

Package ‘KnockoffTrio’

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Title Trio Data Analysis with Knockoff Statistics for FDR Control

Version 1.0.2

Description Identification of putative causal variants in genome-wide association studies with the trio design. The package implements the methods in the paper: Yang, Y., Wang, C., Liu, L., Buxbaum, J., He, Z., & Ionita-Laza, I. (2022). KnockoffTrio: A knockoff framework for the identification of putative causal variants in genome-wide association studies with trio design. *The American Journal of Human Genetics*, 109(10), 1761-1776.

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causal_loci	<i>Identification of causal loci</i>
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Description

Identification of causal loci using KnockoffTrio's feature statistics

Usage

```
causal_loci(window, M = 10, fdr = 0.15)
```

Arguments

window	The result window from KnockoffTrio. If there are multiple windows, please use <code>rbind</code> to combine the windows.
M	A positive integer for the number of knockoffs. The default is 10.
fdr	A real number in a range of (0,1) indicating the target FDR level. The default is 0.15.

Value

A list that contains:

window A data frame for an updated window that includes an extra column for KnockoffTrio's Q-values. A locus with a Q-value \leq the target FDR level, i.e., `window$q` \leq `fdr`, is considered as causal.

thr.w A positive real number indicating the significance threshold for KnockoffTrio's feature statistics. A locus with a feature statistic \geq `thr.w`, i.e., `window$w` \geq `thr.w` is considered as causal. The loci selected by `window$w` \geq `thr.w` are equivalent to those by `window$q` \leq `fdr`. No loci are selected at the target FDR level if `thr.w` = `Inf`.

Examples

```
data(KnockoffTrio.example)
dat.ko<-create_knockoff(KnockoffTrio.example$dat.hap,KnockoffTrio.example$pos,M=10)
window<-KnockoffTrio(KnockoffTrio.example$dat,dat.ko,KnockoffTrio.example$pos)
result<-causal_loci(window,M=10,fdr=0.15)
```

create_knockoff	<i>Create knockoff genotype data</i>
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Description

Create knockoff genotype data using phased haplotype data.

Usage

```
create_knockoff(
  dat.hap,
  pos,
  M = 10,
  maxcor = 0.7,
  maxbp = 80000,
  phasing.dad = NULL,
  phasing.mom = NULL
)
```

Arguments

dat.hap	A $6n \times p$ matrix for the haplotype data, in which n is the number of trios and p is the number of variants. Each trio must consist of father, mother, and offspring (in this order). The haplotypes must be coded as 0 or 1. Missing haplotypes are not allowed.
pos	A numeric vector of length p for the position of p variants.
M	A positive integer for the number of knockoffs. The default is 10.
maxcor	A real number in a range of $[0,1]$ for the correlation threshold in hierarchical clustering, such that variants from two different clusters do not have a correlation greater than maxcor when constructing knockoff parents. The default is 0.7.
maxbp	A positive integer for the size of neighboring base pairs used to generate knock-off parents. The default is 80000.
phasing.dad	A numeric vector of length n that contains 1 or 2 to indicate which paternal haplotype was transmitted to offspring in each trio. If NA, the function will calculate the phasing information based on the input haplotype matrix.
phasing.mom	A numeric vector of length n that contains 1 or 2 to indicate which maternal haplotype was transmitted to offspring in each trio. If NA, the function will calculate the phasing information based on the input haplotype matrix.

Value

A $3n \times p \times M$ array for the knockoff genotype data.

Examples

```
data(KnockoffTrio.example)
dat.ko<-create_knockoff(KnockoffTrio.example$dat.hap,KnockoffTrio.example$pos,M=10)
```

KnockoffTrio

Calculate KnockoffTrio's feature statistics

Description

Calculate KnockoffTrio's feature statistics using original and knockoff genotype data.

