Package ‘compSPOT’

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Type Package

Title compSPOT: Tool for identifying and comparing significantly mutated genomic hotspots

Version 1.2.0

Description Clonal cell groups share common mutations within cancer, precancer, and even clinically normal appearing tissues. The frequency and location of these mutations may predict prognosis and cancer risk. It has also been well established that certain genomic regions have increased sensitivity to acquiring mutations. Mutation-sensitive genomic regions may therefore serve as markers for predicting cancer risk. This package contains multiple functions to establish significantly mutated hotspots, compare hotspot mutation burden between samples, and perform exploratory data analysis of the correlation between hotspot mutation burden and personal risk factors for cancer, such as age, gender, and history of carcinogen exposure. This package allows users to identify robust genomic markers to help establish cancer risk.

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Suggests BiocStyle, knitr, rmarkdown, testthat (>= 3.0.0)

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URL https://github.com/sydney-grant/compSPOT

BugReports https://github.com/sydney-grant/compSPOT/issues

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**Description**

This function performs an exploratory data analysis comparing the relationship between user-input features to hotspot mutation burden.

**Usage**

```r
compare_features(data, regions, feature)
```

**Arguments**

- **data**
  A dataframe containing the clinical features and the mutation count. Dataframe must contain columns with the following names: "Chromosome" <- Chromosome number where the mutation is located "Position" <- Genomic position number where the mutation is located "Sample" <- Unique ID for each sample in dataset "Gene" <- Name of the gene which mutation is located in (optional)

- **regions**
  A dataframe containing the chromosome, start and end base pair position of each region of interest

- **feature**
  A list containing all the features.
**Details**

This function is used to classify the features into sequential features if values are numerical or classifies them into categorical features. Sequential features are compared to the mutation count using Pearson correlation. Similarly, in categorical features either Wilcoxon or Kruskal-Wallis test is used to compare between the groups in the features based on the mutational count. Scatter plot is used to represent the sequential features along with the R and p-value from the Pearson correlation. Violin plots are used to plot the groups in the categorical data and Wilcoxon or Kruskal-Wallis values are shown on the graph.

**Value**

A grid of all the violin plots for the categorical data and scatter plot for the sequential data.

**Examples**

```r
data("compSPOT_example_mutations")
data("compSPOT_example_regions")
features <- c("AGE", "SEX", "ADJUVANT_TX", "SMOKING_HISTORY",
              "TUMOR_VOLUME", "KI_67")
compare_features(data = compSPOT_example_mutations,
                 regions = compSPOT_example_regions, feature = features)
```

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**Description**

This function compares the mutation frequency of a panel of genomic regions between two subgroups.

**Usage**

```r
compare_groups(data, regions, pvalue, threshold, name1, name2, include_genes)
```

**Arguments**

- **data**
  a dataframe containing the chromosome, base pair position, and optionally gene name of each mutation. Dataframe must contain columns with the following names: "Chromosome" <- Chromosome number where the mutation is located "Position" <- Genomic position number where the mutation is located "Sample" <- Unique ID for each sample in dataset "Gene" <- Name of the gene which mutation is located in (optional) "Group" <- Group classification ID (group.spot only)

- **regions**
  a dataframe containing the chromosome, start and end base pair position of each region of interest

- **pvalue**
  a threshold p-value for Kolmogorov-Smirnov test
threshold: the cutoff empirical distribution for Kolmogorov-Smirnov test
name1: a string containing the name of one group for the comparison
name2: a string containing the name of the second group for the comparison
include_genes: true or false whether gene names are included in regions dataframe

Details
This function creates a list of mutation frequency per unique sample for each genomic regions separated based on specified sub-groups. The regions with significant differences in mutation distribution are calculated using a Kolmogorov-Smirnov test. The difference in mutation frequency is output in a violin plot.

Value
a list containing the following:
1. A dataframe with the hotspot, group, and mutation count from input sample name
2. A plotly object violin plot comparing the mutation frequency per sample in groups as given by "name1" and "name2" variables
3. An array of ECDF plots comparing the mutation frequency per sample in groups as given by "name1" and "name2" variables

Examples

data("compSPOT_example_mutations")
data("compSPOT_example_regions")
compare_groups(data = compSPOT_example_mutations,
regions = compSPOT_example_regions, pvalue = 0.05, threshold = 0.4,
name1 = "High-Risk", name2 = "Low-Risk", include_genes = TRUE)

compSPOT Mutation hotspot finder and comparison of hotspot burden.

Description
It is well known that numerous clones of cells sharing common mutations exist within cancer, precancer, and even clinically normal appearing tissues. The frequency and location of these mutations may aid in the prediction of cancer risk of certain individuals. It has also been well established that certain genomic regions have increased sensitivity to acquiring mutations. Mutation-sensitive genomic regions may therefore be used as markers for prediction of cancer risk. This package contains multiple functions for the establishment of significantly mutated hotspots, comparison of hotspot mutation burden between sub-groups, and exploratory data analysis of the correlation between hotspot mutation burden, and personal risk factors for cancer such as age, gender, and history of carcinogen exposure. This package aims to allow users to identify robust genomic markers which may serve as markers of cancer risk.
**compSPOT_example_mutations**

**Value**

A package containing functions which find statistically significant mutation hotspots and compare mutation hotspot burden between groups and correlation between clinical features.

