Package 'STAAR'

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Type Package

Title STAAR Procedure for Dynamic Incorporation of Multiple Functional Annotations in Whole-Genome Sequencing Studies

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Description An R package for performing STAAR procedure in whole-genome sequencing studies.

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Imports Rcpp, GMMAT, GENESIS, Matrix, methods

Encoding UTF-8

LazyData true

Depends R (>= 3.2.0)

LinkingTo Rcpp, RcppArmadillo

RoxygenNote 7.2.3

Suggests knitr, rmarkdown

VignetteBuilder knitr

R topics documented:

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CCT — *An analytical p-value combination method using the Cauchy distribution*

Description

The CCT function takes in a numeric vector of p-values, a numeric vector of non-negative weights, and return the aggregated p-value using Cauchy method.

Usage

```
CCT(pvals, weights = NULL)
```

Arguments

pvals	a numeric vector of p-values, where each of the element is between 0 to 1, to be combined.
weights	a numeric vector of non-negative weights. If NULL, the equal weights are assumed (default = NULL).

Value

The aggregated p-value combining p-values from the vector pvals.

References

Liu, Y., & Xie, J. (2020). Cauchy combination test: a powerful test with analytic p-value calculation under arbitrary dependency structures. *Journal of the American Statistical Association*, *115*(529), 393-402. (pub)

Liu, Y., et al. (2019). Acat: A fast and powerful p value combination method for rare-variant analysis in sequencing studies. *The American Journal of Human Genetics*, *104*(3), 410-421. (pub)

Examples

```
pvalues <- c(2e-02, 4e-04, 0.2, 0.1, 0.8)
CCT(pvals = pvalues)
```

fit_null_glm — *Fit generalized linear model under the null hypothesis for unrelated samples.*

Description

The fit_null_glm function is a wrapper of the glm function from the stats package that fits a regression model under the null hypothesis for unrelated samples, which provides the preliminary step for subsequent variant-set tests in whole-genome sequencing data analysis. See glm for more details.

Usage

```
fit_null_glm(fixed, data, family = binomial(link = "logit"), ...)
```

Arguments

fixed	an object of class formula (or one that can be coerced to that class): a symbolic description of the fixed effects model to be fitted.
data	a data frame or list (or object coercible by as.data.frame to a data frame) containing the variables in the model.
family	a description of the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function. (See family for details of family functions). Can be either "gaussian" for continuous phenotype or "binomial" for binary phenotype.
...	additional arguments that could be passed to glm.

Value

The function returns an object of the model fit from glm (obj_nullmodel), with an additional element indicating the samples are unrelated (obj_nullmodel$relatedness = FALSE). See glm for more details.

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fit_null_glmmkin *Fit generalized linear mixed model with known relationship matrices under the null hypothesis for related samples.*

Description

The fit_null_glmmkin function is a wrapper of the glmmkin function from the GMMAT package that fits a regression model under the null hypothesis for related samples, which provides the preliminary step for subsequent variant-set tests in whole-genome sequencing data analysis. See glmmkin for more details.

Usage

```
fit_null_glmmkin(
  fixed,
  data = parent.frame(),
  kins,
  use_sparse = NULL,
  kins_cutoff = 0.022,
  id,
  random.slope = NULL,
  groups = NULL,
  family = binomial(link = "logit"),
  method = "REML",
  method.optim = "AI",
  maxiter = 500,
  tol = 1e-05,
  taumin = 1e-05,
```

```
  taumax = 1e+05,
  tauregion = 10,
  verbose = FALSE,
  ...
)
```

