Package 'AllelicSeries'

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Title Allelic Series Test

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Description Implementation of gene-level rare variant association tests targeting allelic series: genes where increasingly deleterious mutations have increasingly large phenotypic effects. The COding-variant Allelic Series Test (COAST) operates on the benign missense variants (BMVs), deleterious missense variants (DMVs), and protein truncating variants (PTVs) within a gene. COAST uses a set of adjustable weights that tailor the test towards rejecting the null hypothesis for genes where the average magnitude of effect increases monotonically from BMVs to DMVs to PTVs. See McCaw ZR, Somineni H, Bereket M, Klein C, Karaletsos T, Casale FP, Koller D, Soare TW. (2022) ``An allelic series rare variant association test for candidate gene discovery" <doi:10.1101/2022.12.23.521658>.

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Author Zachary McCaw [aut, cre] (<https://orcid.org/0000-0002-2006-9828>), Christoph Klein [ctb] (<https://orcid.org/0000-0002-1748-625X>), insitro [cph]

Maintainer Zachary McCaw <zmccaw@insitro.com>

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R topics documented:

`Aggregator` *Aggregator*

Description

Aggregates genotypes within annotation categories.

Usage

```
Aggregator(
  anno,
  geno,
  drop_empty = TRUE,
  indicator = FALSE,
  method = "none",
  weights = DEFAULT_WEIGHTS
)
```

Arguments

`anno`	(snps x 1) annotation vector with values in c(0, 1, 2).
`geno`	(n x snps) genotype matrix.
`drop_empty`	Drop empty columns? Default: TRUE.
`indicator`	Convert raw counts to indicators? Default: FALSE.
`method`	Method for aggregating across categories: "none", "max", "sum". Default: "none".
`weights`	Annotation category weights.

Value

(n x 3) Numeric matrix without weighting, (n x 1) numeric matrix with weighting.

AllelicSeries-help *Allelic Series Package*

Description

Implementation of gene-level rare variant association tests targeting allelic series: genes where increasingly deleterious mutations have increasingly large phenotypic effects. The COding-variant Allelic Series Test (COAST) operates on the benign missense variants (BMVs), deleterious missense variants (DMVs), and protein truncating variants (PTVs) within a gene. COAST uses a set of adjustable weights that tailor the test towards rejecting the null hypothesis for genes where the average magnitude of effect increases monotonically from BMVs to DMVs to PTVs. See McCaw ZR, Somineni H, Bereket M, Klein C, Karaletsos T, Casale FP, Koller D, Soare TW. (2022) "An allelic series rare variant association test for candidate gene discovery" https://www.biorxiv.org/content/10.1101/2022.12.23.521658v1.

Author(s)

Zachary R. McCaw, Christoph Klein

ASBT *Allelic Series Burden Test*

Description

Burden test with allelic series weights.

Usage

```
ASBT(
  anno,
  geno,
  pheno,
  apply_int = TRUE,
  covar = NULL,
  indicator = FALSE,
  is_pheno_binary = FALSE,
  method = "none",
  score_test = FALSE,
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
geno	(n x snps) genotype matrix.
pheno	(n x 1) phenotype vector.
apply_int	Apply rank-based inverse normal transform to the phenotype? Default: TRUE. Ignored if phenotype is binary.
covar	(n x p) covariate matrix. Defaults to an (n x 1) intercept.
indicator	Convert raw counts to indicators?
is_pheno_binary	Is the phenotype binary? Default: FALSE.
method	Method for aggregating across categories: "none", "max", "sum". Default: "none".
score_test	Run a score test? If FALSE, performs a Wald test.
weights	(3 x 1) annotation category weights.

Value

Numeric p-value.

Examples

```
# Generate data.
data <- DGP(n = 1e3, snps = 1e2)

# Run the Allelic Series Burden Test.
# Note: the output is a scalar p-value.
results <- ASBT(
  anno = data$anno,
  geno = data$geno,
  pheno = data$pheno,
  covar = data$covar
)
```

ASKAT *Allelic Series SKAT Test*

Description

Sequence kernel association test (SKAT) with allelic series weights.

Usage

```
ASKAT(
  anno,
  geno,
  pheno,
  apply_int = TRUE,
  covar = NULL,
  is_pheno_binary = FALSE,
  return_null_model = FALSE,
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
geno	(n x snps) genotype matrix.
pheno	(n x 1) phenotype vector.
apply_int	Apply rank-based inverse normal transform to the phenotype? Default: TRUE. Ignored if phenotype is binary.
covar	(n x p) covariate matrix. Defaults to an (n x 1) intercept.
is_pheno_binary	Is the phenotype binary? Default: FALSE.
return_null_model	Return the null model in addition to the p-value? Useful if running additional SKAT tests. Default: FALSE.
weights	(3 x 1) annotation category weights.

Value

If `return_null_model`, a list containing the p-value and the SKAT null model. Otherwise, a numeric p-value.

