Package 'driveR'

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Title Prioritizing Cancer Driver Genes Using Genomics Data

Version 0.4.1

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Description Cancer genomes contain large numbers of somatic alterations but few genes drive tumor development. Identifying cancer driver genes is critical for precision oncology. Most of current approaches either identify driver genes based on mutational recurrence or using estimated scores predicting the functional consequences of mutations. 'driveR' is a tool for personalized or batch analysis of genomic data for driver gene prioritization by combining genomic information and prior biological knowledge. As features, 'driveR' uses coding impact metaprediction scores, non-coding impact scores, somatic copy number alteration scores, hotspot gene/double-hit gene condition, 'phenolyzer' gene scores and memberships to cancer-related KEGG pathways. It uses these features to estimate cancer-type-specific probability for each gene of being a cancer driver using the related task of a multi-task learning classification model. The method is described in detail in Ulgen E, Sezerman OU. 2021. driveR: driveR: a novel method for prioritizing cancer driver genes using somatic genomics data. BMC Bioinformatics <doi:10.1186/s12859-021-04203-7>.

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Encoding UTF-8

LazyData true

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URL https://egeulgen.github.io/driveR/, https://github.com/egeulgen/driveR/

BugReports https://github.com/egeulgen/driveR/issues

Imports caret, randomForest, GenomicRanges, GenomeInfoDb, GenomicFeatures, TxDb.Hsapiens.UCSC.hg19.knownGene, TxDb.Hsapiens.UCSC.hg38.knownGene, S4Vectors, org.Hs.eg.db, rlang,

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Suggests testthat, covr, knitr, rmarkdown

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create_features_df Create Data Frame of Features for Driver Gene Prioritization

Description

Create Data Frame of Features for Driver Gene Prioritization

Usage

```
create_features_df(
    annovar_csv_path,
    scna_df,
    phenolyzer_annotated_gene_list_path,
    batch_analysis = FALSE,
    prep_phenolyzer_input = FALSE,
    build = "GRCh37",
    log2_ratio_threshold = 0.25,
    gene_overlap_threshold = 25,
```

```
MCR_overlap_threshold = 25,
 hotspot_threshold = 5L,
 log2_hom_loss_threshold = -1,
 verbose = TRUE,
 na.string = "."
)
```

Arguments

′ annovar_csv_pat	:h						
	path to 'ANNOVAR' csv output file						
scna_df	the SCNA segments data frame. Must contain:						
	chr chromosome the segment is located in						
	start start position of the segment						
	end end position of the segment						
	log2ratio log_2 ratio of the segment						
phenolyzer_annotated_gene_list_path							
	path to 'phenolyzer' "annotated_gene_list" file						
-	boolean to indicate whether to perform batch analysis (TRUE, default) or person- alized analysis (FALSE). If TRUE, a column named 'tumor_id' should be present in both the ANNOVAR csv and the SCNA table.						
prep_phenolyzer							
	boolean to indicate whether or not to create a vector of genes for use as the input of 'phenolyzer' (default = FALSE). If TRUE, the features data frame is not created and instead the vector of gene symbols (union of all genes for which scores are available) is returned.						
build	genome build for the SCNA segments data frame (default = "GRCh37")						
log2_ratio_thre	eshold						
	the log_2 ratio threshold for keeping high-confidence SCNA events (default = 0.25)						
gene_overlap_th	nreshold						
	the percentage threshold for the overlap between a segment and a transcript (default = 25). This means that if only a segment overlaps a transcript more than this threshold, the transcript is assigned the segment's SCNA event.						
MCR_overlap_thr							
	the percentage threshold for the overlap between a gene and an MCR region $(default = 25)$. This means that if only a gene overlaps an MCR region more than this threshold, the gene is assigned the SCNA density of the MCR						
hotspot_thresho	bld						
	to determine hotspot genes, the (integer) threshold for the minimum number of cases with certain mutation in COSMIC (default = 5)						
log2_hom_loss_t							
	to determine double-hit events, the log_2 threshold for identifying homozygous loss events (default = -1).						
verbose	boolean controlling verbosity (default = TRUE)						
na.string	string that was used to indicate when a score is not available during annotation with ANNOVAR (default = ".")						

Value

If prep_phenolyzer_input=FALSE (default), a data frame of features for prioritizing cancer driver genes (gene_symbol as the first column and 26 other columns containing features). If prep_phenolyzer_input=TRUE, the functions returns a vector gene symbols (union of all gene symbols for which scores are available) to be used as the input for performing 'phenolyzer' analysis.