Arguments

fixed	an object of class formula (or one that can be coerced to that class): a symbolic description of the fixed effects model to be fitted.
data	a data frame or list (or object coercible by as.data.frame to a data frame) containing the variables in the model.
kins	a known positive semi-definite relationship matrix (e.g. kinship matrix in genetic association studies) or a list of known positive semi-definite relationship matrices. The rownames and colnames of these matrices must at least include all samples as specified in the id column of the data frame data.
use_sparse	a logical switch of whether the provided dense kins matrix should be transformed to a sparse matrix (default = NULL).
kins_cutoff	the cutoff value for clustering samples to make the output matrix sparse block-diagonal (default = 0.022).
id	a column in the data frame data, indicating the id of samples. When there are duplicates in id, the data is assumed to be longitudinal with repeated measures.
random.slope	an optional column indicating the random slope for time effect used in a mixed effects model for longitudinal data. It must be included in the names of data. There must be duplicates in id and method.optim must be "AI" (default = NULL).
groups	an optional categorical variable indicating the groups used in a heteroscedastic linear mixed model (allowing residual variances in different groups to be different). This variable must be included in the names of data, and family must be "gaussian" and method.optim must be "AI" (default = NULL).
family	a description of the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function. (See family for details of family functions).
method	method of fitting the generalized linear mixed model. Either "REML" or "ML" (default = "REML").
method.optim	optimization method of fitting the generalized linear mixed model. Either "AI", "Brent" or "Nelder-Mead" (default = "AI").
maxiter	a positive integer specifying the maximum number of iterations when fitting the generalized linear mixed model (default = 500).
tol	a positive number specifying tolerance, the difference threshold for parameter estimates below which iterations should be stopped (default = 1e-5).
taumin	the lower bound of search space for the variance component parameter τ (default = 1e-5), used when method.optim = "Brent". See Details.
taumax	the upper bound of search space for the variance component parameter τ (default = 1e5), used when method.optim = "Brent". See Details.
tauregion	the number of search intervals for the REML or ML estimate of the variance component parameter τ (default = 10), used when method.optim = "Brent". See Details.

verbose	a logical switch for printing detailed information (parameter estimates in each iteration) for testing and debugging purpose (default = FALSE).
...	additional arguments that could be passed to glm.

Value

The function returns an object of the model fit from glmmkin (obj_nullmodel), with additional elements indicating the samples are related (obj_nullmodel$relatedness = TRUE), and whether the kins matrix is sparse when fitting the null model. See glmmkin for more details.

References

Chen, H., et al. (2016). Control for population structure and relatedness for binary traits in genetic association studies via logistic mixed models. *The American Journal of Human Genetics*, *98*(4), 653-666. (pub)

Chen, H., et al. (2019). Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. *The American Journal of Human Genetics*, *104*(2), 260-274. (pub)

Chen, H. (2023). GMMAT: Generalized linear Mixed Model Association Tests Version 1.4.2. (web)

---

fit_null_glmmkin_Binary_SPA

Fit generalized linear mixed model with known relationship matrices under the null hypothesis for imbalanced case-control related samples.

Description

The fit_null_glmmkin_Binary_SPA function is a wrapper of the glmmkin function from the GMMAT package that fits a regression model under the null hypothesis for imbalanced case-control related samples, which provides the preliminary step for subsequent variant-set tests in whole genome sequencing data analysis. See glmmkin for more details.

Usage

```
fit_null_glmmkin_Binary_SPA(
  fixed,
  data = parent.frame(),
  kins,
  use_sparse = NULL,
  kins_cutoff = 0.022,
  id,
  random.slope = NULL,
  groups = NULL,
  family = binomial(link = "logit"),
  method = "REML",
  method.optim = "AI",
  maxiter = 500,
  tol = 1e-05,
  taumin = 1e-05,
  taumax = 1e+05,
```

```
  tauregion = 10,
  verbose = FALSE,
  ...
)
```

Arguments

fixed	an object of class formula (or one that can be coerced to that class): a symbolic description of the fixed effects model to be fitted.
data	a data frame or list (or object coercible by as.data.frame to a data frame) containing the variables in the model.
kins	a known positive semi-definite relationship matrix (e.g. kinship matrix in genetic association studies) or a list of known positive semi-definite relationship matrices. The rownames and colnames of these matrices must at least include all samples as specified in the id column of the data frame data.
use_sparse	a logical switch of whether the provided dense kins matrix should be transformed to a sparse matrix (default = NULL).
kins_cutoff	the cutoff value for clustering samples to make the output matrix sparse block-diagonal (default = 0.022).
id	a column in the data frame data, indicating the id of samples. When there are duplicates in id, the data is assumed to be longitudinal with repeated measures.
random.slope	an optional column indicating the random slope for time effect used in a mixed effects model for longitudinal data. It must be included in the names of data. There must be duplicates in id and method.optim must be "AI" (default = NULL).
groups	an optional categorical variable indicating the groups used in a heteroscedastic linear mixed model (allowing residual variances in different groups to be different). This variable must be included in the names of data, and family must be "gaussian" and method.optim must be "AI" (default = NULL).
family	a description of the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function. (See family for details of family functions).
method	method of fitting the generalized linear mixed model. Either "REML" or "ML" (default = "REML").
method.optim	optimization method of fitting the generalized linear mixed model. Either "AI", "Brent" or "Nelder-Mead" (default = "AI").
maxiter	a positive integer specifying the maximum number of iterations when fitting the generalized linear mixed model (default = 500).
tol	a positive number specifying tolerance, the difference threshold for parameter estimates below which iterations should be stopped (default = 1e-5).
taumin	the lower bound of search space for the variance component parameter τ (default = 1e-5), used when method.optim = "Brent". See Details.
taumax	the upper bound of search space for the variance component parameter τ (default = 1e5), used when method.optim = "Brent". See Details.
tauregion	the number of search intervals for the REML or ML estimate of the variance component parameter τ (default = 10), used when method.optim = "Brent". See Details.
verbose	a logical switch for printing detailed information (parameter estimates in each iteration) for testing and debugging purpose (default = FALSE).
...	additional arguments that could be passed to glm.

