Package ‘PanomiR’

April 6, 2024

Title Detection of miRNAs that regulate interacting groups of pathways

Version 1.7.0

Description PanomiR is a package to detect miRNAs that target groups of pathways from gene expression data. This package provides functionality for generating pathway activity profiles, determining differentially activated pathways between user-specified conditions, determining clusters of pathways via the PCxN package, and generating miRNAs targeting clusters of pathways. These function can be used separately or sequentially to analyze RNA-Seq data.

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Encoding UTF-8

RoxygenNote 7.1.2

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

Config/testthat/edition 3

biocViews GeneExpression, GeneSetEnrichment, GeneTarget, miRNA, Pathways

Imports clusterProfiler, dplyr, forcats, GSEABase, igraph, limma, metap, org.Hs.eg.db, parallel, preprocessCore, RColorBrewer, rlang, tibble, withr, utils

Depends R (>= 4.2.0)

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BugReports https://github.com/pouryany/PanomiR/issues

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** aggInvCoverFn  

*Internal function for modification of prioritization.*

**Description**

Internal function for modification of prioritization.

**Usage**

`aggInvCoverFn(selector, coverName)`

**Arguments**

- `selector`: a prioritization table
- `coverName`: a new column name

**Value**

an updated scoring of miRNAs in a cluster of pathways

---

** aggInvFn  

*The function calculate targeting score of miRNA w.r.t to a cluster of pathways via inverse normal method*  

**Description**

The function calculate targeting score of miRNA w.r.t to a cluster of pathways via inverse normal method

**Usage**

`aggInvFn(enriches, pathways, isSelector = TRUE, thresh = NULL)`

**Arguments**

- `enriches`: a table of miRNA pathway enrichments. Universe
- `pathways`: queried pathways. e.g. cluster pathways
- `isSelector`: internal argument
- `thresh`: internal argument

**Value**

a scoring of miRNAs in a cluster of pathways
aggLogCoverFn

*Internal function for modification of prioritization.*

**Description**
Internal function for modification of prioritization.

**Usage**

```r
aggLogCoverFn(selector, coverName)
```

**Arguments**
- `selector`: a prioritization table
- `coverName`: a new column name

**Value**
an updated scoring of miRNAs in a cluster of pathways

---

aggLogFn

*The function calculate targeting score of miRNA w.r.t to a cluster of pathways via log aggregation method.*

**Description**
The function calculate targeting score of miRNA w.r.t to a cluster of pathways via log aggregation method.

**Usage**

```r
aggLogFn(enriches, pathways, isSelector, thresh = 0)
```

**Arguments**
- `enriches`: a table of miRNA pathway enrichments. Universe
- `pathways`: queried pathways. e.g. cluster pathways
- `isSelector`: internal argument
- `thresh`: internal argument

**Value**
a scoring of miRNAs in a cluster of pathways
alignToUniverse

**Description**
function to align a list of sets and a reference universe

**Usage**
alignToUniverse(pathwaySets, universe)

**Arguments**
- pathwaySets: a list of sets
- universe: all set elements must be a subset of universe

**Value**
a list of sets, aligned to universe

---

clusterPlot

*Plots clusters of pathways with associated directionality.*

**Description**
Plots clusters of pathways with associated directionality.

**Usage**
clusterPlot(
  subNet,
  subplot = FALSE,
  topClusters = 2,
  prefix = "",
  outDir = ".",
  plotSave = TRUE
)

**Arguments**
- subNet: pathways network (edge list of pathways)
- subplot: if TRUE, store individual clusters plots and connected plots in Figures directory of plots
- topClusters: plot figures for top x clusters
- prefix: add prefix to plots
- outDir: output directory
- plotSave: saves the plot if set true. Otherwise display
differentialPathwayAnalysis

Value

a set of plots for DE-PCXN and subclusters

Examples

data(miniTestsPanomiR)
clusterPlot(miniTestsPanomiR$miniPathClusts$DE_PCXN, plotSave = FALSE)

differentialPathwayAnalysis

Differential Expression Analysis For Pathways

Description

Performs differential expression analysis for pathways using LIMMA package with gene counts

