Package 'driveR'

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Title Prioritizing Cancer Driver Genes Using Genomics Data

Version 0.3.0

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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 RoxygenNote 7.1.2

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

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

biocViews

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

Depends R (>= 4.0)

create_features_df

Suggests testthat, covr, knitr, rmarkdown

VignetteBuilder knitr

NeedsCompilation no

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 ${\it create_features_df} \qquad {\it Create\ Data\ Frame\ of\ Features\ for\ Driver\ Gene\ Prioritization}$

Description

Create Data Frame of Features for Driver Gene Prioritization

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Usage

```
create_features_df(
  annovar_csv_path,
  scna_df,
  phenolyzer_annotated_gene_list_path,
  batch_analysis = FALSE,
  prep_phenolyzer_input = FALSE,
  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.

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

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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

```
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, 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 log2 ratio of the segment

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.

Description

Create Non-coding Impact Score Data Frame

Usage

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

Arguments

Value

data frame of meta-prediction scores containing 2 columns:

```
gene_symbol HGNC gene symbol
CADD_phred PHRED-scaled CADD score
```

```
{\tt create\_SCNA\_score\_df} \quad \textit{Create SCNA Score Data Frame}
```

Description

Create SCNA Score Data Frame

Usage

```
create_SCNA_score_df(
  gene_SCNA_df,
  log2_ratio_threshold = 0.25,
  MCR_overlap_threshold = 25
)
```

Arguments

```
\label{eq:gene_SCNA_df} \begin{array}{ll} \text{data frame of gene-level SCNAs (output of create\_gene\_level\_scna\_df)} \\ \text{log2\_ratio\_threshold} \\ \text{the } log2\_\text{ratio threshold for keeping high-confidence SCNA events (default = 0.25)} \\ \text{MCR\_overlap\_threshold} \end{array}
```

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

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

Value

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

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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 cancerrelated 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 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.

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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 KEGG "Pathways in cancer"-related Pathways - Gene Sets

Description

A list containing the genes involved in each Homo sapiens KEGG "Pathways in cancer" (hsa05200)related Pathways. Each element is a vector of gene symbols located in the given pathway. Names correspond to the KEGG ID of the pathway. Generated on Nov 24, 2020.

Usage

KEGG_cancer_pathways

Format

list containing 21 vectors of gene symbols. Each vector corresponds to a pathway.

See Also

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

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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

MCR_table

Table of Pan-Cancer Minimal Common Regions

Description

A data set containing the minimal common regions (MCRs) across all cancer types studied in Kim TM, Xi R, Luquette LJ, Park RW, Johnson MD, Park PJ. Functional genomic analysis of chromosomal aberrations in a compendium of 8000 cancer genomes. Genome Res. 2013;23(2):217-27. Coordinates were converted to hg19 (from hg18) using UCSC Genome Browser's LiftOver tool.

Usage

MCR_table

Format

A data frame with 165 rows and 5 variables:

chr chromosome the MCR is located in

start start position of the MCR **end** end position of the MCR

MCR_type the type ("Amp" or "Del") of the MCR peak

SCNA_density SCNA per Mb within the MCR

Source

https://pubmed.ncbi.nlm.nih.gov/23132910/

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metapredictor_model

Random Forest Model for Coding Impact Metaprediction

Description

A Random Forest model object for metaprediction of coding variants' impact, using 12 impact scores from different coding impact predictors. The model was trained on 711 coding variants, with 10-folds repeated 3 times cross-validation.

Usage

```
metapredictor_model
```

Format

model object

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

See Also

```
TCGA_MTL_fit for the MTL model.
```

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

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 17

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. TCGA_MTL_fit for details on the MTL model
used for prediction.

Examples

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

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 $specific_thresholds$

Tumor type specific probability thresholds

Description

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

Usage

specific_thresholds

Format

vector with 21 elements

See Also

TCGA_MTL_fit for the Multi-Task Learning model.

TCGA_MTL_fit

Multi-Task Learning Model for Predicting Cancer Driver Genes

Description

A Multi-Task Learning (MTL) classification model object for determining cancer driver genes based on 26 features. The model was trained using TCGA data (obtained from ICGC release 28) with lasso regularization. It contains 21 sub-models for different cancer types.

Usage

 $TCGA_MTL_fit$

Format

MTL model object

See Also

MTL_submodel_descriptions for short names and descriptions of all sub-models.

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