ID
disease Integer
lab_value Numeric
outcome Integer

`objectHasPlaceholder` *Check if placeholder is present in object formula*

Description

`isTRUEorFALSE` check if object is a flag (a length one logical vector) except NA.

Usage

```
objectHasPlaceholder(object, placeholder)
```

Arguments

`object`	statistical model to test.
`placeholder`	string specifying name of placeholder.

Value

Logical indicating if placeholder is present in object formula.

omnibusTest *Omnibus test*

Description

OmnibusTest calculates overall p-value for linear combination of variables using likelihood ratio test.

Usage

```
omnibusTest(
  object,
  omnibus_groups,
  placeholder = "term",
  correction = "bonferroni",
  n_correction = NULL
)
```

Arguments

object	An existing fit from a model function such as lm, glm and many others.
omnibus_groups	List of character vectors giving sets of variables for which omnibus test should be applied.
placeholder	String specifying term in object's formula which should be substituted with variables during analysis.
correction	String specifying multiple testing correction method. See details for further information.
n_correction	Integer specifying number of comparisons to consider during multiple testing correction calculations. For Bonferroni correction it is possible to specify a number lower than the number of comparisons being made. This is useful in cases when knowledge about the biology or redundance of alleles reduces the need for correction. For other methods it must be at least equal to the number of comparisons being made; only set this (to non-default) when you know what you are doing!

Details

Likelihood ratio test is conducted by comparing a model given in an object with an extended model, that is created by including the effect of variables given in variables as their linear combination.

Value

Data frame with columns:

- "group" Omnibus group name

- "term" Elements of omnibus group added to base model
- "df" Difference in degrees of freedom between base and extended model
- "logLik" Difference in log likelihoods between base and extended model
- "statistic" Chisq statistic
- "p.value" P-value
- "p.adjusted" Adjusted p-value

Examples

```
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_aa")

# define base model
object <- lm(disease ~ term, data = midas)
omnibusTest(object,
            omnibus_groups = list(
              A_29 = c("A_29_D", "A_29_A"),
              A_43 = c("A_43_Q", "A_43_R")
            ))
```

`prepareMiDAS` *Construct a MiDAS object*

Description

`prepareMiDAS` transform HLA alleles calls and KIR calls according to selected `experiments` creating a `MiDAS` object.

