

# Package ‘PCAN’

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**Title** Phenotype Consensus ANalysis (PCAN)

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**Description** Phenotypes comparison based on a pathway consensus approach. Assess the relationship between candidate genes and a set of phenotypes based on additional genes related to the candidate (e.g. Pathways or network neighbors).

**biocViews** Annotation, Sequencing, Genetics, FunctionalPrediction, VariantAnnotation, Pathways, Network

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calcHpSim	<i>Compare HP terms based on semantic similarity</i>
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**Description**

This function compares 2 HP terms based on provided Information Content and ancestors

**Usage**

```
calcHpSim(term1, term2, method = c("Resnik"), IC, ancestors)
```

**Arguments**

term1	one of the HP term to compare
term2	the other HP term to compare
method	the method for computing semantic similarity (default: "Resnik" returns the IC of the MICA: Most Informative common ancestor)
IC	a named vector of Information Content by HP term
ancestors	a named list of ancestors by HP term

**Value**

A numeric value

**Author(s)**

Patrice Godard

**See Also**[compareHPSets](#)**Examples**

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

## Compute similarity between different couples of HP terms
data(hp_ancestors, hpDef, package="PCAN")
hp1 <- "HP:0000518"
hp2 <- "HP:0030084"
hp3 <- "HP:0002119"
hp4 <- "HP:0001305"
hpDef[which(hpDef$id %in% c(hp1, hp2)), 1:2]
calcHpSim(hp1, hp2, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp3)), 1:2]
calcHpSim(hp2, hp3, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp4)), 1:2]
calcHpSim(hp2, hp4, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp3, hp4)), 1:2]
calcHpSim(hp3, hp4, IC=ic, ancestors=hp_ancestors)
```

compareHPSets

*Compare 2 sets of HP terms based on semantic similarity***Description**

This function compares each couple of HP terms from each of the 2 provided sets based on Information Content (IC)

**Usage**

```
compareHPSets(hpSet1, hpSet2, IC, ancestors, method = "Resnik",
              BPPARAM = bpparam())
```

**Arguments**

hpSet1	a set of HP terms
hpSet2	another set of HP terms
IC	a named vector of Information Content by HP term
ancestors	a named list of ancestors by HP term

method	the method for computing semantic similarity among those available in <code>calcHpSim</code> (default: "Resnik" returns the IC of the MICA: Most Informative common ancestor)
BPPARAM	An optional <code>BiocParallelParam</code> instance defining the parallel back-end to be used during evaluation (used internally by the <code>bpmapply</code> function).

**Value**

A matrix of semantic similarity

**Author(s)**

Patrice Godard

**See Also**

[calcHpSim](#)

**Examples**

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPSets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
## Get the symmetric semantic similarity score
hpSetCompSummary(compMat, method="bma", direction="symSim")
bm <- hpSetCompBestMatch(compMat, "b")
hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]
## Assessing the significance of this score by comparing to all other genes
```

```

hpGeneResnik <- compareHPSets(
  hpSet1=names(ic), hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
hpMatByGene <- lapply(
  hpByGene,
  function(x){
    hpGeneResnik[x, , drop=FALSE]
  }
)
resnSss <- unlist(lapply(
  hpMatByGene,
  hpSetCompSummary,
  method="bma", direction="symSim"
))
candScore <- resnSss[entrez]
hist(
  resnSss,
  breaks=100, col="grey",
  ylim=c(0,300),
  xlab=expression(Sim[sym]),
  ylab="Number of genes",
  main=paste(
    "Distribution of symmetric semantic similarity scores\nfor all the",
    length(resnSss), "genes"
  )
)
polygon(
  x=c(candScore, 10, 10, candScore),
  y=c(-10, -10, 1000, 1000),
  border="#BE0000",
  col="#BE000080",
  lwd=3
)
withHigher <- sum(resnSss >= candScore)
text(
  x=candScore, y=mean(par())$usr[3:4],
  paste0(
    withHigher, " genes (",
    signif(withHigher*100/length(resnSss), 2), "%)\n",
    "show a symmetric semantic\n",
    "similarity score greater than\n",
    "the gene candidate for\n",
    "for the HPs under focus."
  ),
  pos=4,
  cex=0.6
)

```

---

computeHpIC	<i>Compute Information Content (IC) for each HP based on genes by HP</i>
-------------	--

---

### Description

Compute Information Content (IC) for each HP based on genes by HP

### Usage

```
computeHpIC(content, hp.descendants)
```

### Arguments

content            a list providing the content associated to each HP  
 hp.descendants    a list providing for each HP all its descendant HP terms

### Details

This function assumes that all the HP terms taken into account belong to the same family of terms(i.e they are all descendants of the same term).

