

Package ‘phers’

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Type Package

Title Calculate Phenotype Risk Scores

Version 1.0.5

Description Use phenotype risk scores based on linked clinical and genetic data to study Mendelian disease and rare genetic variants. See Bastarache et al. 2018 <[doi:10.1126/science.aal4043](https://doi.org/10.1126/science.aal4043)>.

URL <https://phers.hugheylab.org>, <https://github.com/hugheylab/phers>

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demoSample	<i>Sample table of demographic information</i>
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Description

The data are artificial and do not correspond to real patients.

Usage

demoSample

Format

A data table with the following columns:

- person_id: Character vector of the identifier for each person in the cohort
- sex: Character vector indicating biological sex

See Also

[getWeights\(\)](#), [getScores\(\)](#)

diseaseDxIcdMap	<i>Mapping of diseases and diagnostic ICD codes</i>
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Description

This table provides a mapping between 27 Mendelian diseases and the corresponding ICD-9 and ICD-10 codes that indicate a genetic diagnosis.

Usage

diseaseDxIcdMap

Format

A data.table with the following columns:

- disease_id: Numeric vector of OMIM disease identifiers
- disease_name: Character vector of disease names
- icd: Character vector of ICD codes indicating a genetic diagnosis
- flag: Integer vector of the vocabulary of the ICD code (**9**: ICD-9-CM, **10**: ICD-10-CM)
- icd_name: Character vector containing the description of each ICD code

See Also

[getPhecodeOccurrences\(\)](#), [getDxStatus\(\)](#)

diseaseHpoMap

Mapping of Mendelian diseases and their clinical features

Description

This table provides a mapping between Mendelian diseases and their clinical features, represented as Human Phenotype Ontology (HPO) terms. The mapping is based on annotations from Online Mendelian Inheritance in Man (OMIM).

Usage

```
diseaseHpoMap
```

Format

A data.table with the following columns:

- disease_id: Numeric vector of OMIM disease identifiers
- disease_name: Character vector of disease names
- hpo_term_id: Character vector of HPO identifiers corresponding to each disease's clinical features
- hpo_term_name: Character vector of HPO term descriptions

Source

<https://hpo.jax.org/data/annotations>

See Also

[mapDiseaseToPhecode\(\)](#)

getDxStatus

Identify cases and controls for Mendelian diseases

Description

This function is useful for verifying that raw or residual phenotype risk scores of diagnosed individuals (cases) tend to be higher than scores of undiagnosed individuals (controls).

Usage

```
getDxStatus(
  demos,
  icdOccurrences,
  minUniqueAges = 2L,
  diseaseDxIcdMap = phers::diseaseDxIcdMap
)
```

Arguments

demos A data.table having one row per person in the cohort. Must have a column `person_id`.

icdOccurrences A data.table of occurrences of ICD codes for each person in the cohort. Must have columns `person_id`, `icd`, `flag`, and `occurrence_age`.

minUniqueAges Integer indicating the minimum number of unique ICD code entry ages required to classify a person as a case. Persons with at least one, but fewer than `minUniqueAges` entry ages, are assigned as neither cases nor controls.

diseaseDxIcdMap A data.table of the mapping between diseases and the corresponding ICD codes that indicate a diagnosis. Must have columns `disease_id`, `icd`, and `flag`. Default is [diseaseDxIcdMap](#).

Value

A data.table with columns `person_id`, `disease_id`, and `dx_status` (1 indicates a case, 0 indicates a control, -1 indicates neither).

Examples

```
library('data.table')
setDTthreads(1) # default for examples

icdSample1 = merge(icdSample, demoSample[, .(person_id, dob)], by = 'person_id')
icdSample1[, occurrence_age := as.numeric((entry_date - dob)/365.25)]
icdSample1[, `:=`(entry_date = NULL, dob = NULL)]

dxStatus = getDxStatus(demoSample, icdSample1)
```

`getGeneticAssociations`*Perform association tests between phenotype risk scores and genotypes*

Description

The association test for each disease-variant pair is based on a linear model, with the phenotype risk score as the dependent variable.