Usage

```
prepareMiDAS(
  hla_calls = NULL,
  kir_calls = NULL,
  colData,
  experiment = c("hla_alleles", "hla_aa", "hla_g_groups", "hla_supertypes",
    "hla_NK_ligands", "kir_genes", "kir_haplotypes", "hla_kir_interactions",
    "hla_divergence", "hla_het", "hla_custom", "kir_custom"),
  placeholder = "term",
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL,
  indels = TRUE,
  unkchar = FALSE,
  hla_divergence_aa_selection = "binding_groove",
  hla_het_resolution = 8,
  hla_dictionary = NULL,
  kir_dictionary = NULL
)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
kir_calls	KIR calls data frame, as returned by readKirCalls function.
colData	Data frame holding additional variables like phenotypic observations or covariates. It have to contain 'ID' column holding samples identifiers corresponding to identifiers in hla_calls and kir_calls. Importantly rows of hla_calls and kir_calls without corresponding phenotype are discarded.
experiment	Character vector indicating analysis type for which data should be prepared. Valid choices are "hla_alleles", "hla_aa", "hla_g_groups", "hla_supertypes", "hla_NK_ligands", "kir_genes", "hla_kir_interactions", "hla_divergence", "hla_het". See details for further explanations.
placeholder	String giving name for dummy variable inserted to colData. This variable can be than used to define base statistical model used by runMiDAS.
lower_frequency_cutoff	Number giving lower frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
upper_frequency_cutoff	Number giving upper frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.
indels	Logical indicating whether indels should be considered when checking amino acid variability in 'hla_aa' experiment.
unkchar	Logical indicating whether unknown characters in the alignment should be considered when checking amino acid variability in 'hla_aa' experiment.
hla_divergence_aa_selection	String specifying variable region in peptide binding groove which should be considered for Grantham distance calculation. Valid choices includes: "binding_groove", "B_pocket", "F_pocket". See details for more information.
hla_het_resolution	Number specifying HLA alleles resolution used to calculate heterogeneity in "hla_het" experiment.
hla_dictionary	Data frame giving HLA allele dictionary used in 'hla_custom' experiment. See hlaToVariable for more details.
kir_dictionary	Data frame giving KIR genes dictionary used in 'kir_custom' experiment. See countsToVariables for more details.

Details

experiment specifies analysis types for which hla_calls and kir_call should be prepared.

'hla_alleles' hla_calls are transformed to counts matrix describing number of allele occurrences for each sample. This experiment is used to test associations on HLA alleles level.

'hla_aa' hla_calls are transformed to a matrix of variable amino acid positions. See hlaToAAVariation for more details. This experiment is used to test associations on amino acid level.

"hla_g_groups" hla_calls are translated into HLA G groups and transformed to matrix describing number of G group occurrences for each sample. See hlaToVariable for more details. This experiment is used to test associations on HLA G groups level.

"hla_supertypes" hla_calls are translated into HLA supertypes and transformed to matrix describing number of G group occurrences for each sample. See hlaToVariable for more details. This experiment is used to test associations on HLA supertypes level.

"hla_NK_ligands" hla_calls are translated into NK ligands, which includes HLA Bw4/Bw6 and HLA C1/C2 groups and transformed to matrix describing number of their occurrences for each sample. See hlaToVariable for more details.This experiment is used to test associations on HLA NK ligands level.

"kir_genes" kir_calls are transformed to counts matrix describing number of KIR gene occurrences for each sample. This experiment is used to test associations on KIR genes level.

"hla_kir_interactions" hla_calls and kir_calls are translated to HLA - KIR interactions as defined in Pende et al., 2019.. See getHlaKirInteractions for more details. This experiment is used to test associations on HLA - KIR interactions level.

"hla_divergence" Grantham distance for class I HLA alleles is calculated based on hla_calls using original formula by Grantham R. 1974.. See hlaCallsGranthamDistance for more details. This experiment is used to test associations on HLA divergence level measured by Grantham distance.

"hla_het" hla_calls are transformed to heterozygosity status, where 1 designates a heterozygote and 0 homozygote. Heterozygosity status is calculated only for classical HLA genes (A, B, C, DQA1, DQB1, DRA, DRB1, DPA1, DPB1). This experiment is used to test associations on HLA divergence level measured by heterozygosity.

Value

Object of class MiDAS

Examples

```
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      kir_calls = MiDAS_tut_KIR,
                      colData = MiDAS_tut_pheno,
                      experiment = "hla_alleles")
```

---

prepareMiDAS_hla_aa *Prepare MiDAS data on HLA amino acid level*

Description

Prepare MiDAS data on HLA amino acid level

Usage

```
prepareMiDAS_hla_aa(hla_calls, indels = TRUE, unkchar = FALSE, ...)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
indels	Logical indicating whether indels should be considered when checking variability.
unkchar	Logical indicating whether unknown characters in the alignment should be considered when checking variability.
...	Not used

Value

SummarizedExperiment

---

prepareMiDAS_hla_alleles

Prepare MiDAS data on HLA allele level

Description

Prepare MiDAS data on HLA allele level

Usage

```
prepareMiDAS_hla_alleles(hla_calls, ...)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
...	Not used

Value

Matrix

`prepareMiDAS_hla_custom` *Prepare MiDAS data on custom HLA level*

Description

Prepare MiDAS data on custom HLA level

Usage

```
prepareMiDAS_hla_custom(hla_calls, hla_dictionary, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`hla_dictionary`	Data frame giving HLA allele dictionary. See `hlaToVariable` for more details.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_divergence` *Prepare MiDAS data on HLA divergence level*

Description

Prepare MiDAS data on HLA divergence level

Usage

```
prepareMiDAS_hla_divergence(
  hla_calls,
  hla_divergence_aa_selection = "binding_groove",
  ...
)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`hla_divergence_aa_selection`	String specifying variable region in peptide binding groove which should be considered for Grantham distance calculation. Valid choices includes: `"binding_groove"`, `"B_pocket"`, `"F_pocket"`. See details for more information.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_g_groups` *Prepare MiDAS data on HLA allele's G groups level*

Description

Prepare MiDAS data on HLA allele's G groups level

Usage

```
prepareMiDAS_hla_g_groups(hla_calls, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_het` *Prepare MiDAS data on HLA heterozygosity level*

