Package 'driveR'

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Title Prioritizing Cancer Driver Genes Using Genomics Data

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Maintainer Ege Ulgen <egeulgen@gmail.com>

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

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

biocViews

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Author Ege Ulgen [aut, cre, cph] (<https://orcid.org/0000-0003-2090-3621>)

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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_path`
: 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

`batch_analysis`
: boolean to indicate whether to perform batch analysis (`TRUE`, default) or personalized analysis (`FALSE`). If `TRUE`, a column named 'tumor_id' should be present in both the ANNOVAR csv and the SCNA table.

`prep_phenolyzer_input`
: 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_threshold`
: the log_2 ratio threshold for keeping high-confidence SCNA events (default = 0.25)

`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.

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

`log2_hom_loss_threshold`
: 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

```
path2annovar_csv <- system.file("extdata/example.hg19_multianno.csv",
                                package = "driveR")
path2phenolyzer_out <- system.file("extdata/example.annotated_gene_list",
                                   package = "driveR")
features_df <- create_features_df(annovar_csv_path = path2annovar_csv,
                                  scna_df = example_scna_table,
                                phenolyzer_annotated_gene_list_path = path2phenolyzer_out)
```

---

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_threshold`	the log_2 ratio threshold for keeping high-confidence SCNA events (default = 0.25)
`MCR_overlap_threshold`	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_path`
: 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 personalized 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.

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 sorafenib-sensitive 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 log_2 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

```
path2annovar_csv <- system.file("extdata/example.hg19_multianno.csv",
                                package = "driveR")
metapred_df <- predict_coding_impact(path2annovar_csv)
```

`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 (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

`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")

See Also

create_features_df for creating the features table.

Examples

```
drivers_df <- prioritize_driver_genes(example_features_table, "LUAD")
```

---

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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