Value

The function returns an object of the model fit from glmmkin (obj_nullmodel), with additional elements indicating the samples are related (obj_nullmodel$relatedness = TRUE), indicating the smaples are under imbalanced case-control design (obj_nullmodel$use_SPA = TRUE) and whether the kins matrix is sparse when fitting the null model. See glmmkin for more details.

References

Chen, H., et al. (2016). Control for population structure and relatedness for binary traits in genetic association studies via logistic mixed models. *The American Journal of Human Genetics*, *98*(4), 653-666. (pub)

Chen, H., et al. (2019). Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. *The American Journal of Human Genetics*, *104*(2), 260-274. (pub)

Chen, H. (2023). GMMAT: Generalized linear Mixed Model Association Tests Version 1.4.2. (web)

---

fit_null_glm_Binary_SPA

Fit generalized linear model under the null hypothesis for imbalanced case-control unrelated samples.

Description

The fit_null_glm_Binary_SPA function is a wrapper of the glm function from the stats package that fits a regression model under the null hypothesis for imbalanced case-control unrelated samples, which provides the preliminary step for subsequent variant-set tests in whole genome sequencing data analysis. See glm for more details.

Usage

```
fit_null_glm_Binary_SPA(fixed, data, family = binomial(link = "logit"), ...)
```

Arguments

fixed	an object of class formula (or one that can be coerced to that class): a symbolic description of the fixed effects model to be fitted.
data	a data frame or list (or object coercible by as.data.frame to a data frame) containing the variables in the model.
family	a description of the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function. (See family for details of family functions). Can be either "gaussian" for continuous phenotype or "binomial" for binary phenotype.
...	additional arguments that could be passed to glm.

Value

The function returns an object of the model fit from glm (obj_nullmodel), with additional elements indicating the samples are unrelated (obj_nullmodel$relatedness = FALSE), and indicating the samples are under imbalanced case-control design (obj_nullmodel$use_SPA = TRUE). See glm for more details.

References

Dey, R., et al. (2017). A fast and accurate algorithm to test for binary phenotypes and its application to PheWAS. *The American Journal of Human Genetics*, *101*(1), 37-49. (pub)

`Indiv_Score_Test_Region` *Score test for individual variants in a given variant-set*

Description

The `Indiv_Score_Test_Region` function takes in genotype and the object from fitting the null model to analyze the associations between a quantitative/dichotomous phenotype and all individual variants in a given variant-set by using score test.

Usage

```
Indiv_Score_Test_Region(
  genotype,
  obj_nullmodel,
  rare_maf_cutoff = 0.01,
  rv_num_cutoff = 2,
  rv_num_cutoff_max = 1e+09
)
```

Arguments

`genotype`	an n*p genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p is the number of genetic variants.
`obj_nullmodel`	an object from fitting the null model, which is the output from either `fit_null_glm` function for unrelated samples or `fit_null_glmmkin` function for related samples. Note that `fit_null_glmmkin` is a wrapper of the `glmmkin` function from the `GMMAT` package.
`rare_maf_cutoff`	the cutoff of maximum minor allele frequency in defining rare variants (default = 0.01).
`rv_num_cutoff`	the cutoff of minimum number of variants of analyzing a given variant-set (default = 2).
`rv_num_cutoff_max`	the cutoff of maximum number of variants of analyzing a given variant-set (default = 1e+09).