The features data frame contains the following columns:

gene_symbol HGNC gene symbol

metaprediction_score the maximum metapredictor (coding) impact score for the gene

noncoding_score the maximum non-coding PHRED-scaled CADD score for the gene

- scna_score SCNA proxy score. SCNA density (SCNA/Mb) of the minimal common region (MCR) in which the gene is located
- hotspot_double_hit boolean indicating whether the gene is a hotspot gene (indication of oncogenes) or subject to double-hit (indication of tumor-suppressor genes)

phenolyzer_score 'phenolyzer' score for the gene

hsa03320 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04010 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04020 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04024 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04060 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04066** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04110** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04115** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04150** boolean indicating whether or not the gene takes part in this KEGG pathway hsa04151 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04210 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04310 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04330 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04340** boolean indicating whether or not the gene takes part in this KEGG pathway hsa04350 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04370 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04510** boolean indicating whether or not the gene takes part in this KEGG pathway hsa04512 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04520 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04630 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04915 boolean indicating whether or not the gene takes part in this KEGG pathway

See Also

prioritize_driver_genes for prioritizing cancer driver genes

Examples

create_gene_level_scna_df

Create Gene-level SCNA Data Frame

Description

Create Gene-level SCNA Data Frame

Usage

```
create_gene_level_scna_df(
   scna_df,
   build = "GRCh37",
   gene_overlap_threshold = 25
)
```

Arguments

scna_df	the SCNA segments data frame. Must contain:			
_	chr chromosome the segment is located in			
	start start position of the segment			
	end end position of the segment			
	log2ratio log_2 ratio of the segment			
build	genome build for the SCNA segments data frame (default = "GRCh37")			
gene_overlap_threshold				
	the percentage threshold for the overlap between a segment and a transcript (default = 25). This means that if only a segment overlaps a transcript more than this threshold, the transcript is assigned the segment's SCNA event.			

Value

data frame of gene-level SCNA events, i.e. table of genes overlapped by SCNA segments.

create_noncoding_impact_score_df

Create Non-coding Impact Score Data Frame

Description

Create Non-coding Impact Score Data Frame

Usage

```
create_noncoding_impact_score_df(annovar_csv_path, na.string = ".")
```

Arguments

annovar_csv_path

	path to 'ANNOVAR' csv output file
na.string	string that was used to indicate when a score is not available during annotation with ANNOVAR (default = ".")

Value

data frame of meta-prediction scores containing 2 columns:

gene_symbol HGNC gene symbol

CADD_phred PHRED-scaled CADD score

create_SCNA_score_df Create SCNA Score Data Frame

Description

Create SCNA Score Data Frame

Usage

```
create_SCNA_score_df(
  gene_SCNA_df,
  build = "GRCh37",
  log2_ratio_threshold = 0.25,
  MCR_overlap_threshold = 25
)
```

Arguments

gene_SCNA_df	data frame of gene-level SCNAs (output of create_gene_level_scna_df)
build	genome build for the SCNA segments data frame (default = "GRCh37")
log2_ratio_thre	shold
	the log_2 ratio threshold for keeping high-confidence SCNA events (default = 0.25)
MCR_overlap_thr	reshold
	the percentage threshold for the overlap between a gene and an MCR region (default = 25). This means that if only a gene overlaps an MCR region more than this threshold, the gene is assigned the SCNA density of the MCR

Details

The function first aggregates SCNA log_2 ratio on gene-level (by keeping the ratio with the maximal $|log_2|$ ratio over all the SCNA segments overlapping a gene). Next, it identifies the minimal common regions (MCRs) that the genes overlap and finally assigns the SCNA density (SCNA/Mb) values as proxy SCNA scores.

Value

data frame of SCNA proxy scores containing 2 columns:

gene_symbol HGNC gene symbol

SCNA_density SCNA proxy score. SCNA density (SCNA/Mb) of the minimal common region (MCR) in which the gene is located.

determine_double_hit_genes

Determine Double-Hit Genes

Description

Determine Double-Hit Genes

Usage

```
determine_double_hit_genes(
    annovar_csv_path,
    gene_SCNA_df,
    log2_hom_loss_threshold = -1,
    batch_analysis = FALSE
)
```

Arguments

annovar_csv_pat	:h					
	path to 'ANNOVAR' csv output file					
gene_SCNA_df	data frame of gene-level SCNAs (output of create_gene_level_scna_df)					
log2_hom_loss_threshold						
	to determine double-hit events, the log_2 threshold for identifying homozygous loss events (default = -1).					
batch_analysis	boolean to indicate whether to perform batch analysis (TRUE, default) or person- alized analysis (FALSE). If TRUE, a column named 'tumor_id' should be present in both the ANNOVAR csv and the SCNA table.					