Description

Prepare MiDAS data on HLA heterozygosity level

Usage

```
prepareMiDAS_hla_het(hla_calls, hla_het_resolution = 8, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`hla_het_resolution`	Number specifying HLA alleles resolution used to calculate heterogeneity.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_kir_interactions` *Prepare MiDAS data on HLA - KIR interactions level*

Description

Prepare MiDAS data on HLA - KIR interactions level

Usage

```
prepareMiDAS_hla_kir_interactions(hla_calls, kir_calls, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`kir_calls`	KIR calls data frame, as returned by `readKirCalls` function.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_NK_ligands` *Prepare MiDAS data on HLA allele's groups level*

Description

Prepare MiDAS data on HLA allele's groups level

Usage

```
prepareMiDAS_hla_NK_ligands(hla_calls, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`...`	Not used

Value

Matrix

`prepareMiDAS_hla_supertypes` *Prepare MiDAS data on HLA allele's supertypes level*

Description

Prepare MiDAS data on HLA allele's supertypes level

Usage

```
prepareMiDAS_hla_supertypes(hla_calls, ...)
```

Arguments

`hla_calls`	HLA calls data frame, as returned by `readHlaCalls` function.
`...`	Not used

Value

Matrix

`prepareMiDAS_kir_custom` *Prepare MiDAS data on custom KIR level*

Description

Prepare MiDAS data on custom KIR level

Usage

```
prepareMiDAS_kir_custom(kir_calls, kir_dictionary, ...)
```

Arguments

`kir_calls`	KIR calls data frame, as returned by `readKirCalls` function.
`kir_dictionary`	Data frame giving KIR genes dictionary. See `countsToVariables` for more details.
`...`	Not used

Value

Matrix

prepareMiDAS_kir_genes *Prepare MiDAS data on KIR genes level*

Description

Prepare MiDAS data on KIR genes level

Usage

```
prepareMiDAS_kir_genes(kir_calls, ...)
```

Arguments

kir_calls	KIR calls data frame, as returned by readKirCalls function.
...	Not used

Value

Matrix

prepareMiDAS_kir_haplotypes *Prepare MiDAS data on KIR haplotypes level*

Description

Prepare MiDAS data on KIR haplotypes level

Usage

```
prepareMiDAS_kir_haplotypes(kir_calls, ...)
```

Arguments

kir_calls	KIR calls data frame, as returned by readKirCalls function.
...	Not used

Value

Matrix

`readHlaAlignments` *Read HLA allele alignments*

Description

`readHlaAlignments` read HLA allele alignments from file.

Usage

```
readHlaAlignments(file, gene = NULL, trim = FALSE, unkchar = "")
```

Arguments

`file`	Path to input file.
`gene`	Character vector of length one specifying the name of a gene for which alignment is required. See details for further explanations.
`trim`	Logical indicating if alignment should be trimmed to start codon of the mature protein.
`unkchar`	Character to be used to represent positions with unknown sequence.

Details

HLA allele alignment file should follow EBI database format, for details see ftp://ftp.ebi.ac.uk/pub/databases/ipd/imgt/hla/alignments/README.md.

All protein alignment files from the EBI database are shipped with the package. They can be easily accessed using `gene` parameter. If `gene` is set to `NULL`, `file` parameter is used instead and alignment is read from the provided file. In EBI database alignments for DRB1, DRB3, DRB4 and DRB5 genes are provided as a single file, here they are separated.

Additionally, for the alleles without sequence defined in the original alignment files we have infered thier sequence based on known higher resolution alleles.

Value

Matrix containing HLA allele alignments.

Rownames correspond to allele numbers and columns to positions in the alignment. Sequences following the termination codon are marked as empty character (`""`). Unknown sequences are marked with a character of choice, by default `""`. Stop codons are represented by a hash (X). Insertion and deletions are marked with period (.).

Examples

```
hla_alignments <- readHlaAlignments(gene = "A")
```

readHlaCalls *Read HLA allele calls*

Description

readHlaCalls read HLA allele calls from file

Usage

