Package ‘DominoEffect’

March 1, 2024

Type Package

Title Identification and Annotation of Protein Hotspot Residues

Version 1.22.0

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Description The functions support identification and annotation of hotspot residues in proteins. These are individual amino acids that accumulate mutations at a much higher rate than their surrounding regions.

License GPL (>= 3)

Encoding UTF-8

LazyData true

Depends R(>= 3.5)

Imports biomaRt, data.table, utils, stats, Biostrings, SummarizedExperiment, VariantAnnotation, AnnotationDbi, GenomeInfoDb, IRanges, GenomicRanges, methods

Suggests knitr, testthat, rmarkdown

RoxygenNote 6.0.1

VignetteBuilder knitr

biocViews Software, SomaticMutation, Proteomics, SequenceMatching, Alignment

NeedsCompilation no

git_url https://git.bioconductor.org/packages/DominoEffect

git_branch RELEASE_3_18

git_last_commit 58def55

git_last_commit_date 2023-10-24

Repository Bioconductor 3.18

Date/Publication 2024-03-01
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Description

This function aligns the Ensembl protein region with a hotspot to the UniProt sequence. The
Ensembl region encompasses 15 amino acids where the hotspot is in the middle. If the hotspot was
at the protein start or end the region is still 15 amino acids long, but the hotspot position is shifted.

Usage

align_to_unip(ens.seq, uni.seq, ensembl_mut_position)

Arguments

ens.seq          AAString object with the Ensembl protein sequence corresponding to the representative transcript.
uni.seq          AAString with the UniProt sequence for the identifier matching the Ensembl
gene name.
ensm.mut_position Numeric vector defining the hotspot position in the Ensembl sequence, i.e. in the ens.seq

Value

Returns a list where the first element is a character vector defining whether there was a significant
alignment and the second element provides the hotspot position in the UniProt sequence.

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library(Biostrings)

ens.seq <- AAString("MDLSALREEVQVINAMQKILECPICLIEPVLSTCDHIIFCKFCLMK")
uni.seq <- AAString("MDLSALVRVEVQVINAMQKILECPICLIEPVLSTCDHIIFCKFCLMA")
ensembl_mut_position <- 25

align_to_unip(ens.seq, uni.seq, ensembl_mut_position)

calculate_boundary(mut_pos_numeric, length_aa, flanking_region)

Arguments

mut_pos_numeric
  Amino acid position of mutation

length_aa
  Length of transcript in amino acids

flanking_region
  Vector containing two flanking regions

Value

returns a list with the boundaries for the two regions

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Examples

calculate_boundary(250, 500, c(200, 300))
calculate_boundary(250, 500, 300)
DominoEffect

Identification of significant mutation hotspot residues.

Description
The function identifies individual amino acid residues, which accumulate a high fraction of the overall mutation load within a protein. After detecting mutation hotspots, the function obtains UniProt/Swiss-Prot KB functional and structural annotations for the affected protein regions and checks for the sequence agreement.

Usage
```
DominoEffect(mutation_dataset, gene_data, snp_data,
             min_n_muts = 5, MAF_thresh = 0.01,
             flanking_region = c(200, 300),
             poisson.thr = 0.01, percentage.thr = 0.15,
             ratio.thr = 45, approach = "percentage", write_to_file = "NO")
```

Arguments
- **mutation_dataset**: Object containing a table with the mutation data (e.g. TCGA point mutations mapped to protein level).
- **gene_data**: DominoData object containing information about Ensembl gene annotations: gene identifiers and representative transcript cDNA length.
- **snp_data**: Object containing a table with information on population SNPs.
- **min_n_muts**: Numeric vector defining a minimum number of mutations that need to occur at the same residue. Default: 5
- **MAF_thresh**: Numeric vector that defines Minor allele frequency threshold for considering reported mutations as population SNPs.
- **flanking_region**: Numeric vector that defines size of a window around the mutation that will be considered. Up to two window sizes are allowed.
- **poisson.thr**: Numeric vector that defines a threshold for considering a mutation to be significant in a Poisson model.
- **percentage.thr**: Numeric vector that defines a threshold for considering a mutation to be significant based on percentage of mutations.
- **ratio.thr**: Numeric vector that defines a threshold for considering a mutation to be significant based on ratio of mutations.
- **approach**: Character string specifying the approach for calculating significance. Options are "percentage" or "ratio".
- **write_to_file**: Character string specifying whether to write the results to a file. Options are "YES" or "NO".

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**poisson.thr**  Numeric vector that defines a threshold for the adjusted p-value. Residues with an associated p-value that is lower than the defined value are reported. Default: 0.01

**percentage.thr**  Number defining the fraction of mutations within the window that need to fall on a single residue in order for it to be classified as a hotspot. Default: 0.15

**ratio.thr**  Number defining a requirement that a number of mutations on a single residue should exceed what would be expected by chance given a background mutation rate in the window (i.e. the surrounding region). Default: 45

**approach**  Option to define selection criteria to use percentage.thr or ratio.thr as criterion for finding single residue mutation clusters. Options: "both", "percentage" or "ratio". Default = "percentage"

**write_to_file**  Option if the identified and annotated hotspots should be written to a file (YES or NO). Default: NO

**Description**

This function converts the genomic information on hotspot mutations into a GPo object.