Value

vector of gene symbols that are subject to double-hit event(s), i.e. non-synonymous mutation + homozygous copy-number loss

determine_hotspot_genes

Determine Hotspot Containing Genes

Description

Determine Hotspot Containing Genes

Usage

```
determine_hotspot_genes(annovar_csv_path, hotspot_threshold = 5L)
```

Arguments

annovar_csv_path

path to 'ANNOVAR' csv output file

hotspot_threshold

to determine hotspot genes, the (integer) threshold for the minimum number of cases with certain mutation in COSMIC (default = 5)

Value

vector of gene symbols of genes containing hotspot mutation(s)

driveR

driveR: An R Package for Prioritizing Cancer Driver Genes Using Genomics Data

Description

Cancer genomes contain large numbers of somatic alterations but few genes drive tumor development. Identifying cancer driver genes is critical for precision oncology. Most of current approaches either identify driver genes based on mutational recurrence or using estimated scores predicting the functional consequences of mutations.

Details

driveR is a tool for personalized or batch analysis of genomic data for driver gene prioritization by combining genomic information and prior biological knowledge. As features, driveR uses coding impact metaprediction scores, non-coding impact scores, somatic copy number alteration scores, hotspot gene/double-hit gene condition, 'phenolyzer' gene scores and memberships to cancer-related KEGG pathways. It uses these features to estimate cancer-type-specific probabilities for each gene of being a cancer driver using the related task of a multi-task learning classification model.

Author(s)

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See Also

predict_coding_impact for metaprediction of impact of coding variants. create_features_df for creating the features table to be used to prioritize cancer driver genes. See prioritize_driver_genes for prioritizing cancer driver genes

example_cohort_features_table

Example Cohort-level Features Table for Driver Prioritization

Description

The example dataset containing features for prioritizing cancer driver genes for 10 randomly selected samples from TCGA's LAML (Acute Myeloid Leukemia) cohort

Usage

example_cohort_features_table

Format

A data frame with 349 rows and 27 variables:

gene_symbol HGNC gene symbol

metaprediction_score the maximum metapredictor (coding) impact score for the gene

- **noncoding score** the maximum non-coding PHRED-scaled CADD score for the gene
- scna_score SCNA proxy score. SCNA density (SCNA/Mb) of the minimal common region (MCR)
 in which the gene is located

hotspot_double_hit boolean indicating whether the gene is a hotspot gene (indication of oncogenes) or subject to double-hit (indication of tumor-suppressor genes)

phenolyzer_score 'phenolyzer' score for the gene

hsa03320 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04010** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04020** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04024** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04060** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04066** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04110** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04115** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04150** boolean indicating whether or not the gene takes part in this KEGG pathway hsa04151 boolean indicating whether or not the gene takes part in this KEGG pathway hsa04210 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04310** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04330** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04340** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04350** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04370** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04510** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04512** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04520** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04630** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04915** boolean indicating whether or not the gene takes part in this KEGG pathway

See Also

KEGG_cancer_pathways_descriptions for descriptions of KEGG "Pathways in cancer"-related pathways.

example_cohort_scna_table

Example Cohort-level Somatic Copy Number Alteration Table

Description

A data set containing the somatic copy number alteration data for 10 randomly selected samples from TCGA's LAML (Acute Myeloid Leukemia) cohort

Usage

example_cohort_scna_table

Format

A data frame with 126147 rows and 5 variables:

chr chromosome the segment is located in

start start position of the segment

end end position of the segment

log2ratio log_2 ratio of the segment

tumor_id ID for the tumor containing the SCNA segment

Source

https://dcc.icgc.org/releases/release_28

example_features_table

Example Features Table for Driver Prioritization

Description

The example dataset containing features for prioritizing cancer driver genes for the lung adenocarcinoma patient studied in Imielinski M, Greulich H, Kaplan B, et al. Oncogenic and sorafenibsensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014;124(4):1582-6.

Usage

example_features_table

Format

A data frame with 4901 rows and 27 variables:

gene_symbol HGNC gene symbol

metaprediction_score the maximum metapredictor (coding) impact score for the gene

- **noncoding_score** the maximum non-coding PHRED-scaled CADD score for the gene
- scna_score SCNA proxy score. SCNA density (SCNA/Mb) of the minimal common region (MCR)
 in which the gene is located
- hotspot_double_hit boolean indicating whether the gene is a hotspot gene (indication of oncogenes) or subject to double-hit (indication of tumor-suppressor genes)

phenolyzer_score 'phenolyzer' score for the gene

hsa03320 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04010** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04020** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04024** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04060** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04066** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04110** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04115** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04150** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04151** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04210** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04310** boolean indicating whether or not the gene takes part in this KEGG pathway hsa04330 boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04340** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04350** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04370** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04510** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04512** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04520** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04630** boolean indicating whether or not the gene takes part in this KEGG pathway **hsa04915** boolean indicating whether or not the gene takes part in this KEGG pathway

See Also

KEGG_cancer_pathways_descriptions for descriptions of KEGG "Pathways in cancer"-related pathways.

example_scna_table Example Somatic Copy Number Alteration Table

Description

A data set containing the somatic copy number alteration data for the lung adenocarcinoma patient studied in Imielinski M, Greulich H, Kaplan B, et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014;124(4):1582-6.

