Package ‘PanomiR’

May 16, 2024

Title  Detection of miRNAs that regulate interacting groups of pathways

Version  1.8.0

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.

License  MIT + file LICENSE

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)

URL  https://github.com/pouryany/PanomiR

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

VignetteBuilder  knitr

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**aggInvCoverFn**

*Internal function for modification of prioritization.*

**Description**

Internal function for modification of prioritization.

**Usage**

```r
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**

```r
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
**Description**

Internal function for modification of prioritization.

**Usage**

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

**Arguments**

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

**Value**

an updated scoring of miRNAs in a cluster of pathways

---

**Description**

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

**Usage**

```
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 function to align a list of sets and a reference universe

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/thlvairam/CovariateAnalysis](https://github.com/thlvairam/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)

---

**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

**Description**

Function imported from https://github.com/th1vairam/CovariateAnalysis
Modified from http://stackoverflow.com/questions/13088770/ Function to find linearly dependednt columns of a matrix

**Usage**

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**

```r
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
- `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
- `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
- `topClusters`: number of top clusters to return
- `prefix`: prefix for output file names
- `outDir`: output directory
- `saveNameCSV`: name of output CSV file
- `weighted`: if TRUE, use weighted network
methodProbBase

- **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)
```

**methodProbBase**

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

**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  

Readouts and datasets for minimal reproducible examples of the PanomiR.

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

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

data(miniTestsPanomiR)
miRNAPathwayEnrichment

Entenrichment 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

arg1 mirSets Table of miRNAs and a list of their interactions with genes in ENTREZ ID.
arg2 pathwaySets Table of pathways and a list of their interactions with genes in ENTREZ ID.
arg3 geneSelection Table of genes with dtype; if not NULL, select only genes from a given table.
arg4 mirSelection Table of miRNA names; if not NULL, select only miRNAs from given table.
arg5 fromID ID of genes in geneSelection.
arg6 toID ID of genes used in pcxn and pathways set.
arg7 minPathSize Filter out pathways with sets less than given value.
arg8 numCores Number of CPU cores to use, must be at least one.
arg9 outDir Output directory.
arg10 saveOutName If not NULL, saves output as RDS using save name.

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**

```r
data(msigdb_c2)
```

**Format**

A list of 1143 pathways

**Source**


**Examples**

```r
data(msigdb_c2)
```

### pathwayGeneTab

**Pathway-Gene Associations**

**Description**

Generates a table of pathways and genes associations.

**Usage**

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

Arguments

pathAdress 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
)
path_gene_table

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

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")

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

Description

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

Usage

data(path_gene_table)
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

```r
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.
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
samplingDataBase

Examples

```r
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**

```r
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

**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

Internal function for modification of prioritization.

Description
Internal function for modification of prioritization.

Usage
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
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**
```
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**
```
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**
```
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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