Usage

differentialPathwayAnalysis(
  geneCounts,
  pathways,
  covariates,
  condition,
  adjustCovars = NULL,
  covariateCorrection = FALSE,
  quantileNorm = FALSE,
  outDir = ".",
  saveOutName = NULL,
  id = "ENSEMBL",
  deGenes = NULL,
  minPathSize = 10,
  method = "x2",
  trim = 0.025,
  geneCountsLog = TRUE,
  contrastConds = NA
)

Arguments

geneCounts  Gene counts, rows refer to genes and columns to samples.
pathways    Pathways table, containing pathway names and genes with id specified.
covariates  Covariates/metadata file; rows matches the columns of geneCounts.
condition   Condition to be examined (tumor vs normal etc); must exist in covariates column.
adjustCovars Adjustment covariates like batch; if NULL, no adjustments performed.
enrichAllPairs

**Description**

Pairwise enrichment analysis between two given lists of sets

**Usage**

enrichAllPairs(mirSets, pathwaySets, pathsRef, numCores)
getDesignMatrix

**Arguments**

- `mirSets`  
a list of targets of miRNAs
- `pathwaySets`  
a list of pathways
- `pathsRef`  
universe of genes.
- `numCores`  
number of cores to calculate the results.

**Value**

enrichment analysis results

---

**getDesignMatrix**  
*Obtain Design Matrix*

---

**Description**

Modified from covariates pipeline of Menachem Former. Imported from [https://github.com/th1vairam/CovariateAnalysis](https://github.com/th1vairam/CovariateAnalysis)

**Usage**

```r
getDesignMatrix(covariatesDataFrame, intercept = TRUE, reLevels = list())
```

**Arguments**

- `covariatesDataFrame`  
Dataframe of covariates.
- `intercept`  
intercept in the linear model.
- `reLevels`  
TBA.

**Value**

List containing a design matrix.

**Examples**

```r
data(iris)
getDesignMatrix(iris)
```
getDiffExpTable

function to get a DE table

Description

function to get a DE table

Usage

getDiffExpTable(expMat, designMat, contrastsName)

Arguments

expMat an expression matrix
designMat a design Matrix
contrastsName the contrast to perform

Value

a table of differential expression

getResidual

function to get residuals with respect to a set of covariates

Description

function to get residuals with respect to a set of covariates

Usage

getResidual(covariates, adjustCovars, pathSumStats)

Arguments

covariates a covariate dataframe.
adjustCovars covariates to adjust for
pathSumStats an expression matrix

Value

a matrix of adjusted expression
gscExample       Example genesets from MSigDB

Description
Example genesets from MSigDB

Usage
data(gscExample)

Format
A GeneSet Collection object containing two genesets.

Source
http://www.gsea-msigdb.org/gsea/index.jsp

Examples
data(gscExample)

data(gscExample)

jackKnifeBase       Outputs a table with col x (miRNA), probability of observing k (depending on methodology) against a random distribution with jack-knifing of the pathway cluster (removing a pathway at a time)

Description
Outputs a table with col x (miRNA), probability of observing k (depending on methodology) against a random distribution with jack-knifing of the pathway cluster (removing a pathway at a time)

Usage
jackKnifeBase(
  selector,
  pathways,
  enrichNull,
  fn,
  jackKnifeData,
  m,
  numCores = 1
)
linColumnFinder

Arguments

selector Table with x(miRNA) in pathway cluster and observed k (depending on methodology).
pathways Pathways in pathway cluster.
enrichNull Enrichment dataset with x (miRNA), y (pathway) and pval (probability of observing x in pathway cluster).
fn Methodology function.
jackKnifeData Random distribution data with jack-knifing (i.e. one less pathway)
m method name
numCores number of cores

Value

Outputs a new selector table with col x, pval_jk

linColumnFinder(mat)

Arguments

mat an input design matrix.