Value

A data frame with p rows corresponding to the p genetic variants in the given variant-set and three columns: `Score` (the score test statistic), `SE` (the standard error associated with the score test statistic), and `pvalue` (the score test p-value). If a variant in the given variant-set has minor allele frequency = 0 or greater than `rare_maf_cutoff`, the corresponding row will be `NA`. If a variant in the given variant-set has standard error equal to 0, the p-value will be set as 1.

References

Chen, H., et al. (2016). Control for population structure and relatedness for binary traits in genetic association studies via logistic mixed models. *The American Journal of Human Genetics*, *98*(4), 653-666. (pub)

`Indiv_Score_Test_Region_cond` *Conditional score test for individual variants in a given variant-set*

Description

The `Indiv_Score_Test_Region_cond` function takes in genotype, the genotype of variants to be adjusted for in conditional analysis, and the object from fitting the null model to analyze the conditional associations between a quantitative/dichotomous phenotype and all individual variants in a given variant-set by using score test, adjusting for a given list of variants.

Usage

```
Indiv_Score_Test_Region_cond(
  genotype,
  genotype_adj,
  obj_nullmodel,
  rare_maf_cutoff = 0.01,
  rv_num_cutoff = 2,
  rv_num_cutoff_max = 1e+09,
  method_cond = c("optimal", "naive")
)
```

Arguments

`genotype`	an n*p genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p is the number of genetic variants.
`genotype_adj`	an n*p_adj genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p_adj is the number of genetic variants to be adjusted for in conditional analysis (or a vector of a single variant with length n if p_adj is 1).
`obj_nullmodel`	an object from fitting the null model, which is the output from either `fit_null_glm` function for unrelated samples or `fit_null_glmmkin` function for related samples. Note that `fit_null_glmmkin` is a wrapper of the `glmmkin` function from the `GMMAT` package.
`rare_maf_cutoff`	the cutoff of maximum minor allele frequency in defining rare variants (default = 0.01).
`rv_num_cutoff`	the cutoff of minimum number of variants of analyzing a given variant-set (default = 2).
`rv_num_cutoff_max`	the cutoff of maximum number of variants of analyzing a given variant-set (default = 1e+09).

`method_cond` a character value indicating the method for conditional analysis. `optimal` refers to regressing residuals from the null model on `genotype_adj` as well as all covariates used in fitting the null model (fully adjusted) and taking the residuals; `naive` refers to regressing residuals from the null model on `genotype_adj` and taking the residuals (default = `optimal`).

Value

A data frame with p rows corresponding to the p genetic variants in the given variant-set and three columns: `Score_cond` (the conditional score test statistic adjusting for variants in `genotype_adj`), `SE_cond` (the standard error associated with the conditional score test statistic), and `pvalue_cond` (the conditional score test p-value). If a variant in the given variant-set has minor allele frequency = 0 or greater than `rare_maf_cutoff`, the corresponding row will be `NA`. If a variant in the given variant-set has standard error equal to 0, the p-value will be set as 1.

References

Chen, H., et al. (2016). Control for population structure and relatedness for binary traits in genetic association studies via logistic mixed models. *The American Journal of Human Genetics*, *98*(4), 653-666. (pub)

Sofer, T., et al. (2019). A fully adjusted two-stage procedure for rank-normalization in genetic association studies. *Genetic Epidemiology*, *43*(3), 263-275. (pub)

STAAR *STAAR procedure using omnibus test*

Description

The `STAAR` function takes in genotype, the object from fitting the null model, and functional annotation data to analyze the association between a quantitative/dichotomous phenotype and a variant-set by using STAAR procedure. For each variant-set, the STAAR-O p-value is a p-value from an omnibus test that aggregated SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) together with p-values of each test weighted by each annotation using Cauchy method.

Usage

```
STAAR(
  genotype,
  obj_nullmodel,
  annotation_phred = NULL,
  rare_maf_cutoff = 0.01,
  rv_num_cutoff = 2,
  rv_num_cutoff_max = 1e+09
)
```

Arguments

`genotype` an n*p genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p is the number of genetic variants.

`obj_nullmodel` an object from fitting the null model, which is the output from either `fit_null_glm` function for unrelated samples or `fit_null_glmmkin` function for related samples. Note that `fit_null_glmmkin` is a wrapper of the `glmmkin` function from the `GMMAT` package.