Examples

```
# Generate data.
data <- DGP(n = 1e3, snps = 1e2)

# Run the Allelic Series SKAT Test.
# Note: the output is a scalar p-value.
results <- ASKAT(
  anno = data$anno,
  geno = data$geno,
  pheno = data$pheno,
  covar = data$covar
)
```

CalcRegParam *Calculate Regression Parameters*

Description

Calculate phenotypic regression coefficients and the residual variation based on proportion of variation explained (PVE) by each factor. Note that the proportion of variation explained by genotype is required, but genetic effects are not generated here.

Usage

```
CalcRegParam(pve_age = 0.1, pve_pcs = 0.2, pve_sex = 0.1)
```

Arguments

pve_age	PVE by age.
pve_pcs	PVE by PCs (collectively).
pve_sex	PVE by sex.

Value

List containing the (5 x 1) regression coefficient vector "coef" and the residual standard deviation "sd".

CheckInputs *Check Inputs*

Description

Check Inputs

Usage

```
CheckInputs(anno, covar, geno, is_pheno_binary, pheno, weights)
```

Arguments

anno	(snps x 1) annotation vector.
covar	(n x p) covariate matrix.
geno	(n x snps) genotype matrix.
is_pheno_binary	Is the phenotype binary?
pheno	(n x 1) phenotype vector.
weights	(3 x 1) annotation category weights.

Value

None.

COAST *COding-variant Allelic Series Test*

Description

Main allelic series test. Performs both Burden and SKAT type tests, then combines the results to calculate an omnibus p-value.

Usage

```
COAST(
  anno,
  geno,
  pheno,
  apply_int = TRUE,
  covar = NULL,
  include_orig_skato_all = FALSE,
  include_orig_skato_ptv = FALSE,
  is_pheno_binary = FALSE,
  return_omni_only = FALSE,
  score_test = FALSE,
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
geno	(n x snps) genotype matrix.
pheno	(n x 1) phenotype vector.
apply_int	Apply rank-based inverse normal transform to the phenotype? Default: TRUE. Ignored if phenotype is binary.
covar	(n x p) covariate matrix. Defaults to an (n x 1) intercept.
include_orig_skato_all	Include the original version of SKAT-O applied to all variants in the omnibus test? Default: FALSE.
include_orig_skato_ptv	Include the original version of SKAT-O applied to PTV variants only in the omnibus test? Default: FALSE.
is_pheno_binary	Is the phenotype binary? Default: FALSE.
return_omni_only	Return only the omnibus p-value? Default: FALSE.
score_test	Use a score test for burden analysis? If FALSE, uses a Wald test.
weights	(3 x 1) annotation category weights.

Value

Numeric p-value.

Examples

```
# Generate data.
data <- DGP(n = 1e3, snps = 1e2)

# Run the COding-variant Allelic Series Test.
results <- COAST(
  anno = data$anno,
  geno = data$geno,
  pheno = data$pheno,
  covar = data$covar
)
show(results)
```

`Comparator` *Comparator Test*

Description

Runs burden, SKAT, and SKAT-O, using default settings.

Usage

```
Comparator(covar, geno, pheno, apply_int = TRUE, is_pheno_binary = FALSE)
```

Arguments

`covar`	(n x p) covariate matrix.
`geno`	(n x snps) genotype matrix.
`pheno`	(n x 1) phenotype vector.
`apply_int`	Apply rank-based inverse normal transform to the phenotype? Default: TRUE. Ignored if phenotype is binary.
`is_pheno_binary`	Is the phenotype binary? Default: FALSE.

Value

Numeric vector of p-values.

Examples

```
# Generate data.
data <- DGP(n = 1e3, snps = 1e2)

# Run the comparators.
results <- Comparator(
  geno = data$geno,
  pheno = data$pheno,
  covar = data$covar
)
```

DGP *Data Generating Process*

Description

Generate a data set consisting of:

- "anno"A SNP-length annotation vector.
- "covar"A subject by 6 covariate matrix.
- "geno"A subject by SNP genotype matrix.
- "pheno"A subject-length phenotype vector.

Usage

```
DGP(
  anno = NULL,
  beta = c(0, 1, 2),
  binary = FALSE,
  geno = NULL,
  include_residual = TRUE,
  indicator = FALSE,
  maf_range = c(0.005, 0.01),
  method = "none",
  n = 100,
  p_dmv = 0.4,
  p_ptv = 0.1,
  prop_causal = 1,
  random_signs = FALSE,
  random_var = 0,
  snps = 100,
  weights = c(1, 2, 3)
)
```

Arguments

anno	Annotation vector, if providing genotypes. Should match the number of columns in geno.
beta	If method = "none", a (3 x 1) coefficient vector for bmvs, dmvs, and ptvs respectively. If method != "none", a scalar effect size.
binary	Generate binary phenotype? Default: FALSE.
geno	Genotype matrix, if providing genotypes.
include_residual	Include residual? If FALSE, returns the expected value. Intended for testing.
indicator	Convert raw counts to indicators? Default: FALSE.
maf_range	Range of minor allele frequencies: c(MIN, MAX).
method	Genotype aggregation method. Default: "none".
n	Sample size.
p_dmv	Frequency of deleterious missense variants. Default of 40% is based on the frequency of DMVs among rare coding variants in the UK Biobank.
p_ptv	Frequency of protein truncating variants. Default of 10% is based on the frequency of PTVs among rare coding variants in the UK Biobank.
prop_causal	Proportion of variants which are causal. Default: 1.0.
random_signs	Randomize signs? FALSE for burden-type genetic architecture, TRUE for SKAT-type.
random_var	Frailty variance in the case of random signs. Default: 0.
snps	Number of SNP in the gene. Default: 100.
weights	Aggregation weights.

Value

List containing: genotypes, annotations, covariates, phenotypes.

Examples

