

# Package ‘midasHLA’

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**Title** R package for immunogenomics data handling and association analysis

**Version** 1.12.0

**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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**Encoding** UTF-8

**LazyData** true

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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**

|                     |  |
|---------------------|--|
| <code>p</code>      | numeric vector of p-values (possibly with NAs). Any other R object is coerced by <code>as.numeric</code> .   |
| <code>method</code> | correction method. Can be abbreviated.   |
| <code>n</code>      | number of comparisons, must be at least <code>length(p)</code> ; 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 <code>length(p)</code> . |

**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 redundancy 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](http://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 <code>tidy</code> . 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 <code>lm</code> , <code>glm</code> and many others.  |
| variables    | Character vector specifying variables to use in association tests.   |
| placeholder  | String specifying term to substitute with value from <code>x</code> . Ignored if set to <code>NULL</code> .  |
| 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 <code>rss_th</code> .   |
| exponentiate | Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to <code>tidy</code> . This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to <code>FALSE</code> .   |

**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 | <i>Check if character matches one of possible values</i> |
|------------------|--|

---

**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 | <i>Check HLA allele format</i> |
|-------------------|--------------------------------|

---

**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](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 | <i>Assert colData data</i> |
|--------------------|----------------------------|

---

### 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 attribute.

**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 | <i>Check column names</i> |
|-----------------|---------------------------|

---

**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 | <i>Convert allele numbers to additional variables</i> |
|-------------------------|---|

---

**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 | <i>Convert counts table to variables</i> |
|-------------------|--|

---

**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 <a href="#">hlaCallsToCounts</a> 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 specifying value for variables with no matching entry in dictionary. Default is to use $\emptyset$ .   |
| 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 | <i>Helper transform data frame to experiment matrix</i> |
|-------------------|---|

---

**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 | <i>Grantham distance</i> |
|--------------------|--------------------------|

---

**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 | <i>Calculate Grantham distance between amino acid sequences</i> |
|--------------|---|

---

**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 | <i>Helper transform experiment matrix to data frame</i> |
|-------------------|---|

---

**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 <a href="#">getOmnibusGroups</a> 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 <code>runMiDAS</code> .  |
| filter_by         | Character vector specifying conditional expression used to filter results, this is equivalent to <code>...</code> argument passed to <code>filter</code> . |
| arrange_by        | Character vector specifying variable names to use for sorting. Equivalent to <code>...</code> argument passed to <code>arrange</code> .                    |
| 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 | <i>Calculate amino acid frequencies</i> |
|------------------|---|

---

**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,  $\text{frequency} = n / (2 * j)$  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 | <i>Get HLA alleles for amino acid position</i> |
|-----------------|--|

---

**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 | <i>Calculate experiment's features frequencies</i> |
|--------------------------|--|

---

**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 <a href="#">getReferenceFrequencies</a> for more details. |

### Value

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

---

```

getExperimentPopulationMultiplier
  Get experiment's population multiplier

```

---

### Description

getExperimentPopulationMultiplier extracts population multiplier from experiment's metadata.

### Usage

```

getExperimentPopulationMultiplier(experiment)

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

## S3 method for class 'SummarizedExperiment'
getExperimentPopulationMultiplier(experiment)

```

**Arguments**

experiment      Matrix or SummarizedExperiment object.

**Value**

Experiment's population multiplier 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 <a href="#">allele_frequencies</a> 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 | <i>Get HLA calls from MiDAS object.</i> |
|-------------|---|

---

**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 | <i>Get HLA calls genes</i> |
|------------------|----------------------------|

---

**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 <a href="#">readHlaCalls</a> 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 <a href="#">allele_frequencies</a> for an example.  |

### Details

Both gene copies are taken into consideration for frequencies calculation,  $\text{frequency} = n / (2 * j)$  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 | <i>Get attributes of statistical model object</i> |
|------------------|---|

---

**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 | <i>Get omnibus groups from MiDAS object.</i> |
|------------------|--|