```
readHlaCalls(file, resolution = 4, na.strings = c("Not typed", "-", "NA"))
```

Arguments

file	Path to input file.
resolution	Number specifying desired resolution.
na.strings	a character vector of strings which are to be interpreted as NA values. Blank fields are also considered to be missing values in logical, integer, numeric and complex fields. Note that the test happens *after* white space is stripped from the input, so na.strings values may need their own white space stripped in advance.

Details

Input file has to be a tsv formatted table with a header. First column should contain sample IDs, further columns hold HLA allele numbers. See system.file("extdata", "MiDAS_tut_HLA.txt", package = "midasHLA") file for an example.

resolution parameter can be used to reduce HLA allele numbers. If reduction is not needed resolution can be set to 8. resolution parameter can take the following values: 2, 4, 6, 8. For more details about HLA allele numbers resolution see http://hla.alleles.org/nomenclature/naming.html.

Value

HLA calls data frame. First column hold sample IDs, further columns hold HLA allele numbers.

Examples

```
file <- system.file("extdata", "MiDAS_tut_HLA.txt", package = "midasHLA")
hla_calls <- readHlaCalls(file)
```

readKirCalls *Read KIR calls*

Description

readKirCalls read KIR calls from file.

Usage

```
readKirCalls(file, na.strings = c("", "NA", "uninterpretable"))
```

Arguments

file	Path to input file.
na.strings	a character vector of strings which are to be interpreted as NA values. Blank fields are also considered to be missing values in logical, integer, numeric and complex fields. Note that the test happens *after* white space is stripped from the input, so na.strings values may need their own white space stripped in advance.

Details

Input file has to be a tsv formatted table. First column should be named "ID" and contain samples IDs, further columns should hold KIR genes presence / absence indicators. See system.file("extdata", "MiDAS_tut_KIR", package = "midasHLA") for an example.

Value

Data frame containing KIR gene's counts. First column hold samples IDs, further columns hold KIR genes presence / absence indicators.

Examples

```
file <- system.file("extdata", "MiDAS_tut_KIR.txt", package = "midasHLA")
readKirCalls(file)
```

reduceAlleleResolution *Reduce HLA alleles*

Description

reduceAlleleResolution reduce HLA allele numbers resolution.

Usage

```
reduceAlleleResolution(allele, resolution = 4)
```

Arguments

allele	Character vector with HLA allele numbers.
resolution	Number specifying desired resolution.

Details

In cases when allele number contain additional suffix their resolution can not be unambiguously reduced. These cases are returned unchanged. Function behaves in the same manner if `resolution` is higher than resolution of input HLA allele numbers.

`NA` values are accepted and returned as `NA`.

TODO here we give such warning when alleles have G or GG suffix (see http://hla.alleles.org/alleles/g_groups.html) "Reducing G groups alleles, major allele gene name will be used." I dond't really remember why we are doing this xd These allele numbers are processed as normal alleles (without suffix). Let me know if this warning is relevant or we could go without it. If we want to leave it lets also add text in documentation.

Value

Character vector containing reduced HLA allele numbers.

Examples

```
reduceAlleleResolution(c("A*01", "A*01:24", "C*05:24:55:54"), 2)
```

`reduceHlaCalls` *Reduce HLA calls resolution*

Description

`reduceHlaCalls` reduces HLA calls data frame to specified resolution.

Usage

```
reduceHlaCalls(hla_calls, resolution = 4)
```

Arguments

hla_calls	HLA calls data frame, as returned by `readHlaCalls` function.
resolution	Number specifying desired resolution.

Details

Alleles with resolution greater than `resolution` or optional suffixes are returned unchanged.

Value

HLA calls data frame reduced to specified resolution.

Examples

```
reduceHlaCalls(MiDAS_tut_HLA, resolution = 2)
```

---

runMiDAS *Run MiDAS statistical analysis*

Description

`runMiDAS` perform association analysis on MiDAS data using statistical model of choice. Function is intended for use with `prepareMiDAS`. See examples section.

Usage