```
# Generate data.
data <- DGP(n = 100)

# View components.
table(data$anno)
head(data$covar)
head(data$geno[, 1:5])
hist(data$pheno)
```

FilterGenos *Filter Noncausal Variants*

Description

Remove a random fraction of variants, which are designated non-causal.

Usage

```
FilterGenos(anno, geno, prop_causal = 1)
```

Arguments

anno	(snps x 1) annotation vector.
geno	(n x snps) genotype matrix.
prop_causal	Proportion of variants which are causal.

Value

List containing the (n x snps) genotype matrix "geno" and the (snps x 1) annotation vector "anno".

GenAnno *Generate Genotype Annotations*

Description

Returns a vector of length = the number of columns (SNPs) in the genotype matrix. Each SNP is classified as a benign missense variant (0), a deleterious missense variant (1), or a protein truncating variant (2).

Usage

```
GenAnno(snps, p_dmv = 0.33, p_ptv = 0.33)
```

Arguments

snps	Number of SNPs in the gene.
p_dmv	Frequency of deleterious missense variants.
p_ptv	Frequency of protein truncating variants.

Value

(snps x 1) integer vector.

GenCovar *Generate Covariates*

Description

Generate an (n x 6) covariate matrix with columns representing an intercept, age, sex, and 3 genetic PCs. Because these simulations address rare variant analysis, correlation between genotypes and the genetic PCs (based on common variants) is unnecessary.

Usage

```
GenCovar(n)
```

Arguments

n	Sample size.

Value

(n x 6) numeric matrix.

GenGeno *Generate Genotypes*

Description

Generate Genotypes

Usage

```
GenGeno(n, snps, maf_range = c(0.005, 0.01), p_dmv = 0.33, p_ptv = 0.33)
```

Arguments

n	Sample size.
snps	Number of SNP in the gene.
maf_range	Range of minor allele frequencies: c(MIN, MAX).
p_dmv	Frequency of deleterious missense variants.
p_ptv	Frequency of protein truncating variants.

Value

List containing the (n x snps) genotype matrix "geno" and the (snps x 1) annotation vector "anno".

GenGenoMat *Generate Genotype Matrix*

Description

Generate Genotype Matrix

Usage

```
GenGenoMat(n, snps, maf_range = c(0.005, 0.01))
```

Arguments

n	Sample size.
snps	Number of SNP in the gene.
maf_range	Range of minor allele frequencies: c(MIN, MAX).

Value

(n x snps) numeric matrix.

GenPheno *Generate Phenotypes*

Description

Generate Phenotypes

Usage

```
GenPheno(
  anno,
  beta,
  covar,
  geno,
  reg_param,
  binary = FALSE,
  include_residual = TRUE,
  indicator = FALSE,
  method = "none",
  prop_causal = 1,
  random_signs = FALSE,
  random_var = 0,
  weights = c(0, 1, 2)
)
```

Arguments

anno	(snps x 1) annotation vector.
beta	(3 x 1) coefficient vector for bmvs, dmvs, and ptvs respectively.
covar	Covariate matrix.
geno	(n x snps) genotype matrix.
reg_param	Regression parameters.
binary	Generate binary phenotype? Default: FALSE.
include_residual	Include residual? If FALSE, returns the expected value. Intended for testing.
indicator	Convert raw counts to indicators? Default: FALSE.
method	Genotype aggregation method. Default: "none".
prop_causal	Proportion of variants which are causal.
random_signs	Randomize signs? FALSE for burden-type genetic architecture, TRUE for SKAT-type.
random_var	Frailty variance in the case of random signs. Default: 0.
weights	Aggregation weights.

Value

(n x 1) numeric vector.

OLS *Ordinary Least Squares*

Description

Fits the standard OLS model.

Usage

```
OLS(y, X)
```

Arguments

y	(n x 1) Numeric vector.
X	(n x p) Numeric matrix.

Value

List containing the following:

- BetaRegression coefficient.
- VOutcome variance.
- SEStandard errors.
- ZZ-scores.

ResidVar *Calculate Residual Variance*

Description

Calculate Residual Variance

Usage

```
ResidVar(y, X)
```

Arguments

y	(n x 1) Numeric phenotype vector.
X	(n x q) Numeric covariate matrix.

Value

Scalar residual variance.

Score *Calculate Score Statistic*

Description

Calculate Score Statistic

Usage

```
Score(y, G, X, v)
```

Arguments

y	(n x 1) Numeric phenotype vector.
G	(n x p) Numeric genotype matrix.
X	(n x q) Numeric covariate matrix.
v	Scalar residual variance.

Value

Scalar score statistic.

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