Value

a list of independent columns

Examples

data("iris")
designMat <- getDesignMatrix(iris)
linColumnFinder(designMat$design)
mappingPathwaysClusters

Outputs a table with pathways and their respective clusters

Description

Outputs a table with pathways and their respective clusters

Usage

mappingPathwaysClusters(
  pcxn,  
dePathways,  
clusteringFunction = NULL,  
edgeFDR = 0.05,  
correlationCutOff = 0.316,  
pathwayFDR = 0.05,  
topPathways = 200,  
plotOut = TRUE,  
subplot = TRUE,  
topClusters = 2,  
prefix = "",  
outDir = ".",  
saveNameCSV = NULL,  
weighted = FALSE
)

Arguments

pcxn               pathways network (edge list of pathways)
dePathways         differential expressed pathways, obtained from *DifferentialPathwayAnalysis*
clusteringFunction clustering algorithm
dgeFDR             FDR threshold for pathway-pathway adjusted p-values; filter edges with adjusted p-values less than given threshold
correlationCutOff  cut-off threshold for pathway-pathway correlation; filter pathways with correlation less than given threshold
pathwayFDR         FDR threshold for DE pathways adjusted p-values; filter pathways with adjusted p-values less than given threshold
topPathways        use only top x paths; if NULL, use all paths
plotOut            if TRUE, store graph plot in Figures directory of plots
subplot            if TRUE, store individual clusters plots and connected plots in Figures directory of plots
methodProbBase

```r
topClusters  plot figures for top x clusters
prefix       add prefix to plots
outDir       output directory
saveNameCSV  if not NULL, saves output as csv using save name
weighted     True if you wish to include correlation weights in clustering
```

## Value

A list where the first item is a table with each row containing a pathway and its respective cluster. The second item is an igraph object.

## Examples

```r
data("miniTestsPanomiR")
mappingPathwaysClusters(pcxn = miniTestsPanomiR$miniPCXN,
dePathways = miniTestsPanomiR$miniDEP,
topPathways = 200,
outDir=".",
plot = FALSE,
subplot = FALSE,
prefix='',
clusteringFunction = "cluster_louvain",
correlationCutOff = 0.1)
```

## Description

Outputs a table with col x, miRNA, probability of observing k against a random distribution of the cover of methodology

## Usage

```r
methodProbBase(samplingData, selector, m, nPaths = 100, coverFn = NULL)
```

## Arguments

- `samplingData`: Random distribution data.
- `selector`: Table with x(miRNA) in pathway cluster and observed k (depending on methodology).
- `m`: Method name.
- `nPaths`: Number of pathways used to generate the samplingData at each iteration. Default is set at 100.
- `coverFn`: Cover of methodology function.
miniTestsPanomiR

**Value**

Outputs a new selector table with col x, pval and cover.

---

**Description**

The item miniEnrich is a reduced representation of the TargetScan For full table use miRNAPathwayEnrichment function in the package along with msigdb_c2 and targetScan_03 datasets.

**Usage**

```r
data(miniTestsPanomiR)
```

**Format**

A list of 5:

- `mini_LIHC_Exp` a reduced expression dataset from TCGA LIHC data
- `mini_LIHC_Cov` a reduced covariates dataset from TCGA LIHC data
- `miniEnrich` a reduced table of miRNA-pathway enrichment, TargetScan.
- `miniDEP` Differentially activated pathways from reduced TCGA LIHC
- `miniPCXN` reduced representation of PCXN network
- `miniPathClusts` miniDEP mapped to miniPCXN

**Details**

These datasets include reduced representation of TCGA LIHC data for reproducing the pipeline. doi: 10.1016/j.cell.2017.05.046

A reduced representation of PCxN is provided. For full dataset and method please refer to pcxn.org or https://doi.org/10.1371/journal.pcbi.1006042

**Examples**

```r
data(miniTestsPanomiR)
```
miRNAPathwayEnrichment

Enrichment Probability Of miRNAs

Description

Outputs enrichment probability of miRNAs based on pathway clusters.