Usage

```
getGeneticAssociations(  
  scores,  
  genotypes,  
  demos,  
  diseaseVariantMap,  
  lmFormula,  
  modelType = c("genotypic", "additive", "dominant", "recessive"),  
  level = 0.95,  
  dopar = FALSE  
)
```

Arguments

<code>scores</code>	A data.table of phenotype risk scores. Must have columns <code>person_id</code> , <code>disease_id</code> , <code>score</code> .
<code>genotypes</code>	A matrix or 'BEDMatrix' object containing genetic data, with rownames corresponding to <code>person_ids</code> in <code>demos</code> and <code>scores</code> , and colnames corresponding to <code>variant_ids</code> in <code>diseaseVariantMap</code> .
<code>demos</code>	A data.table of characteristics for each person in the cohort. Must have column <code>person_id</code> .
<code>diseaseVariantMap</code>	A data.table indicating which genetic variants to test for association with phenotype risk scores for which diseases. Must have columns <code>disease_id</code> and <code>variant_id</code> .
<code>lmFormula</code>	A formula representing the linear model (excluding the term for genotype) to use for the association tests. All terms in the formula must correspond to columns in <code>demos</code> .
<code>modelType</code>	A string indicating how to encode genotype in the model.
<code>level</code>	A number indicating the level of the confidence interval. Default is 0.95.
<code>dopar</code>	Logical indicating whether to run calculations in parallel if a parallel backend is already set up, e.g., using <code>doParallel::registerDoParallel()</code> . Recommended to minimize runtime.

Value

A data.table of statistics for the association tests (if a model fails to converge, NAs will be reported):

- disease_id: Disease identifier
- variant_id: Variant identifier
- n_total: Number of persons with non-missing genotype data for the given variant.
- n_wt: Number of persons homozygous for the wild-type allele.
- n_het: Number of persons having one copy of the alternate allele.
- n_hom: Number of persons homozygous for the alternate allele.
- beta: Coefficient for the association of genotype with score
- se: Standard error for beta
- pval: P-value for beta being non-zero
- ci_lower: Lower bound of the confidence interval for beta
- ci_upper: Upper bound of the confidence interval for beta

If modelType is "genotypic", the data.table will include separate statistics for heterozygous and homozygous genotypes.

See Also

`stats::lm()`, `stats::confint()`, `getScores()`

Examples

```
library('data.table')
library('BEDMatrix')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)

# calculate weights
weights = getWeights(demoSample, phecodeOccurrences)

# OMIM disease IDs for which to calculate phenotype risk scores
diseaseId = 154700

# map diseases to phecodes
diseasePhecodeMap = mapDiseaseToPhecode()

# calculate scores
scores = getScores(weights, diseasePhecodeMap[disease_id == diseaseId])

# map diseases to genetic variants
nvar = 10
diseaseVariantMap = data.table(disease_id = diseaseId, variant_id = paste0('snp', 1:nvar))

# load sample genetic data
```

```
npop = 50
genoSample = BEDMatrix(system.file('extdata', 'geno_sample.bed', package = 'phers'))
colnames(genoSample) = paste0('snp', 1:nvar)
rownames(genoSample) = 1:npop

# run genetic association tests
genoStats = getGeneticAssociations(
  scores, genoSample, demoSample, diseaseVariantMap, lmFormula = ~ sex,
  modelType = 'additive')
```

getPhecodeOccurrences *Map ICD code occurrences to phecode occurrences*

Description

This is typically the first step of an analysis using phenotype risk scores, the next is [getWeights\(\)](#).

Usage

```
getPhecodeOccurrences(
  icdOccurrences,
  icdPhecodeMap = phers::icdPhecodeMap,
  dxIcd = phers::diseaseDxIcdMap
)
```

Arguments

icdOccurrences A data.table of occurrences of ICD codes for each person in the cohort. Must have columns `person_id`, `icd`, and `flag`.

icdPhecodeMap A data.table of the mapping between ICD codes and phecodes. Must have columns `icd`, `phecode`, and `flag`. Default is the map included in this package.

dxIcd A data.table of ICD codes to exclude from mapping to phecodes. Must have columns `icd` and `flag`. Default is the table of Mendelian diseases and the corresponding ICD codes that indicate a genetic diagnosis. If NULL, no ICD codes will be excluded.

Value

A data.table of phecode occurrences for each person.