`annotation_phred`
a data frame or matrix of functional annotation data of dimension p*q (or a vector of a single annotation score with length p). Continuous scores should be given in PHRED score scale, where the PHRED score of j-th variant is defined to be -10*log10(rank(-score_j)/total) across the genome. (Binary) categorical scores should be taking values 0 or 1, where 1 is functional and 0 is non-functional. If not provided, STAAR will perform the SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), ACAT-V(1,1) and ACAT-O tests (default = NULL).

`rare_maf_cutoff`
the cutoff of maximum minor allele frequency in defining rare variants (default = 0.01).

`rv_num_cutoff` the cutoff of minimum number of variants of analyzing a given variant-set (default = 2).

`rv_num_cutoff_max`
the cutoff of maximum number of variants of analyzing a given variant-set (default = 1e+09).

Value

A list with the following members:

`num_variant`: the number of variants with minor allele frequency > 0 and less than `rare_maf_cutoff` in the given variant-set that are used for performing the variant-set using STAAR.

`cMAC`: the cumulative minor allele count of variants with minor allele frequency > 0 and less than `rare_maf_cutoff` in the given variant-set.

`RV_label`: the boolean vector indicating whether each variant in the given variant-set has minor allele frequency > 0 and less than `rare_maf_cutoff`.

`results_STAAR_O`: the STAAR-O p-value that aggregated SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) together with p-values of each test weighted by each annotation using Cauchy method.

`results_ACAT_O`: the ACAT-O p-value that aggregated SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) using Cauchy method.

`results_STAAR_S_1_25`: a vector of STAAR-S(1,25) p-values, including SKAT(1,25) p-value weighted by MAF, the SKAT(1,25) p-values weighted by each annotation, and a STAAR-S(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_S_1_1`: a vector of STAAR-S(1,1) p-values, including SKAT(1,1) p-value weighted by MAF, the SKAT(1,1) p-values weighted by each annotation, and a STAAR-S(1,1) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_B_1_25`: a vector of STAAR-B(1,25) p-values, including Burden(1,25) p-value weighted by MAF, the Burden(1,25) p-values weighted by each annotation, and a STAAR-B(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_B_1_1`: a vector of STAAR-B(1,1) p-values, including Burden(1,1) p-value weighted by MAF, the Burden(1,1) p-values weighted by each annotation, and a STAAR-B(1,1) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_A_1_25`: a vector of STAAR-A(1,25) p-values, including ACAT-V(1,25) p-value weighted by MAF, the ACAT-V(1,25) p-values weighted by each annotation, and a STAAR-A(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_A_1_1`: a vector of STAAR-A(1,1) p-values, including ACAT-V(1,1) p-value weighted by MAF, the ACAT-V(1,1) p-values weighted by each annotation, and a STAAR-A(1,1) p-value by aggregating these p-values using Cauchy method.

References

Li, X., Li, Z., et al. (2020). Dynamic incorporation of multiple in silico functional annotations empowers rare variant association analysis of large whole-genome sequencing studies at scale. *Nature Genetics*, *52*(9), 969-983. (pub)

Li, Z., Li, X., et al. (2022). A framework for detecting noncoding rare-variant associations of large-scale whole-genome sequencing studies. *Nature Methods*, *19*(12), 1599-1611. (pub)

Liu, Y., et al. (2019). Acat: A fast and powerful p value combination method for rare-variant analysis in sequencing studies. *The American Journal of Human Genetics*, *104*(3), 410-421. (pub)

Li, Z., Li, X., et al. (2020). Dynamic scan procedure for detecting rare-variant association regions in whole-genome sequencing studies. *The American Journal of Human Genetics*, *104*(5), 802-814. (pub)

STAAR_Binary_SPA *STAAR-SPA procedure using omnibus test*

Description

The `STAAR_Binary_SPA` function takes in genotype, the object from fitting the null model, and functional annotation data to analyze the association between a imbalanced case-control phenotype and a variant-set by using STAAR-SPA procedure. For each variant-set, the STAAR-B p-value is a p-value from an omnibus test that aggregated Burden(1,25) and Burden(1,1) together with p-values of each test weighted by each annotation using Cauchy method.