---

**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 "h1a\_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 | <i>Get placeholder name from MiDAS object.</i> |
|----------------|--|

---

**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 | <i>Helper transforming reference frequencies</i> |
|-------------------------|--|

---

**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 | <i>Find variable positions in sequence alignment</i> |
|------------------|--|

---

**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 <a href="#">readHlaAlignments</a> ,  |
| 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]" occurrence 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 | <i>Check if tidy method for class exist</i> |
|---------------|---|

---

**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 | <i>Helper function returning alignment for Grantham distance calculations</i> |
|----------------------|---|

---

**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

|                           |   |
|---------------------------|---|
| <code>hla_calls</code>    | HLA calls data frame, as returned by <a href="#">readHlaCalls</a> function.   |
| <code>genes</code>        | Character vector specifying genes for which allelic distance should be calculated.  |
| <code>aa_selection</code> | 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 | <i>Transform HLA calls to counts table</i> |
|------------------|--|

---

**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 <a href="#">readHlaCalls</a> 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 | <i>Generate amino acid variation matrix</i> |
|------------------|---|

---

**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 <a href="#">readHlaCalls</a> 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 | <i>Convert HLA calls to variables</i> |
|---------------|---------------------------------------|

---

**Description**

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

**Usage**

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

**Arguments**

|                         |   |
|-------------------------|---|
| <code>hla_calls</code>  | HLA calls data frame, as returned by <a href="#">readHlaCalls</a> function.   |
| <code>dictionary</code> | Path to file containing HLA allele dictionary or a data frame.  |
| <code>reduce</code>     | Logical indicating if function should try to reduce allele resolution when no matching entry in the dictionary is found. See details. |
| <code>na.value</code>   | Vector of length one specifying value for alleles with no matching entry in dictionary. Default is to use 0.                          |
| <code>nacols.rm</code>  | 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 | <i>Check if object is character vector or NULL</i> |
|-------------------|--|

---

**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 | <i>Check if object is of class x</i> |
|---------|--------------------------------------|

---

**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 | <i>Check if object is of class x or null</i> |
|---------------|--|

---

**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 | <i>Check if object is count or NULL</i> |
|---------------|---|

---

**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\_applicable" 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 | <i>Check if object is TRUE or FALSE flag</i> |
|---------------|--|

---

**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 | <i>Iterative likelihood ratio test</i> |
|--------------|--|

---

**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 | <i>Iteratively evaluate model for different variables</i> |
|----------------|---|

---

**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 | <i>Create association analysis results table in HTML or LaTeX</i> |
|--------------|---|

---

**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 <code>runMiDAS</code> .  |
| colnames          | Character vector of form <code>c("new_name" = "old_name")</code> , 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](http://www.allelefrequencies.net)

---

|                 |                                     |
|-----------------|-------------------------------------|
| lapply_tryCatch | <i>lapply with tryCatch routine</i> |
|-----------------|-------------------------------------|

---

### 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 <a href="#">expression</a> 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.