Usage

```
KnockoffTrio(
  dat,
  dat.ko = NA,
  pos,
  start = NA,
  end = NA,
  size = c(1, 1000, 5000, 10000, 20000, 50000),
  p_value_only = FALSE,
  adjust_for_cov = FALSE,
  y = NA,
  chr = "1",
  xchr = FALSE,
  sex = NA
)
```

Arguments

<code>dat</code>	A $3n \times p$ matrix for the original genotype data, in which n is the number of trios and p is the number of variants. Each trio must consist of father, mother, and offspring (in this order). The genotypes must be coded as 0, 1, or 2. Missing genotypes are not allowed.
<code>dat.ko</code>	A $3n \times p \times M$ array for the knockoff genotype data created by function <code>create_knockoff</code> . M is the number of knockoffs.
<code>pos</code>	A numeric vector of length p for the position of p variants.
<code>start</code>	An integer for the first position of sliding windows. If NA, <code>start=min(pos)</code> . Only used if you would like to use the same starting position for different cohorts/analyses.
<code>end</code>	An integer for the last position of sliding windows. If NA, <code>end=max(pos)</code> . Only used if you would like to use the same ending position for different cohorts/analyses.
<code>size</code>	A numeric vector for the size(s) of sliding windows when scanning the genome
<code>p_value_only</code>	A logical value indicating whether to perform the knockoff analysis. When <code>p_value_only</code> is TRUE, only the ACAT-combined p-values are to be calculated for each window. When <code>p_value_only</code> is FALSE, <code>dat.ko</code> is required and KnockoffTrio's feature statistics are to be calculated for each window in addition to the p-values.

<code>adjust_for_cov</code>	A logical value indicating whether to adjust for covariates. When <code>adjust_for_cov</code> is TRUE, <code>y</code> is required.
<code>y</code>	A numeric vector of length <code>n</code> for the residual $Y - \hat{Y}$. \hat{Y} is the predicted value from the regression model in which the quantitative trait Y is regressed on the covariates. If Y is dichotomous, you may treat Y as quantitative when applying the regression model.
<code>chr</code>	A character for the name of the chromosome, e.g., "1", "2", ..., "22", and "X".
<code>xchr</code>	A logical value indicating whether the analysis is for the X chromosome. When <code>xchr</code> is TRUE, the analysis is for the X chromosome and sex is required. When <code>xchr</code> is FALSE, the analysis is for the autosomes.
<code>sex</code>	A numeric vector of length <code>n</code> for the sex of offspring. 0s indicate females and 1s indicate males. Sex is required when <code>xchr</code> is TRUE.

Value

A data frame for the analysis results. Each row contains the p-values and, if `p_value_only` is FALSE, KnockoffTrio's feature statistics for a window.

Examples

```
data(KnockoffTrio.example)
dat.ko<-create_knockoff(KnockoffTrio.example$dat.hap,KnockoffTrio.example$pos,M=10)
window<-KnockoffTrio(KnockoffTrio.example$dat,dat.ko,KnockoffTrio.example$pos)
```

`KnockoffTrio.example` *Example data for KnockoffTrio*

Description

A toy example of the haplotype and genotype data for original trios

Usage

```
KnockoffTrio.example
```

Format

`KnockoffTrio.example` contains the following items:

dat A numeric genotype matrix of 3 trios and 5 variants. Each trio contains 3 rows in the order of father, mother and offspring. Each column represents a variant.

dat.hap A numeric haplotype matrix of 3 trios and 5 variants. Each trio contains 6 rows in the order of father, mother and offspring. Each column represents a variant.

pos A numeric vector of length 5 for the position of 5 variants.

meta_analysis	<i>Meta-analysis for KnockoffTrio</i>
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Description

Meta-analysis for KnockoffTrio

Usage

```
meta_analysis(window, n = NA, M = 10)
```

Arguments

window	A list of windows for the analysis results from different cohorts/studies.
n	A positive integer vector for the number of trios in each cohort/study. For weighted meta-analysis, a study's weight is based on the number of trios. The default is NA for unweighted meta-analysis.
M	A positive integer for the number of knockoffs. The default is 10.

Value

A data frame for the meta-analysis results.

Examples

```
data(KnockoffTrio.example)
dat.ko<-create_knockoff(KnockoffTrio.example$dat.hap,KnockoffTrio.example$pos,M=10)
window<-data.matrix(KnockoffTrio(KnockoffTrio.example$dat,dat.ko,KnockoffTrio.example$pos))
window.list<-list(window,window)
window.meta<-meta_analysis(window.list,M=10)
result<-causal_loci(window.meta,M=10,fdr=0.15)
```

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