Usage

```
STAAR_Binary_SPA(
  genotype,
  obj_nullmodel,
  annotation_phred = NULL,
  rare_maf_cutoff = 0.01,
  rv_num_cutoff = 2,
  rv_num_cutoff_max = 1e+09,
  tol = .Machine$double.eps^0.25,
  max_iter = 1000,
  SPA_p_filter = FALSE,
  p_filter_cutoff = 0.05
)
```

Arguments

genotype	an n*p genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p is the number of genetic variants.
obj_nullmodel	an object from fitting the null model, which is the output from either fit_null_glm function for unrelated samples or fit_null_glmmkin function for related samples. Note that fit_null_glmmkin is a wrapper of the glmmkin function from the GMMAT package.
annotation_phred	a data frame or matrix of functional annotation data of dimension p*q (or a vector of a single annotation score with length p). Continuous scores should be given in PHRED score scale, where the PHRED score of j-th variant is defined to be -10*log10(rank(-score_j)/total) across the genome. (Binary) categorical scores should be taking values 0 or 1, where 1 is functional and 0 is non-functional. If not provided, STAAR will perform the Burden(1,25) and Burden(1,1) tests (default = NULL).
rare_maf_cutoff	the cutoff of maximum minor allele frequency in defining rare variants (default = 0.01).
rv_num_cutoff	the cutoff of minimum number of variants of analyzing a given variant-set (default = 2).
rv_num_cutoff_max	the cutoff of maximum number of variants of analyzing a given variant-set (default = 1e+09).
tol	a positive number specifying tolerance, the difference threshold for parameter estimates in saddlepoint apporximation algorithm below which iterations should be stopped (default = ".Machine$double.eps^0.25").
max_iter	a positive integers pecifying the maximum number of iterations for applying the saddlepoint approximation algorithm (default = "1000").
SPA_p_filter	logical: are only the variants with a normal approximation based p-value smaller than a pre-specified threshold use the SPA method to recalculate the p-value, only used for imbalanced case-control setting (default = FALSE).
p_filter_cutoff	threshold for the p-value recalculation using the SPA method, only used for imbalanced case-control setting (default = 0.05)

Value

A list with the following members:

num_variant: the number of variants with minor allele frequency > 0 and less than rare_maf_cutoff in the given variant-set that are used for performing the variant-set using STAAR.

cMAC: the cumulative minor allele count of variants with minor allele frequency > 0 and less than rare_maf_cutoff in the given variant-set.

RV_label: the boolean vector indicating whether each variant in the given variant-set has minor allele frequency > 0 and less than rare_maf_cutoff.

results_STAAR_B: the STAAR-B p-value that aggregated Burden(1,25) and Burden(1,1) together with p-values of each test weighted by each annotation using Cauchy method.

results_STAAR_B_1_25: a vector of STAAR-B(1,25) p-values, including Burden(1,25) p-value weighted by MAF, the Burden(1,25) p-values weighted by each annotation, and a STAAR-B(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_B_1_1`: a vector of STAAR-B(1,1) p-values, including Burden(1,1) p-value weighted by MAF, the Burden(1,1) p-values weighted by each annotation, and a STAAR-B(1,1) p-value by aggregating these p-values using Cauchy method.

References

Li, X., Li, Z., et al. (2020). Dynamic incorporation of multiple in silico functional annotations empowers rare variant association analysis of large whole-genome sequencing studies at scale. *Nature Genetics*, *52*(9), 969-983. (pub)

Li, Z., Li, X., et al. (2022). A framework for detecting noncoding rare-variant associations of large-scale whole-genome sequencing studies. *Nature Methods*, *19*(12), 1599-1611. (pub)

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`STAAR_cond` *STAAR procedure for conditional analysis using omnibus test*

Description

The `STAAR_cond` function takes in genotype, the genotype of variants to be adjusted for in conditional analysis, the object from fitting the null model, and functional annotation data to analyze the conditional association between a quantitative/dichotomous phenotype and a variant-set by using STAAR procedure, adjusting for a given list of variants. For each variant-set, the conditional STAAR-O p-value is a p-value from an omnibus test that aggregated conditional SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) together with conditional p-values of each test weighted by each annotation using Cauchy method.