See Also

[getWeights\(\)](#), [getScores\(\)](#)

Examples

```
library('data.table')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)

# calculate weights (using the prevalence method)
weights = getWeights(demoSample, phecodeOccurrences)

# OMIM disease IDs for which to calculate phenotype risk scores
diseaseId = 154700

# map diseases to phecodes
diseasePhecodeMap = mapDiseaseToPhecode()

# calculate scores
scores = getScores(weights, diseasePhecodeMap[disease_id == diseaseId])

# calculate residual scores
rscores = getResidualScores(demoSample, scores, lmFormula = ~ sex)
```

getResidualScores *Calculate residual phenotype risk scores*

Description

The residual score indicates to what extent a person's phenotype risk score for a given disease deviates from the expected score, after adjusting for the person's characteristics in a linear model.

Usage

```
getResidualScores(demos, scores, lmFormula)
```

Arguments

demos	A data.table of characteristics for each person in the cohort. Must have column person_id.
scores	A data.table containing the phenotype risk score for each person for each disease. Must have columns person_id, disease_id, and score.
lmFormula	A formula representing the linear model to use for calculating residual scores. All terms in the formula must correspond to columns in demos.

Value

A data.table, based on scores, with an additional column resid_score. Residual scores for each disease are standardized to have unit variance.

See Also

[stats::rstandard\(\)](#), [getScores\(\)](#)

Examples

```
library('data.table')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)

# calculate weights (using the prevalence method)
weights = getWeights(demoSample, phecodeOccurrences)

# OMIM disease IDs for which to calculate phenotype risk scores
diseaseId = 154700

# map diseases to phecodes
diseasePhecodeMap = mapDiseaseToPhecode()

# calculate scores
scores = getScores(weights, diseasePhecodeMap[disease_id == diseaseId])

# calculate residual scores
rscores = getResidualScores(demoSample, scores, lmFormula = ~ sex)
```

getScores

Calculate phenotype risk scores

Description

A person's phenotype risk score for a given disease corresponds to the sum of the weights of the disease-relevant phecodes that the person has received.

Usage

```
getScores(weights, diseasePhecodeMap)
```

Arguments

weights A data.table of phecodes and their corresponding weights. Must have columns person_id, phecode and w.

diseasePhecodeMap A data.table of the mapping between diseases and phecodes. Must have columns disease_id and phecode.

Value

A data.table containing the phenotype risk score for each person for each disease.

See Also

[mapDiseaseToPhecode\(\)](#), [getPhecodeOccurrences\(\)](#), [getWeights\(\)](#), [getResidualScores\(\)](#)

Examples

```
library('data.table')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)

# calculate weights (using the prevalence method)
weights = getWeights(demoSample, phecodeOccurrences)

# OMIM disease IDs for which to calculate phenotype risk scores
diseaseId = 154700

# map diseases to phecodes
diseasePhecodeMap = mapDiseaseToPhecode()

# calculate scores
scores = getScores(weights, diseasePhecodeMap[disease_id == diseaseId])

# calculate residual scores
rscores = getResidualScores(demoSample, scores, lmFormula = ~ sex)
```

getWeights

Calculate phecode-specific weights for phenotype risk scores

Description

This is typically the second step of an analysis using phenotype risk scores, the next is [getScores\(\)](#).

Usage

```
getWeights(
  demos,
  phecodeOccurrences,
  method = c("prevalence", "logistic", "cox", "loglinear", "prevalence_precalc"),
  methodFormula = NULL,
  negativeWeights = FALSE,
  dopar = FALSE
)
```

Arguments

demos A `data.table` having one row per person in the cohort. Must have a column `person_id`. When the `cox` method is used, `demos` must have columns `first_age` and `last_age` corresponding to first and last age of visit (in years).

phecodeOccurrences	A data.table of phecode occurrences for each person in the cohort. Must have columns person_id and phecode under the "prevalence" or "logistic" methods, columns person_id, phecode, and num_occurrences under the "loglinear" method, and columns person_id, phecode, and occurrence_age under the "cox" method. num_occurrences refers to the number of unique dates a phecode was recorded for a person. occurrence_age refers to the first age (in years) a person acquired a phecode.
method	A string indicating the statistical model for calculating weights.
methodFormula	A formula representing the right-hand side of the model corresponding to method. All terms in the formula must correspond to columns in demos. A method formula is not required for the "prevalence" and "prevalence_precalc" methods. Do not use age-related covariates with the "cox" method.
negativeWeights	Logical indicating whether to allow negative weights for individuals with no occurrences of a phecode. This option is not required for the "loglinear" method since under this method, individuals with a nonzero phecode occurrence can also have negative weights.
dopar	Logical indicating whether to run calculations in parallel if a parallel backend is already set up, e.g., using <code>doParallel::registerDoParallel()</code> . Recommended to minimize runtime.

