Package 'AllelicSeries'

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Title Allelic Series Test

Version 0.1.0.2

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, O'Dushlaine C, Somineni H, Bereket M, Klein C, Karaletsos T, Casale FP, Koller D, Soare TW. (2023) ``An allelic series rare variant association test for candidate gene discovery'' <doi:10.1016/j.ajhg.2023.07.001>.

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Contents

`Aggregator` *Aggregator*

Description

Aggregates genotypes within annotation categories.

Usage

```
Aggregator(
  anno,
  geno,
  drop_empty = TRUE,
  indicator = FALSE,
```

```
  method = "none",
  min_mac = 0,
  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".
min_mac	Minimum minor allele count for inclusion. Default: 0.
weights	Annotation category weights.

Value

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

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",
  min_mac = 0,
  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".
min_mac	Minimum minor allele count for inclusion. Default: 0.
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
)
```

ASBTSS *Allelic Series Burden Test from Summary Statistics*

Description

Allelic series burden test from summary statistics.

Usage

```
ASBTSS(
  anno,
  beta,
  se,
  check = TRUE,
  eps = 1,
  lambda = 1,
  ld = NULL,
  maf = NULL,
  method = "none",
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
beta	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
se	(snps x 1) vector of standard errors for the effect sizes.
check	Run input checks? Default: TRUE.
eps	Epsilon added to the diagonal of the LD matrix if not positive definite. Note, smaller values increase the chances of a false positive.
lambda	Optional genomic inflation factor. Defaults to 1, which results in no rescaling.
ld	(snps x snps) matrix of correlations among the genetic variants. Although ideally provided, an identity matrix is assumed if not.
maf	(snps x 1) vector of minor allele frequencies. Although ideally provided, defaults to the zero vector.
method	Method for aggregating across categories: ("none", "sum"). Default: "none".
weights	(3 x 1) vector of annotation category weights.

Value

Numeric p-value of the allelic series burden test.

Examples

```
# Generate data.
data <- DGP(n = 1e3)
sumstats <- CalcSumstats(data = data)

# Run allelic series burden test from sumstats.
results <- ASBTSS(
  anno = sumstats$anno,
  beta = sumstats$sumstats$beta,
  maf = sumstats$maf,
  se = sumstats$sumstats$se,
  ld = sumstats$ld
```

```
)
show(results)
```

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,
  min_mac = 0,
  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.
min_mac	Minimum minor allele count for inclusion. Default: 0.
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
)
```

ASKATSS *Allelic Series SKAT-O from Summary Statistics*

Description

Allelic series sequence kernel association test from summary statistics.

Usage

```
ASKATSS(
  anno,
  beta,
  se,
  check = TRUE,
  eps = 1,
  lambda = 1,
  ld = NULL,
  maf = NULL,
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
beta	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
se	(snps x 1) vector of standard errors for the effect sizes.
check	Run input checks? Default: TRUE.
eps	Epsilon added to the diagonal of the LD matrix if not positive definite. Note, smaller values increase the chances of a false positive.
lambda	Optional genomic inflation factor. Defaults to 1, which results in no rescaling.
ld	(snps x snps) matrix of correlations among the genetic variants. Although ideally provided, an identity matrix is assumed if not.

maf	(snps x 1) vector of minor allele frequencies. Although ideally provided, defaults to the zero vector.
weights	(3 x 1) vector of annotation category weights.

Value

Numeric p-value of the allelic series SKAT-O test.

Examples

```
# Generate data.
data <- DGP(n = 1e3)
sumstats <- CalcSumstats(data = data)

# Run allelic series SKAT test from sumstats.
results <- ASKATSS(
  anno = sumstats$anno,
  beta = sumstats$sumstats$beta,
  maf = sumstats$maf,
  se = sumstats$sumstats$se,
  ld = sumstats$ld
)
show(results)
```

BaselineSS *Baseline Counts Test from Sumstats*

Description

Baseline Counts Test from Sumstats

Usage

```
BaselineSS(anno, beta, ld, se)
```

Arguments

anno	(snps x 1) annotation vector.
beta	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
ld	(snps x snps) matrix of correlations among the genetic variants.
se	(snps x 1) vector of standard errors for the effect sizes.

Value

Numeric p-value.

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".

CalcSumstats *Calculate Summary Statistics*

Description

Calculate Summary Statistics

Usage

```
CalcSumstats(
  anno = NULL,
  covar = NULL,
  data = NULL,
  geno = NULL,
  pheno = NULL,
  is_binary = FALSE
)
```

Arguments

anno	(snps x 1) annotation vector.
covar	(subjects x covars) covariate matrix.
data	List of data containing the annotation vector anno, the covariate data covar, the genotype matrix geno, and the phenotype vector pheno, as returned by DGP. Overrides the other arguments if provided.
geno	(subjects x snps) genotype matrix.
pheno	(subjects x 1) phenotype vector.
is_binary	Is the phenotype binary? Default: FALSE.

Value

List containing the following items:

- anno: A SNP-length annotation vector.
- ld: A SNP x SNP correlation (LD) matrix.
- maf: Minor allele frequency of each variant.
- sumstats: A SNP x 4 matrix of summary statistics.
- type: Either "binary" or "quantitative".

Examples

```
data <- DGP()
sumstats <- CalcSumstats(data = data)
```

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.

`CheckInputsSS` *Input Checks for Summary Statistics*

Description

Input Checks for Summary Statistics

Usage