---

LRTtest *Likelihood ratio test*

---

### Description

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

### Usage

```
LRTtest(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                 | <a href="#">MiDAS</a> 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 <a href="#">allele_frequencies</a> 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 <a href="#">getOmnibusGroups</a> 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 | <i>Transform MiDAS to wide format data.frame</i> |
|-------------|--|

---

**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 | <i>MiDAS tutorial HLA data</i> |
|---------------|--------------------------------|

---

**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 examples 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 redundancy 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 <a href="#">readHlaCalls</a> function.  |
| kir_calls                   | KIR calls data frame, as returned by <a href="#">readKirCalls</a> 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 <a href="#">runMiDAS</a> .  |
| 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 <a href="#">hlaToVariable</a> for more details.   |
| kir_dictionary              | Data frame giving KIR genes dictionary used in 'kir_custom' experiment. See <a href="#">countsToVariables</a> 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 <a href="#">readHlaCalls</a> 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 <a href="#">readHlaCalls</a> 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 <a href="#">readHlaCalls</a> function.                  |
| hla_dictionary | Data frame giving HLA allele dictionary. See <a href="#">hlaToVariable</a> 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 <a href="#">readHlaCalls</a> 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 <a href="#">readHlaCalls</a> 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 <a href="#">readHlaCalls</a> 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**

|                        |   |
|------------------------|---|
| <code>hla_calls</code> | HLA calls data frame, as returned by <a href="#">readHlaCalls</a> function. |
| <code>kir_calls</code> | KIR calls data frame, as returned by <a href="#">readKirCalls</a> function. |
| <code>...</code>       | 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**

|                        |   |
|------------------------|---|
| <code>hla_calls</code> | HLA calls data frame, as returned by <a href="#">readHlaCalls</a> function. |
| <code>...</code>       | 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**

|                        |   |
|------------------------|---|
| <code>kir_calls</code> | KIR calls data frame, as returned by <a href="#">readKirCalls</a> function. |
| <code>...</code>       | 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**

|                        |   |
|------------------------|---|
| <code>kir_calls</code> | KIR calls data frame, as returned by <a href="#">readKirCalls</a> function. |
| <code>...</code>       | 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 inferred their 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 | <i>Read HLA allele calls</i> |
|--------------|------------------------------|

---

### 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 <i>after</i> 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 | <i>Read KIR calls</i> |
|--------------|-----------------------|

---

**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 <i>after</i> 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 | <i>Reduce HLA alleles</i> |
|------------------------|---------------------------|

---

**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](http://hla.alleles.org/alleles/g_groups.html)) "Reducing G groups alleles, major allele gene name will be used." I don'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)
```

---

|                             |                                    |
|-----------------------------|------------------------------------|
| <code>reduceHlaCalls</code> | <i>Reduce HLA calls resolution</i> |
|-----------------------------|------------------------------------|

---

**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 <a href="#">prepareMiDAS</a> for more information. |

|                                     |  |
|-------------------------------------|--|
| <code>inheritance_model</code>      | String specifying inheritance model to use. Available choices are "dominant", "recessive", "additive".   |
| <code>conditional</code>            | Logical flag indicating if conditional analysis should be performed.   |
| <code>omnibus</code>                | Logical flag indicating if omnibus test should be used.  |
| <code>omnibus_groups_filter</code>  | Character vector specifying omnibus groups to use.   |
| <code>lower_frequency_cutoff</code> | Number giving lower frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.  |
| <code>upper_frequency_cutoff</code> | Number giving upper frequency threshold. Numbers greater than 1 are interpreted as the number of feature occurrences, numbers between 0 and 1 as fractions.  |
| <code>correction</code>             | String specifying multiple testing correction method. See details for further information.   |
| <code>n_correction</code>           | 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 redundancy 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! |
| <code>exponentiate</code>           | Logical flag indicating whether or not to exponentiate the coefficient estimates. Internally this is passed to <code>tidy</code> . This is typical for logistic and multinomial regressions, but a bad idea if there is no log or logit link. Defaults to FALSE.   |
| <code>th</code>                     | Number specifying threshold for a variable to be considered significant.   |
| <code>th_adj</code>                 | Logical flag indicating if adjusted p-value should be used as threshold criteria, otherwise unadjusted p-value is used.  |
| <code>keep</code>                   | 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.  |
| <code>rss_th</code>                 | 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 <code>rss_th</code> .   |

## 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 applied 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 | <i>Check if string matches one of possible values</i> |
|---------------|---|

---

**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 | <i>Summarize amino acid position</i> |
|---------------------|--------------------------------------|

---

**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 <a href="#">readHlaCalls</a> function.  |
| aa_pos    | String specifying gene and amino acid position, example "A_9".   |
| aln       | Matrix containing amino acid sequence alignments as returned by <a href="#">readHlaAlignments</a> 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 | <i>Extend and Re-fit a Model Call</i> |
|-------------|---------------------------------------|

---

**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 | <i>Validate frequency cutoffs</i> |
|--------------------------|-----------------------------------|

---

**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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