Value

A data.table with columns person_id, phecode, pred, and w. The column pred represents a different quantity depending on method. Under the "prevalence" method, it is fraction of the cohort that has at least one occurrence of the given phecode. The "prevalence_precalc" method is similar to the "prevalence" method but pred is calculated based on EHR data from the Vanderbilt University Medical Center. Under "logistic" or "cox" method, it is the predicted probability of given individual having a given phecode based on methodFormula. Under the "loglinear" method, it is the predicted $\log_2(\text{num_occurrences} + 1)$ of a given phecode for a given individual based on methodFormula. For the "prevalence", "prevalence_precalc", "cox", and "logistic" methods, weight is calculated as $-\log_{10}(\text{pred})$ when an individual has non-zero phecode occurrence and $\log_{10}(1 - \text{pred})$ when an individual has zero phecode occurrence. For the "loglinear" method weight is calculated as the difference between the observed $\log_2(\text{num_occurrences} + 1)$ and pred.

See Also

[getPhecodeOccurrences\(\)](#), [getScores\(\)](#)

Examples

```
library('data.table')
library('survival')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)
```

```

# calculate weights using the prevalence method
weightsPrev = getWeights(demoSample, phecodeOccurrences)

# calculate weights using the prevalence method
# (assign negative weights to those with zero phecode occurrence)
weightsPrevNeg = getWeights(
  demoSample, phecodeOccurrences, negativeWeights = TRUE)

# calculate weights using the logistic method
weightsLogistic = getWeights(
  demoSample, phecodeOccurrences, method = 'logistic', methodFormula = ~ sex)

# calculate weights using the loglinear method
phecodeOccurrences2 = phecodeOccurrences[, .(
  num_occurrences = uniqueN(entry_date)), by = .(person_id, phecode)]
weightsLoglinear = getWeights(
  demoSample, phecodeOccurrences2, method = 'loglinear', methodFormula = ~ sex)

# calculate weights using the cox method
phecodeOccurrences3 = phecodeOccurrences[, .(
  first_occurrence_date = min(entry_date)), by = .(person_id, phecode)]
phecodeOccurrences3 = merge(
  phecodeOccurrences3, demoSample[, .(person_id, dob)], by = 'person_id')
phecodeOccurrences3[,
  occurrence_age := as.numeric((first_occurrence_date - dob)/365.25)]
phecodeOccurrences3[, `:=`(first_occurrence_date = NULL, dob = NULL)]
demoSample3 = demoSample[, .(
  person_id, sex,
  first_age = as.numeric((first_visit_date - dob)/365.25),
  last_age = as.numeric((last_visit_date - dob)/365.25))]
weightsCox = getWeights(
  demoSample3, phecodeOccurrences3, method = 'cox', methodFormula = ~ sex)

# calculate weights using pre-calculated weights based on data from
# Vanderbilt University Medical Center
weightsPreCalc = getWeights(
  demoSample, phecodeOccurrences, method = 'prevalence_precalc')

```

hpoPhecodeMap

Mapping of HPO terms and phecodes

Description

This table provides a mapping between Human Phenotype Ontology (HPO) terms and phecodes, and is useful for using phecodes to represent the clinical features of Mendelian diseases (version 1.2).

Usage

hpoPhecodeMap

Format

A data.table with the following columns:

- hpo_term_id: Character vector of HPO term identifiers
- hpo_term_name: Character vector of HPO term descriptions
- phecode: Character vector of phecodes
- phecode_name: Character vector of phecode descriptions

See Also

[mapDiseaseToPhecode\(\)](#)

icdPhecodeMap

Mapping of ICD codes and phecodes

Description

This table provides a mapping between International Classification of Diseases 9th and 10th revisions (ICD-9-CM and ICD-10-CM) and phecodes (version 1.2).