Usage

miRNAPathwayEnrichment(
  mirSets,
  pathwaySets,
  geneSelection = NULL,
  mirSelection = NULL,
  fromID = "ENSEMBL",
  toID = "ENTREZID",
  minPathSize = 9,
  numCores = 1,
  outDir = ".",
  saveOutName = NULL
)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>mirSets</td>
<td>Table of miRNAs and a list of their interactions with genes in ENTREZ ID.</td>
</tr>
<tr>
<td>pathwaySets</td>
<td>Table of pathways and a list of their interactions with genes in ENTREZ ID.</td>
</tr>
<tr>
<td>geneSelection</td>
<td>Table of genes with dtype; if not NULL, select only genes from a given table.</td>
</tr>
<tr>
<td>mirSelection</td>
<td>Table of miRNA names; if not NULL, select only miRNAs from given table.</td>
</tr>
<tr>
<td>fromID</td>
<td>ID of genes in geneSelection.</td>
</tr>
<tr>
<td>toID</td>
<td>ID of genes used in pcxn and pathways set.</td>
</tr>
<tr>
<td>minPathSize</td>
<td>Filter out pathways with sets less than given value.</td>
</tr>
<tr>
<td>numCores</td>
<td>Number of CPU cores to use, must be at least one.</td>
</tr>
<tr>
<td>outDir</td>
<td>Output directory.</td>
</tr>
<tr>
<td>saveOutName</td>
<td>If not NULL, saves output as RDS using save name.</td>
</tr>
</tbody>
</table>

Value

Table of enrichment, each row contains mirna-pathway and its enrichment p-values.

Examples

data(msigdb_c2)
data(targetScan_03)
miRNAPathwayEnrichment(targetScan_03[1:20],msigdb_c2[1:20])
**msigdb_c2**

*Canonical pathways from Molecular Signatures Database, MsigDb V6.2*

**Description**
Canonical pathways from Molecular Signatures Database, MsigDb V6.2

**Usage**
```
data(msigdb_c2)
```

**Format**
A list of 1143 pathways

**Source**

**Examples**
```
data(msigdb_c2)
```

---

**pathwayGeneTab**

*Pathway-Gene Associations*

**Description**
Generates a table of pathways and genes associations.

**Usage**
```
pathwayGeneTab(
    pathAdress = NA,
    pathwayList = NA,
    fromType = "ENTREZID",
    toType = "ENSEMBL",
    outDir = NA
)
```
pathwaySummary

Arguments

pathAdres  Address to an RDS file containing list of pathways where each element is a list of genes similar to GMT format.
pathwayList  If you wish to use a list of pathways instead of a file use this argument instead. The list must contain no NA values.
fromType  gene annotation type used in your input data.
toType  gene annotation type to be produced in the output.
outDir  Address to save an RDS for a table of pathway-gene association

Value

pathExpTab  Table of pathway-gene association.

Examples

```
pathway1 <- c("125", "3099", "126")
pathway2 <- c("5232", "5230", "5162")
pathList <- list("Path1" = pathway1, "Path2" = pathway2)
res <- pathwayGeneTab(pathwayList = pathList)

data(msigdb_c2)
pathwayGeneTab(pathwayList = msigdb_c2[1:2])
```

pathwaySummary  Pathway Summary Statistics

Description

Generates a table of pathway activity profiles per sample

Usage

```
pathwaySummary(
  exprsMat,
  pathwayRef,
  id = "ENSEMBL",
  zNormalize = FALSE,
  method = FALSE,
  deGenes = NULL,
  trim = 0,
  tScores = NULL
)
```
Arguments

exprsMat  Gene expression matrix with row names as genes and samples as columns.
pathwayRef  Table of pathway-gene associations. Created from `pathwayGeneTab` function.
id  Gene annotation type in the row name of gene expression data.
zNormalize  Normalization of pathway summary score.
method  Choice of how to summarize gene ranks into pathway statistics.
deGenes  List of differentially expressed genes along with t-scores. Only necessary if working on Top 50% summary method.
trim  Percentage of top and bottom ranked genes to be excluded from pathway summary statistics.
tScores  Argument for-top-50-percent-genes method.

Value

`pathExp` Table of pathway activity profiles per sample.

Examples

```r
pathTab <- tibble::tribble(
  ~Pathway, ~ENTREZID, ~ENSEMBL,
  "Path1", "125", "ENSG00000196616",
  "Path1", "3099", "ENSG00000159399",
  "Path2", "5230", "ENSG00000102144",
  "Path2", "5162", "ENSG00000168291"
)
exprsMat <- matrix(2 * (seq_len(12)), 4, 3)
rownames(exprsMat) <- pathTab$ENSEMBL
colnames(exprsMat) <- LETTERS[seq_len(3)]
pathwaySummary(exprsMat, pathTab, method = "x2")
```

Description

A table of gene-pathway association. based on the pathways of MSigDB.