**Usage**

```r
GPo_of_hotspots(hotspot_mutations)
```

**Arguments**

- **hotspot_mutations**  Data frame with information on hotspot mutations generated by the DominoEffect package.
identify_hotspots

Value

GPo object that contains the genomic information on hotspot mutations.

Author(s)

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Examples

data("SnpData", package = "DominoEffect")
data("TestData", package = "DominoEffect")
data("DominoData", package = "DominoEffect")

hotspot_mutations <- DominoEffect(mutation_dataset = TestData,
gene_data = DominoData, snp_data = SnpData)
GPo_of_hotspots(hotspot_mutations)

identify_hotspots Identify hotspots

Description

The function identify protein hotspot mutation residues

Usage

identify_hotspots(mutation_dataset, gene_data,
snp_data, min_n_muts = 5, MAF_thresh = 0.01, flanking_region = c(200, 300),
poisson.thr = 0.01, percentage.thr = 0.15, ratio.thr = 45, approach = "percentage")

Arguments

mutation_dataset
  Object containing a table with the mutation data (e.g. TCGA point mutations mapped to protein level).

gene_data
  Data frame or Txdb object containing information about Ensembl gene annotations: gene identifiers and representative transcript cDNA length.

snp_data
  Object containing a table or vcf object with information on population SNPs.

min_n_muts
  Numeric vector defining a minimum number of mutations that need to occur at the same residue. Default: 5

MAF_thresh
  Numeric vector that defines Minor allele frequency threshold for considering reported mutations as population SNPs.

flanking_region
  Numeric vector that defines size of a window around the mutation that will be considered. Up to two window sizes are allowed.
poisson.thr Numeric vector that defines a threshold for the adjusted p-value. Residues with an associated p-value that is lower than the defined value are reported. Default: 0.01

percentage.thr Number defining the fraction of mutations within the window that need to fall on a single residue in order for it to be classified as a hotspot. Default: 0.15

ratio.thr Number defining a requirement that a number of mutations on a single residue should exceed what would be expected by chance given a background mutation rate in the window (i.e. the surrounding region). Default: 45

approach Option to define selection criteria to use percentage.thr or ratio.thr as criterion for finding single residue mutation clusters. Options: "both", "percentage" or "ratio". Default = "percentage"

Value
An object containing information on the significant hotspots, associated Gene and protein identifiers, number of mutations, percentage of mutations within defined windows that map to the same residue and associated p-values.

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Examples
```
data("SnpData", package = "DominoEffect")
data("TestData", package = "DominoEffect")
data("DominoData", package = "DominoEffect")
hotspot_mutations <- identify_hotspots(mutation_dataset = TestData,
genome_data = DominoData, snp_data = SnpData)
```

---

**Description**
This function imports txdb data and converts into a data frame used in the DominoEffect package only extracting the required information from the txdb object.

**Usage**
```
import_txdb(txdb_object)
```

**Arguments**
- **txdb_object** TxDB Object, e.g. from makeTxDbFromEnsembl
map_to_func_elem

Value

Data frame that can be used in DominoEffect package.

Author(s)

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Examples

```
#EnsTxDB <- makeTxDbFromEnsembl(organism="Homo sapiens", release=73,
#       server="ensembldb.ensembl.org")
#DominoData <- import_txdb(EnsTxDB)
#head(DominoData)
```

map_to_func_elem  

*Functional annotation of significant hotspot residues.*

Description

This function retrieves Uniprot annotations for the functional elements in the proteins with significant hotspots and overlaps and maps the hotspot residues to these.

Usage

```
map_to_func_elem(hotspot_results, write_to_file = "NO", ens_release = "75")
```

Arguments

- **hotspot_results**: Object containing information about the hotspot residues identified using the function `identify_hotspots()`.
- **write_to_file**: A character vector defining whether the resulting annotated hotspots should be saved in a file (YES or NO).
- **ens_release**: A character vector defining whether the default gene annotations are used, i.e. Ensembl release 75, or if the gene_data correspond to a different Ensembl release. For the current Ensembl version this should be set to: `ens_release="www.ensembl.org"`. For the archive versions to the corresponding archive website.

Value

Updated results file containing an additional columns with the information on the annotated functional and structural region within which the mutation is mapped.

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Examples

data("TestData", package = "DominoEffect")
data("DominoData", package = "DominoEffect")
data("SnpData", package = "DominoEffect")

hotspot_mutations <- identify_hotspots(TestData, DominoData, SnpData)
hotspot_mutations <- map_to_func_elem(hotspot_mutations,
write_to_file = "NO", ens_release = "75")

head(hotspot_mutations)
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