Usage

```
icdPhecodeMap
```

Format

A data.table with the following columns:

- icd: Character vector of ICD codes
- flag: Integer vector of the vocabulary of the ICD code (**9**: ICD-9-CM, **10**: ICD-10-CM)
- icd_name: Character vector of ICD code descriptions
- phecode: Character vector of phecodes
- phecode_name: Character vector of phecode descriptions

Source

<https://phewascatalog.org/phecodes>

See Also

[getPhecodeOccurrences\(\)](#)

icdSample	<i>Sample table of ICD occurrences</i>
-----------	--

Description

The data are artificial and do not correspond to real patients.

Usage

```
icdSample
```

Format

A data.table with the following columns:

- person_id: Character vector of the identifier for each person
- icd: Character vector of the ICD codes recorded for each person
- flag: Integer vector of the vocabulary of the ICD code (**9**: ICD-9-CM, **10**: ICD-10-CM)
- entry_date: Vector of type Date indicating the date each ICD code was recorded.

See Also

[getPhecodeOccurrences\(\)](#), [getWeights\(\)](#), [getScores\(\)](#)

mapDiseaseToPhecode	<i>Map diseases to phecodes via HPO terms</i>
---------------------	---

Description

A mapping of diseases to their clinical features, represented as phecodes, is required for calculating phenotype risk scores.

Usage

```
mapDiseaseToPhecode(
  diseaseHpoMap = phers::diseaseHpoMap,
  hpoPhecodeMap = phers::hpoPhecodeMap
)
```

Arguments

diseaseHpoMap	A data.table containing the mapping between diseases and HPO terms. Must have columns disease_id and term_id. Default is the map included in this package.
hpoPhecodeMap	A data.table containing the mapping between HPO terms and phecodes. Must have columns term_id and phecode. Default is the map included in this package.

Value

A data.table with columns disease_id and phecode.

See Also

[getScores\(\)](#)

Examples

```
library('data.table')
library('survival')
setDTthreads(1) # default for examples

# map ICD codes to phecodes
phecodeOccurrences = getPhecodeOccurrences(icdSample)

# calculate weights using the prevalence method
weightsPrev = getWeights(demoSample, phecodeOccurrences)

# calculate weights using the prevalence method
# (assign negative weights to those with zero phecode occurrence)
weightsPrevNeg = getWeights(
  demoSample, phecodeOccurrences, negativeWeights = TRUE)

# calculate weights using the logistic method
weightsLogistic = getWeights(
  demoSample, phecodeOccurrences, method = 'logistic', methodFormula = ~ sex)

# calculate weights using the loglinear method
phecodeOccurrences2 = phecodeOccurrences[, .(
  num_occurrences = uniqueN(entry_date)), by = .(person_id, phecode)]
weightsLoglinear = getWeights(
  demoSample, phecodeOccurrences2, method = 'loglinear', methodFormula = ~ sex)

# calculate weights using the cox method
phecodeOccurrences3 = phecodeOccurrences[, .(
  first_occurrence_date = min(entry_date)) , by = .(person_id, phecode)]
phecodeOccurrences3 = merge(
  phecodeOccurrences3, demoSample[, .(person_id, dob)], by = 'person_id')
phecodeOccurrences3[,
  occurrence_age := as.numeric((first_occurrence_date - dob)/365.25)]
phecodeOccurrences3[, `:=`(first_occurrence_date = NULL, dob = NULL)]
demoSample3 = demoSample[, .(
  person_id, sex,
  first_age = as.numeric((first_visit_date - dob)/365.25),
  last_age = as.numeric((last_visit_date - dob)/365.25))]
weightsCox = getWeights(
  demoSample3, phecodeOccurrences3, method = 'cox', methodFormula = ~ sex)

# calculate weights using pre-calculated weights based on data from
# Vanderbilt University Medical Center
weightsPreCalc = getWeights(
```

```
demoSample, phecodeOccurrences, method = 'prevalence_precalc')
```

preCalcWeights

Pre-calculated weights for calculating phenotype risk scores

Description

The weights are based on EHR data from the Vanderbilt University Medical Center Synthetic Derivative (SD) and ICD-phecode map version 1.2 and are calculated using the "prevalence" method.

Usage

```
preCalcWeights
```

Format

A data.table with the following columns:

- phecode: Character vector of phecodes
- prev: Numeric vector of prevalences, i.e., fraction of subjects in the SD that have at least one occurrence of the given phecode
- w: Numeric vector of weights, calculated as $-\log_{10}(\text{prev})$

See Also

[getWeights\(\)](#)

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