```
CheckInputsSS(anno, beta, se, lambda, ld, maf)
```

Arguments

`anno`	(snps x 1) annotation vector with values in c(0, 1, 2).
`beta`	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
`se`	(snps x 1) vector of standard errors for the effect sizes.
`lambda`	Genomic inflation factor.
`ld`	(snps x snps) matrix of correlations among the genetic variants. Although ideally provided, an identity matrix is assumed if not.
`maf`	(snps x 1) vector of minor allele frequencies. Although ideally provided, defaults to the zero vector.

Value

Logical indicating whether the matrix was positive definite.

`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,
  min_mac = 0,
  pval_weights = NULL,
  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.
min_mac	Minimum minor allele count for inclusion. Default: 0.
pval_weights	Optional vector of relative weights for combining the component tests to perform the omnibus test. By default, 50% of weight is given to the 6 burden tests, and 50% to the 1 SKAT test. If specified, the weight vector should have length 7, and the length should be increased if either include_orig_skato_all or include_orig_skato_ptv is active.
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)
```

COAST-class *Allelic Series Output Class*

Description

Allelic Series Output Class

Slots

`Counts` Allele, variant, and carrier counts.

`Pvals` Result p-values.

COASTSS *COding-variant Allelic Series Test from Summary Statistics*

Description

Main function for performing the allelic series test from summary statistics. Performs both Burden and SKAT type tests, then combines the results to calculate an omnibus p-value. Note that not all tests included in `COAST` are available when working with summary statistics.

Usage

```
COASTSS(
  anno,
  beta,
  se,
  check = TRUE,
  eps = 1,
  lambda = c(1, 1, 1),
  maf = NULL,
```

```
  ld = NULL,
  pval_weights = c(1, 1, 2),
  weights = DEFAULT_WEIGHTS
)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
beta	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
se	(snps x 1) vector of standard errors for the effect sizes.
check	Run input checks? Default: TRUE.
eps	Epsilon added to the diagonal of the LD matrix if not positive definite. Note, epsilon should increase as the sample size decreases.
lambda	Optional (3 x 1) vector of inflation factors, one for each component test. Defaults to a 1s vector, which results in no rescaling.
maf	(snps x 1) vector of minor allele frequencies. Although ideally provided, defaults to the zero vector.
ld	(snps x snps) matrix of correlations among the genetic variants. Although ideally provided, an identity matrix is assumed if not.
pval_weights	(3 x 1) vector of relative weights for combining the component tests to perform the omnibus test.
weights	(3 x 1) vector of annotation category weights. The default of c(1, 1, 2) gives the SKAT test equal weight to the two burden tests.

Value

Numeric p-value.

Examples

```
# Generate data.
data <- DGP(n = 1e3)
sumstats <- CalcSumstats(data = data)

# Run the Coding-variant Allelic Series Test from summary statistics.
results <- COASTSS(
  anno = sumstats$anno,
  beta = sumstats$sumstats$beta,
  maf = sumstats$maf,
  se = sumstats$sumstats$se,
  ld = sumstats$ld
)
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
)
```

CorCpp *Correlation C++*

Description

Correlation C++

Usage

```
CorCpp(x)
```

Arguments

x	Numeric matrix.

Value

Numeric matrix of correlation among the columns.

Notes

Verified this function is faster that R's built-in correlation function for large genotype matrices.

Counts *Count Variants and Carriers*

Description

Count Variants and Carriers

Usage

```
Counts(anno, geno, min_mac = 0L)
```

Arguments

anno	(snps x 1) annotation vector with values in c(0, 1, 2).
geno	(n x snps) genotype matrix.
min_mac	Minimum minor allele count for inclusion. Default: 0.

Value

Data.frame of allele, variant, and carrier counts.

DfOrNULL-class *Data.frame or Null Class*

Description

Data.frame or Null Class

DGP *Data Generating Process*

Description

Generate a data set consisting of:

- anno: (snps x 1) annotation vector.
- covar: (subjects x 6) covariate matrix.
- geno: (subjects x snps) genotype matrix.
- pheno: (subjects x 1) phenotype vector.
- type: Either "binary" or "quantitative".

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.

GenomicControl *Genomic Control*

Description

Genomic Control

Usage

```
GenomicControl(lambda, pval, df = 1)
```

Arguments

lambda	Genomic inflation factor.
pval	Numeric p-value.
df	Degrees of freedom. Should not require modification in most cases.

Value

Corrected p-value.

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.

`isPD` *Check if Positive Definite*

Description

Check if Positive Definite

Usage

```
isPD(x, force_symmetry = FALSE, tau = 1e-08)
```

Arguments

`x`	Numeric matrix.
`force_symmetry`	Force the matrix to be symmetric?
`tau`	Threshold the minimum eigenvalue must exceed for the matrix to be considered positive definite.

Value

Logical indicating whether the matrix is PD.

`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:

- beta: Regression coefficients.
- v: Residual variance.
- se: Standard errors.
- z: Z-scores.
- pval: P-values based on the chi2 distribution.

---

print.COAST *Print Method for COAST Object.*

Description

Print method for objects of class COAST.

Usage

```
## S3 method for class 'COAST'
print(x, ...)
```

Arguments

x	An object of class COAST.
...	Unused.

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.

show,COAST-method *Show Method for COAST Object*

Description

Show Method for COAST Object

Usage

```
## S4 method for signature 'COAST'
show(object)
```

Arguments

object	An object of class COAST.

SumCountSS *Allelic Sum Test from Sumstats*

Description

Allelic Sum Test from Sumstats

Usage

```
SumCountSS(anno, beta, ld, se, weights)
```

Arguments

anno	(snps x 1) annotation vector.
beta	(snps x 1) vector of effect sizes for the coding genetic variants within a gene.
ld	(snps x snps) matrix of correlations among the genetic variants.
se	(snps x 1) vector of standard errors for the effect sizes.
weights	(3 x 1) vector of annotation category weights.

Value

Numeric p-value.

Index