```
runMiDAS(
  object,
  experiment,
  inheritance_model = NULL,
  conditional = FALSE,
  omnibus = FALSE,
  omnibus_groups_filter = NULL,
  lower_frequency_cutoff = NULL,
  upper_frequency_cutoff = NULL,
  correction = "bonferroni",
  n_correction = NULL,
  exponentiate = FALSE,
  th = 0.05,
  th_adj = TRUE,
  keep = FALSE,
  rss_th = 1e-07
)
```

Arguments

`object`	An existing fit from a model function such as lm, glm and many others.
`experiment`	String indicating the experiment associated with `object`'s `MiDAS` data to use. Valid values includes: `"hla_alleles"`, `"hla_aa"`, `"hla_g_groups"`, `"hla_supertypes"`, `"hla_NK_ligands"`, `"kir_genes"`, `"kir_haplotypes"`, `"hla_kir_interactions"`, `"hla_divergence"`, `"hla_het"`, `"hla_custom"`, `"kir_custom"`. See `prepareMiDAS` for more information.

`inheritance_model`
: String specifying inheritance model to use. Available choices are `"dominant"`, `"recessive"`, `"additive"`.

`conditional`
: Logical flag indicating if conditional analysis should be performed.

`omnibus`
: Logical flag indicating if omnibus test should be used.

`omnibus_groups_filter`
: Character vector specifying omnibus groups to use.

`lower_frequency_cutoff`
: Number giving lower frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.

`upper_frequency_cutoff`
: Number giving upper frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.

`correction`
: String specifying multiple testing correction method. See details for further information.

`n_correction`
: Integer specifying number of comparisons to consider during multiple testing correction calculations. For Bonferroni correction it is possible to specify a number lower than the number of comparisons being made. This is useful in cases when knowledge about the biology or redundance of alleles reduces the need for correction. For other methods it must be at least equal to the number of comparisons being made; only set this (to non-default) when you know what you are doing!

`exponentiate`
: Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to `tidy`. This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to FALSE.

`th`
: Number specifying threshold for a variable to be considered significant.

`th_adj`
: Logical flag indicating if adjusted p-value should be used as threshold criteria, otherwise unadjusted p-value is used.

`keep`
: Logical flag indicating if the output should be a list of results resulting from each selection step. Default is to return only the final result.

`rss_th`
: Number specifying residual sum of squares threshold at which function should stop adding additional variables. As the residual sum of squares approaches `0` the perfect fit is obtained making further attempts at variable selection nonsense. This behavior can be controlled using `rss_th`.

Details

By default statistical analysis is performed iteratively on each variable in selected experiment. This is done by substituting `placeholder` in the `object`'s formula with each variable in the experiment.

Setting `conditional` argument to `TRUE` will cause the statistical analysis to be performed in a stepwise conditional testing manner, adding the previous top-associated variable as a covariate to `object`'s formula. The analysis stops when there is no more significant variables, based on self-defined threshold (`th` argument). Either adjusted or unadjusted p-values can be used as the selection criteria, which is controlled using `th_adj` argument.

Setting `omnibus` argument to `TRUE` will cause the statistical analysis to be performed iteratively on groups of variables (like residues at particular amino acid position) using likelihood ratio test.

Argument `inheritance_model` specifies the inheritance model that should be applyed to experiment's data. Following choices are available:

- "dominant" carrier status is sufficient for expression of the phenotype (non-carrier: 0, heterozygous & homozygous carrier: 1).
- "recessive" two copies are required for expression of the phenotype (non-carrier & heterozygous carrier: 0, homozygous carrier: 1).
- "additive" allele dosage matters, homozygous carriers show stronger phenotype expression or higher risk than heterozygous carriers (non-carrier = 0, heterozygous carrier = 1, homozygous carrier = 2).
- "overdominant" heterozygous carriers are at higher risk compared to non-carriers or homozygous carriers (non-carrier & homozygous carrier = 0, heterozygous carrier = 1).

`correction` specifies p-value adjustment method to use, common choice is Benjamini & Hochberg (1995) (`"BH"`). Internally this is passed to p.adjust.

Value

Analysis results, depending on the parameters:

`conditional=FALSE, omnibus=FALSE` Tibble with first column `"term"` holding names of tested variables (eg. alleles). Further columns depends on the used model and are determined by associated `tidy` function. Generally they will include `"estimate"`, `"std.error"`, `"statistic"`, `"p.value"`, `"conf.low"`, `"conf.high"`, `"p.adjusted"`.

`conditional=TRUE, omnibus=FALSE` Tibble or a list of tibbles, see `keep` argument. The first column `"term"` hold names of tested variables. Further columns depends on the used model and are determined by associated `tidy` function. Generally they will include `"estimate"`, `"std.error"`, `"statistic"`, `"p.value"`, `"conf.low"`, `"conf.high"`, `"p.adjusted"`.

`conditional=FALSE, omnibus=TRUE` Tibble with first column holding names of tested omnibus groups (eg. amino acid positions) and second names of variables in the group (eg. residues). Further columns are: `"df"` giving difference in degrees of freedom between base and extended model, `"statistic"` giving Chisq statistic, `"p.value"` and `"p.adjusted"`.

`conditional=TRUE, omnibus=TRUE` Tibble or a list of tibbles, see `keep` argument. The first column hold names of tested omnibus groups (eg. amino acid positions), second column hold names of variables in the group (eg. residues). Further columns are: `"df"` giving difference in degrees of freedom between base and extended model, `"statistic"` giving Chisq statistic, `"p.value"` and `"p.adjusted"`.

Examples

