Package ‘STAAR’

August 12, 2019

Type Package

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

Version 0.9.3

Date 2019-08-12

Author Xihao Li [aut, cre], Zilin Li [aut, cre], Han Chen [aut]

Maintainer Xihao Li <xihaoli@g.harvard.edu>, Zilin Li <li@hsph.harvard.edu>

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

License GPL-3

Copyright See COPYRIGHTS for details.

Imports Rcpp, GMMAT, GENESIS, Matrix, methods

Encoding UTF-8

LazyData true

Depends R (>= 3.0.0)

LinkingTo Rcpp, RcppArmadillo

RoxygenNote 6.1.1

Suggests knitr, rmarkdown

VignetteBuilder knitr

R topics documented:

CCT.pval ................................................................. 2
fit_null_glm .......................................................... 2
fit_null_glmmkin ................................................... 3
STAAR ................................................................. 5

Index 7
CCT.pval An analytical p-value combination method using the Cauchy distribution

Description
The CCT.pval function takes in a vector of p-values, and return the aggregated p-value using Cauchy method.

Usage
CCT.pval(Pvals)

Arguments
Pvals a numeric vector of p-values, where each of the element is between 0 to 1, to be combined.

Value
pval: the aggregated p-value combining p-values from the vector Pvals.

References

Examples
p.values <- c(2e-02,4e-04,0.2,0.1,0.8)
CCT.pval(Pvals=p.values)

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.

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.

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. More details see `glmmkin`.

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`) 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).
fit_null_glmmkin

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 $\tau$ (default = 1e-5), used when method.optim = "Brent". See Details.

taumax the upper bound of search space for the variance component parameter $\tau$ (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 $\tau$ (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


STAAR

STAAR procedure using omnibus test

Description

The STAAR function takes in genotype, the object from fitting the null model, and functional annotation data, and analyzes 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

\[
\text{STAAR}(\text{genotype}, \text{obj_nullmodel}, \text{annotation_phred} = \text{NULL}, \\
rare_maf_cutoff = 0.01, \text{rv_num_cutoff} = 2)
\]

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 variants.

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

annotation_phred: a data frame or matrix of functional annotation data of dimension n*q (or a vector of a single annotation score with length n). Continuous scores should be given in phred score scale, where the phred score of j-th variant is defined to be \(-10\log_{10}(-\text{rank}_j)\) 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 is 0.01).

rv_num_cutoff: the cutoff of minimum number of variants of analyzing a given variant-set. (Default is 2).

Value

a list with the following members:

- **num_SNV**: the number of SNVs 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.
- **RV_label**: the boolean vector indicating whether each SNV 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

Index

as.data.frame, 3
CCT.pval, 2
family, 3, 4
fit_null_glm, 2, 5
fit_null_glmmkin, 3, 5
formula, 3

glm, 2–4
glmmkin, 3–5
GMMAT, 3, 5

STAAR, 5
stats, 2