Usage

example_scna_table

Format

A data frame with 3160 rows and 4 variables:

chr chromosome the segment is located in

start start position of the segment

end end position of the segment

log2ratio log2 ratio of the segment

Source

https://pubmed.ncbi.nlm.nih.gov/24569458/

KEGG_cancer_pathways_descriptions KEGG "Pathways in cancer"-related Pathways - Descriptions

Description

A data frame containing descriptions for KEGG "Pathways in cancer" (hsa05200)-related pathways. *Generated on Nov 17, 2020.*

Usage

KEGG_cancer_pathways_descriptions

Format

A data frame with 21 rows and 2 variables:

id KEGG pathway ID

description KEGG pathway description

MTL_submodel_descriptions

MTL Sub-model Descriptions

Description

A data frame containing descriptions for all sub-models of the MTL model.

Usage

MTL_submodel_descriptions

Format

A data frame with 21 rows and 2 variables:

short_name short name for the cancer type **description** description of the cancer type

predict_coding_impact Create Coding Impact Meta-prediction Score Data Frame

Description

Create Coding Impact Meta-prediction Score Data Frame

Usage

```
predict_coding_impact(
    annovar_csv_path,
    keep_highest_score = TRUE,
    keep_single_symbol = TRUE,
    na.string = "."
)
```

Arguments

```
annovar_csv_path

path to 'ANNOVAR' csv output file

keep_highest_score

boolean to indicate whether to keep only the maximal impact score per gene

(default = TRUE). If FALSE, all scores per each gene are returned

keep_single_symbol

in ANNOVAR outputs, a variant may be annotated as exonic in multiple genes.

This boolean argument controls whether or not to keep only the first encountered

symbol for a variant (default = TRUE)

na.string string that was used to indicate when a score is not available during annotation

with ANNOVAR (default = ".")
```

Value

data frame of meta-prediction scores containing 2 columns:

gene_symbol HGNC gene symbol

metaprediction_score metapredictor impact score

Examples

prioritize_driver_genes

Prioritize Cancer Driver Genes

Description

Prioritize Cancer Driver Genes

Usage

prioritize_driver_genes(features_df, cancer_type)

Arguments

features_df	the features data frame for all genes, containing the following columns:					
	gene_symbol HGNC gene symbol					
	metaprediction_score the maximum metapredictor (coding) impact score for the gene					
	noncoding_score the maximum non-coding PHRED-scaled CADD score for the gene					
	scna_score SCNA proxy score. SCNA density (SCNA/Mb) of the minimal common region (MCR) in which the gene is located					
	hotspot_double_hit boolean indicating whether the gene is a hotspot gene (in- dication of oncogenes) or subject to double-hit (indication of tumor-suppressor genes)					
	phenolyzer_score 'phenolyzer' score for the gene					
	hsa03320 boolean indicating whether or not the gene takes part in this KEGG pathway					
	hsa04010 boolean indicating whether or not the gene takes part in this KEGG pathway					
	hsa04020 boolean indicating whether or not the gene takes part in this KEGG pathway					
	hsa04024 boolean indicating whether or not the gene takes part in this KEGG pathway					

hsa04060	boolean	indicating	whether	or not t	he gene	takes j	part in	this	KEGG
pathw	ay								

- hsa04066 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04110 boolean indicating whether or not the gene takes part in this KEGG pathway
- **hsa04115** boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04150 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04151 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04210 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04310 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04330 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04340 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04350 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04370 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04510 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04512 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04520 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04630 boolean indicating whether or not the gene takes part in this KEGG pathway
- hsa04915 boolean indicating whether or not the gene takes part in this KEGG pathway
- cancer_type short name of the cancer type. All available cancer types are listed in MTL_submodel_descriptions

Value

data frame with 3 columns:

gene_symbol HGNC gene symbol

driverness_prob estimated probability for each gene in features_df of being a cancer driver. The probabilities are calculated using the selected (via cancer_type) cancer type's sub-model.

prediction prediction based on the cancer-type-specific threshold (either "driver" or "non-driver")

specific_thresholds

See Also

create_features_df for creating the features table.

Examples

```
drivers_df <- prioritize_driver_genes(example_features_table, "LUAD")</pre>
```

specific_thresholds Tumor type specific probability thresholds

Description

Driver gene probability thresholds for all 21 cancer types (submodels).

Usage

specific_thresholds

Format

vector with 21 elements

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