```
# create MiDAS object
midas <- prepareMiDAS(hla_calls = MiDAS_tut_HLA,
                      colData = MiDAS_tut_pheno,
                      experiment = c("hla_alleles", "hla_aa")
)
```

```
# construct statistical model
object <- lm(disease ~ term, data = midas)

# run analysis
runMiDAS(object, experiment = "hla_alleles", inheritance_model = "dominant")

# omnibus test
# omnibus_groups_filter argument can be used to restrict omnibus test only
# to selected variables groups, here we restrict the analysis to HLA-A
# positions 29 and 43.
runMiDAS(
  object,
  experiment = "hla_aa",
  inheritance_model = "dominant",
  omnibus = TRUE,
  omnibus_groups_filter = c("A_29", "A_43")
)
```

`runMiDASGetVarsFreq` *Get variables frequencies from MiDAS*

Description

Helper getting variables frequencies from MiDAS object. Additionally for binary test covariate frequencies per phenotype are added. Used in scope of `runMiDAS`.

Usage

```
runMiDASGetVarsFreq(midas, experiment, test_covar)
```

Arguments

`midas`	MiDAS object.
`experiment`	String specifying experiment from `midas`.
`test_covar`	String giving name of test covariate.

Value

Data frame with variable number of columns. First column, `"term"` holds experiment's variables, further columns hold number of variable occurrence and their frequencies.

stringMatches *Check if string matches one of possible values*

Description

stringMatches checks if string is equal to one of the choices.

Usage

```
stringMatches(x, choice)
```

Arguments

x	string to test.
choice	Character vector with possible values for x.

Value

Logical indicating if x matches one of the strings in choice.

summariseAAPosition *Summarize amino acid position*

Description

List HLA alleles and amino acid residues at a given position.

Usage

```
summariseAAPosition(hla_calls, aa_pos, aln = NULL, na.rm = FALSE)
```

Arguments

hla_calls	HLA calls data frame, as returned by readHlaCalls function.
aa_pos	String specifying gene and amino acid position, example "A_9".
aln	Matrix containing amino acid sequence alignments as returned by readHlaAlignments function. By default function will use alignment files shipped with the package.
na.rm	Logical flag indicating if NA values should be considered for frequency calculations.

Value

Data frame containing HLA alleles, their corresponding amino acid residues and frequencies at requested position.

Examples

```
summariseAAPosition(MiDAS_tut_HLA, "A_9")
```

`updateModel` *Extend and Re-fit a Model Call*

Description

`updateModel` adds new variables to model and re-fit it.

Usage

```
updateModel(object, x, placeholder = NULL, backquote = TRUE, collapse = " + ")
```

Arguments

`object`	An existing fit from a model function such as lm, glm and many others.
`x`	Character vector specifying variables to be added to model.
`placeholder`	String specifying term to substitute with value from `x`. Ignored if set to `NULL`.
`backquote`	Logical indicating if added variables should be quoted. Elements of this vector are recycled over `x`.
`collapse`	String specifying how variables should be combined. Defaults to `" + "` ie. linear combination.

Value

Updated fitted object.

`validateFrequencyCutoffs`
Validate frequency cutoffs

Description

`validateFrequencyCutoffs` checks if `lower_frequency_cutoff` and `upper_frequency_cutoff` are valid.

Usage

```
validateFrequencyCutoffs(lower_frequency_cutoff, upper_frequency_cutoff)
```

Arguments

lower_frequency_cutoff	Number
upper_frequency_cutoff	Number

Details

lower_frequency_cutoff and upper_frequency_cutoff should be a positive numbers, giving either frequency or counts. lower_frequency_cutoff has to be lower than upper_frequency_cutoff.

Value

Logical indicating if lower_frequency_cutoff and upper_frequency_cutoff are valid.

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