Usage

data(path_gene_table)
**pCutCoverFn**

**Format**
A matrix with 3 columns and 76926 rows:

- **Pathway**: An MSigDB annotated pathway
- **ENTREZID**: The ENTREZID of a gene belonging to the pathway
- **ENSEMBL**: The ENSEMBL of a gene belonging to the pathway

**Examples**

data(path_gene_table)

---

**pCutCoverFn**
Internal function for modification of prioritization.

**Description**
Internal function for modification of prioritization.

**Usage**
pCutCoverFn(selector, coverName)

**Arguments**
- selector: a prioritization table
- coverName: a new column name

**Value**
an updated scoring of miRNAs in a cluster of pathways

---

**pCutFn**
Score miRNAs In a Cluster Of Pathways

**Description**
The function to count the number of enriched pathways for each miRNA.

**Usage**
pCutFn(enriches, pathways, isSelector, thresh = 0.05)
Arguments

enriches     Table of miRNA pathway enrichments.
pathways     Queried pathways, e.g. cluster pathways.
isSelector   Internal argument.
thresh       Threshold from p-value cut-off.

Value

P-value based scoring of miRNAs in a cluster of pathways.

---

`pcxnToNet`

*Creates a network out of pcxn table*

Description

Creates a network out of pcxn table

Usage

`pcxnToNet(pcxn, edgeFDR, correlationCutOff, weighted)`

Arguments

`pcxn`     pathways network edge list of pathways
`edgeFDR`  FDR threshold for pathway-pathway adjusted p-values; filter edges with adjusted p-values less than given threshold
`correlationCutOff`  cut-off threshold for pathway-pathway correlation; filter pathways with correlation less than given threshold
`weighted`  True if you wish to include correlation weights in clustering

Value

enrichment analysis results
prioritizeMicroRNA

**Prioritize miRNA**

### Description
Outputs a table of miRNA ordered with respective p-values derived from method for prioritization

### Usage
```r
prioritizeMicroRNA(
    enriches0,
    pathClust,
    method = "AggInv",
    methodThresh = NULL,
    enrichmentFDR = 0.25,
    topClust = 2,
    sampRate = 1000,
    outDir = ".",
    dataDir = ".",
    saveSampling = TRUE,
    runJackKnife = TRUE,
    saveJackKnife = FALSE,
    numCores = 1,
    saveCSV = TRUE,
    prefix = "",
    autoSeed = TRUE
)
```

### Arguments
- **enriches0**: miRNA-pathway enrichment dataset obtained from miRNAPathwayEnrichment.
- **pathClust**: Pathway clusters, obtained from MappingPathwaysClusters.
- **method**: Vector of methods pCut, AggInv, AggLog, sumz, sumlog.
- **methodThresh**: Vector of methods threshold for each method in method, if NULL use default thresh values in method.
- **enrichmentFDR**: FDR cut-off calculating miRNA-pathway hits in the input cluster based on significant enrichment readouts.
- **topClust**: Top x clusters to perform miRNA prioritization on.
- **sampRate**: Sampling rate for CLT.
- **outDir**: Output directory.
- **dataDir**: Data directory.
- **saveSampling**: If TRUE, saves sampling data as RDS for each cluster in topClust in dataDir.
- **runJackKnife**: If TRUE, jacknifing will be performed.
reportEnrichment

saveJackKnife If TRUE, saves jack-knifed sampling data as RDS for each cluster in topClust in dataDir.

numCores Number of CPU cores to use, must be at least one.

saveCSV If TRUE, saves CSV file for each cluster in topClust in outDir.

prefix Prefix for all saved data.

autoSeed random permutations are generated based on predetermined seeds. TRUE will give identical results in different runs.

Value

Table of miRNA and p-values, each row contains a miRNA and its associated p-values from the methods.