**Description**

A dataframe containing the chromosome number, base pair location, sample ID, gene name, patient features including: age, sex, adjuvant therapy treatment, smoking history, tumor volume, ki67 quantification, and risk-classification for cancer progression. Data curated from cBioPortal dataset: Non-Small Cell Lung Cancer (TRACERx, NEJM & Nature 2017)

**Usage**

`compSPOT_example_mutations`

**Format**

`example_mutations`:

a dataframe with 11 columns and 22947 rows:

- **Sample ID**: assigned to indicate each unique sample
- **Gene**: Name of gene affected by mutation
- **Chromosome**: Chromosome which the mutation is located on
- **Position**: Base pair position of mutation
- **AGE**: Age of the patient
- **SEX**: Sex of the patient
- **ADJUVANT_TX**: Statement of whether or not patient received adjuvant therapy
- **SMOKING_HISTORY**: Patient’s history of smoking
- **TUMOR_VOLUME**: Measured volume of patient’s lung tumor
- **KI_67**: Quantification of ki67 markers observed in each patient
- **Group**: Risk classification of patients based on observed survival

**Details**

`compSPOT_example_mutations`

**Value**

A dataframe containing the chromosome number, base pair location, sample ID, gene name, patient features including: age, sex, adjuvant therapy treatment, smoking history, tumor volume, ki67 quantification, and risk-classification for cancer progression.
References


compSPOT_example_regions

Genomic Coordinates of Regions of Interest

Description

A dataframe containing the chromosome number, lowerbound and upperbound base pair locations of each region of interest along with the name of the gene where the region is located. Each row indicates a unique region. Regions were identified using the seq.hotSPOT package based on Lung Squamous Cell Carcinoma highly mutated regions.

Usage

compSPOT_example_regions

Format

example_regions:

a dataframe with 2 columns and 200 rows:

- **Lowerbound** Base pair position of the start of the region
- **Upperbound** Base pair position of the end of the region
- **Chromosome** Chromosome which the mutation is located on
- **Gene** Name of gene affected by mutation

Details

compSPOT example genomic regions

Value

A dataframe containing the chromosome number, base pair location, and gene names of 200 genomic regions highly mutated in Lung Squamous Cell Carcinoma identified using seq.hotSPOT
References


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**find_hotspots**

**significant hotspot calculator**

**Description**

Based on a panel of genomic regions, this function calculates the regions which are found to have significantly higher mutation frequency compared to less mutated regions.

**Usage**

```
find_hotspots(data, regions, pvalue, threshold, include_genes, rank)
```

**Arguments**

- **data**: a dataframe containing the chromosome, base pair position, and optionally gene name of each mutation. Dataframe must contain columns with the following names: "Chromosome" <- Chromosome number where the mutation is located "Position" <- Genomic position number where the mutation is located "Sample" <- Unique ID for each sample in dataset "Gene" <- Name of the gene which mutation is located in (optional)
- **regions**: a dataframe containing the chromosome, start and end base pair position of each region of interest
- **pvalue**: the p-value cutoff for included hotspots
- **threshold**: the cutoff empirical distribution for Kolmogorov-Smirnov test
- **include_genes**: true or false whether gene names are included in regions dataframe
- **rank**: true or false whether regions dataframe is already ranked and includes mutation count of total dataset

**Details**

This function begins by measuring the mutation frequency for each unique sample for each provided genomic region. Beginning with the top ranked hotspot, a Kolmogorov-Smirnov test is performed on the mutation frequency of the top genomic region compared to the normalized mutation frequency of all the lower-ranked regions. This continues, then running the Kolmogorov-Smirnov test for the normalized mutation frequency of the top 2 genomic regions compared to the normalized mutation frequency of all lower-ranked regions. This process repeats itself, continuously adding an additional genomic regions each time until either the set p-value or empirical distribution threshold is not met. Once this cutoff has been reached, an established list of mutation hotspots is provided.
find_hotspots

Value

A list containing the following:

1. dataframe containing the genomic regions with significant mutation frequency
2. plotly object Dotplot showing the percentage of samples with mutations in each ranked genomic region, highlighting significantly mutated hotspots
3. plotly object ECDF plot showing the difference in mutation frequency between hotspots and non-hotspots

Examples

data("compSPOT_example_mutations")
data("compSPOT_example_regions")
significant_spots <- find_hotspots(data = compSPOT_example_mutations,
regions = compSPOT_example_regions,
pvalue = 0.05, threshold = 0.2, include_genes = TRUE, rank = TRUE)
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