Usage

```
STAAR_cond(
  genotype,
  genotype_adj,
  obj_nullmodel,
  annotation_phred = NULL,
  rare_maf_cutoff = 0.01,
  rv_num_cutoff = 2,
  rv_num_cutoff_max = 1e+09,
  method_cond = c("optimal", "naive")
)
```

Arguments

`genotype`	an n*p genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p is the number of genetic variants.
`genotype_adj`	an n*p_adj genotype matrix (dosage matrix) of the target sequence, where n is the sample size and p_adj is the number of genetic variants to be adjusted for in conditional analysis (or a vector of a single variant with length n if p_adj is 1).

`obj_nullmodel` an object from fitting the null model, which is the output from either `fit_null_glm` function for unrelated samples or `fit_null_glmmkin` function for related samples. Note that `fit_null_glmmkin` is a wrapper of the `glmmkin` function from the `GMMAT` package.

`annotation_phred`
a data frame or matrix of functional annotation data of dimension p*q (or a vector of a single annotation score with length p). Continuous scores should be given in PHRED score scale, where the PHRED score of j-th variant is defined to be -10*log10(rank(-score_j)/total) across the genome. (Binary) categorical scores should be taking values 0 or 1, where 1 is functional and 0 is non-functional. If not provided, STAAR will perform the SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), ACAT-V(1,1) and ACAT-O tests (default = NULL).

`rare_maf_cutoff`
the cutoff of maximum minor allele frequency in defining rare variants (default = 0.01).

`rv_num_cutoff` the cutoff of minimum number of variants of analyzing a given variant-set (default = 2).

`rv_num_cutoff_max`
the cutoff of maximum number of variants of analyzing a given variant-set (default = 1e+09).

`method_cond` a character value indicating the method for conditional analysis. `optimal` refers to regressing residuals from the null model on `genotype_adj` as well as all covariates used in fitting the null model (fully adjusted) and taking the residuals; `naive` refers to regressing residuals from the null model on `genotype_adj` and taking the residuals (default = `optimal`).

Value

A list with the following members:

`num_variant`: the number of variants with minor allele frequency > 0 and less than `rare_maf_cutoff` in the given variant-set that are used for performing the variant-set using STAAR.

`cMAC`: the cumulative minor allele count of variants with minor allele frequency > 0 and less than `rare_maf_cutoff` in the given variant-set.

`RV_label`: the boolean vector indicating whether each variant in the given variant-set has minor allele frequency > 0 and less than `rare_maf_cutoff`.

`results_STAAR_O_cond`: the conditional STAAR-O p-value that aggregated conditional SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) together with conditional p-values of each test weighted by each annotation using Cauchy method.

`results_ACAT_O_cond`: the conditional ACAT-O p-value that aggregated conditional SKAT(1,25), SKAT(1,1), Burden(1,25), Burden(1,1), ACAT-V(1,25), and ACAT-V(1,1) using Cauchy method.

`results_STAAR_S_1_25_cond`: a vector of conditional STAAR-S(1,25) p-values, including conditional SKAT(1,25) p-value weighted by MAF, the conditional SKAT(1,25) p-values weighted by each annotation, and a conditional STAAR-S(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_S_1_1_cond`: a vector of conditional STAAR-S(1,1) p-values, including conditional SKAT(1,1) p-value weighted by MAF, the conditional SKAT(1,1) p-values weighted by each annotation, and a conditional STAAR-S(1,1) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_B_1_25_cond`: a vector of conditional STAAR-B(1,25) p-values, including conditional Burden(1,25) p-value weighted by MAF, the conditional Burden(1,25) p-values weighted by each annotation, and a conditional STAAR-B(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_B_1_1_cond`: a vector of conditional STAAR-B(1,1) p-values, including conditional Burden(1,1) p-value weighted by MAF, the conditional Burden(1,1) p-values weighted by each annotation, and a conditional STAAR-B(1,1) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_A_1_25_cond`: a vector of conditional STAAR-A(1,25) p-values, including conditional ACAT-V(1,25) p-value weighted by MAF, the conditional ACAT-V(1,25) p-values weighted by each annotation, and a conditional STAAR-A(1,25) p-value by aggregating these p-values using Cauchy method.

`results_STAAR_A_1_1_cond`: a vector of conditional STAAR-A(1,1) p-values, including conditional ACAT-V(1,1) p-value weighted by MAF, the conditional ACAT-V(1,1) p-values weighted by each annotation, and a conditional STAAR-A(1,1) p-value by aggregating these p-values using Cauchy method.

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