Examples

data("miniTestsPanomiR")

prioritizeMicroRNA(enriches0 = miniTestsPanomiR$miniEnrich,
pathClust = miniTestsPanomiR$miniPathClusts$Clustering,
topClust = 1,
sampRate = 50,
method = c("aggInv"),
saveSampling = FALSE,
runJackKnife = FALSE,
numCores = 1,
saveCSV = FALSE)

---

reportEnrichment Publication-ready miRNA-Pathway Enrichment table

Description

This function summarizes the outputs

Usage

reportEnrichment(enrichmentTable)

Arguments

enrichmentTable

      Outputs from [miRNAPathwayEnrichment()] function

Value

A summarized miRNA-Pathway enrichment table
Examples

data(msigdb_c2)
data(targetScan_03)
eTab <- miRNAPathwayEnrichment(targetScan_03[1:20],msigdb_c2[1:20])

repTab <- reportEnrichment(eTab)

samplingDataBase

Outputs a table of sampling data(rows are miRNA and cols are samples)

Description

Outputs a table of sampling data(rows are miRNA and cols are samples)

Usage

samplingDataBase(
  enrichNull, selector, sampRate, fn, nPaths, samplingDataFile, jackKnife = FALSE, saveSampling, numCores = 1, autoSeed = TRUE
)

Arguments

enrichNull Enrichment dataset with x (miRNA), y (pathway) and pval (probability of observing x in pathway cluster).
selector Table with x(miRNA) in pathway cluster.
sampRate Sampling rate.
fn Methodology function.
nPaths Number of pathways in pathway cluster.
samplingDataFile If file exists, load. Else, perform random sampling
jackKnife If TRUE, conduct sampling with one less pathway, used for jack knifing
saveSampling If TRUE, data is saved.
numCores number of cores used
autoSeed random permutations are generated based on predetermined seeds. TRUE will give identical results in different runs.
sumlogCoverFn

Description

Internal function for modification of prioritization.

Usage

sumlogCoverFn(selector, coverName)

Arguments

selector a prioritization table
coverName a new column name

Value

an updated scoring of miRNAs in a cluster of pathways

sumlogFn

The function calculate targeting score of miRNA w.r.t to a cluster of pathways via sumlog aggregation method.

Description

The function calculate targeting score of miRNA w.r.t to a cluster of pathways via sumlog aggregation method.

Usage

sumlogFn(enriches, pathways, isSelector, thresh = NULL)

Arguments

enriches a table of miRNA pathway enrichments. Universe
pathways queried pathways. e.g. cluster pathways
isSelector internal argument
thresh internal argument

Value

a scoring of miRNAs in a cluster of pathways
sumzCoverFn

**Description**

Internal function for modification of prioritization.

**Usage**

```r
sumzCoverFn(selector, coverName)
```

**Arguments**

- `selector`  
  a prioritization table

- `coverName`  
  a new column name

**Value**

an updated scoring of miRNAs in a cluster of pathways

---

sumzFn

*The function calculate targeting score of miRNA w.r.t to a cluster of pathways via sumz aggregation method.*

**Description**

The function calculate targeting score of miRNA w.r.t to a cluster of pathways via sumz aggregation method.

**Usage**

```r
sumzFn(enriches, pathways, isSelector, thresh = NULL)
```

**Arguments**

- `enriches`  
  a table of miRNA pathway enrichments. Universe

- `pathways`  
  queried pathways. e.g. cluster pathways

- `isSelector`  
  internal argument

- `thresh`  
  internal argument

**Value**

a scoring of miRNAs in a cluster of pathways
**tableFromGSC**  
*Pathway-Gene Associations from GeneSet collections*

**Description**

This function enables to utilize MSigDB packages and GSEABase objects to incorporate customized genesets into PanomiR.

**Usage**

```r
tableFromGSC(gsCollection, fromType = "ENTREZID", toType = "ENSEMBL")
```

**Arguments**

- `gsCollection`: An GSEABase gene set collection object
- `fromType`: gene annotation type used in your input data
- `toType`: gene annotation type to be produced in the output

**Value**

A table of pathway-gene associations

**Examples**

```r
data(gscExample)
tableFromGSC(gscExample)
```

---

**targetScan_03**  
*A processed list of miRNA target gene sets from the TargetScan dataset. Each list item is a list of genes targeted by the respective miRNA family*

**Description**

The interactions are filtered to only human interactions.

**Usage**

```r
data(targetScan_03)
```

**Format**

A list of 439 items

**Details**

The interactions are filtered to have a Cumulative weighted context++ score of < -0.3
targetScan_03

Source

http://www.targetscan.org/vert_72/

Examples

data(targetScan_03)
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