### Value

a vector of IC named with HP terms

### Examples

```
#####
## Compute information content of each HP according to associated genes
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)
hist(
  ic,
  breaks=100, col="grey",
  main="Distribution of Information Content",
  xlab="IC base on genes associated to HP"
)
```

---

 geneByHp

*Entrez gene IDs associated to HP terms (Example data)*


---

## Description

Each entrez gene IDs is associated to one or several HP terms

## Format

A data frame with 67989 rows and 2 columns:

**entrez** entrez gene IDs

**hp** HP terms

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

Two ressources were used in May 27 2015:

- [ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease\\_2015-05.xml.gz](ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease_2015-05.xml.gz) was used to find genes associated to each OMIM disease with a "Pathogenic" clinical status and one of the following origins: "germline", "de novo", "inherited", "maternal", "paternal", "biparental", "uniparental".
- [http://compbio.charite.de/hudson/job/hpo.annotations/1039/artifact/misc/phenotype\\_annotation.tab](http://compbio.charite.de/hudson/job/hpo.annotations/1039/artifact/misc/phenotype_annotation.tab) was used to find HP associated to each OMIM disease.

## Examples

```
#####
## Compute information content of each HP according to associated genes
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)
hist(
  ic,
  breaks=100, col="grey",
  main="Distribution of Information Content",
  xlab="IC base on genes associated to HP"
)
```

---

 geneByTrait

*Gene associated to trait (Example data)*


---

## Description

Each trait is associated to one or several genes. Only genes associated to OMIM disease with a "Pathogenic" clinical status and one of the following origins: "germline", "de novo", "inherited", "maternal", "paternal", "biparental", "uniparental".

## Format

A data frame with 4569 rows and 3 columns:

**entrez** Entrez gene IDs.

**db** Trait database: always "OMIM" here.

**id** Trait ID: OMI IDs here

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

[ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease\\_2015-05.xml.gz](ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease_2015-05.xml.gz)

## Examples

```
data(geneByTrait, traitDef, geneDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
# Gene associated to this disease
entrez <- geneByTrait[which(geneByTrait$id==omim), "entrez"]
geneDef[which(geneDef$entrez %in% entrez),]
# All diseases associated to this gene
traitDef[
  which(
    traitDef$id %in%
    geneByTrait[which(geneByTrait$entrez==entrez), "id"]
  ),
]
```



---

geneDef	<i>Description of genes (Example data)</i>
---------	--

---

## Description

Basic information about genes Only genes associated to at least one OMIM disease are taken into account.

## Format

A data frame with 3265 rows and 3 columns:

**entrez** Entrez gene ID.

**name** Gene name.

**symbol** Gene symbol.

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

[ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease\\_2015-05.xml.gz](ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease_2015-05.xml.gz)

## Examples

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPSets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
```

```

    IC=ic,
    ancestors=hp_ancestors,
    method="Resnik",
    BPPARAM=SerialParam()
  )
  ## Get the symmetric semantic similarity score
  hpSetCompSummary(compMat, method="bma", direction="symSim")
  bm <- hpSetCompBestMatch(compMat, "b")
  hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]

```

---

hpByTrait

*HP IDs associated to trait (Example data)*

---

## Description

Each trait is associated to one or several HP terms.

## Format

A data frame with 55311 rows and 3 columns:

**hp** HP terms.

**db** Trait database: always "OMIM" here.

**id** Trait ID: OMI IDs here

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

[http://compbio.charite.de/hudson/job/hpo.annotations/1039/artifact/misc/phenotype\\_annotation.tab](http://compbio.charite.de/hudson/job/hpo.annotations/1039/artifact/misc/phenotype_annotation.tab)

## Examples

```

## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]

```

```
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPSets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
## Get the symmetric semantic similarity score
hpSetCompSummary(compMat, method="bma", direction="symSim")
bm <- hpSetCompBestMatch(compMat, "b")
hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]
```

---

hpDef

*Description of HP terms (Example data)*

---

## Description

HP terms basic information. Only descendants of 'Phenotypic abnormality' were taken into account.

## Format

A data frame with 10962 rows and 2 columns:

**id** HP term IDs

**name** HP term names

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

<http://compbio.charite.de/hudson/job/hpo/1529/artifact/hp/hp.obo>

**Examples**

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

## Compute similarity between different couples of HP terms
data(hp_ancestors, hpDef, package="PCAN")
hp1 <- "HP:0000518"
hp2 <- "HP:0030084"
hp3 <- "HP:0002119"
hp4 <- "HP:0001305"
hpDef[which(hpDef$id %in% c(hp1, hp2)), 1:2]
calcHpSim(hp1, hp2, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp3)), 1:2]
calcHpSim(hp2, hp3, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp4)), 1:2]
calcHpSim(hp2, hp4, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp3, hp4)), 1:2]
calcHpSim(hp3, hp4, IC=ic, ancestors=hp_ancestors)
```

---

hpGeneHeatmap

*HP to Gene heatmap*


---

**Description**

This function draw a heatmap corresponding to the result of the pathway consensus method. For each gene of the pathway under focus and each HP of interest it shows the best score.

**Usage**

```
hpGeneHeatmap(hpGeneListRes, genesOfInterest = NULL, geneLabels = NULL,
  hpLabels = NULL, clustByGene = TRUE, clustByHp = TRUE,
  palFun = colorRampPalette(c("white", "red")), goiCol = "blue", ...)
```

**Arguments**

**hpGeneListRes** the result of the [hpGeneListComp](#) function.

**genesOfInterest** a list of gene to highlight.

**geneLabels** a named vector of gene labels (all the genes id found in hpGeneListRes should be in names(geneLabels)).

**hpLabels** a named vector of HP labels (all the HP id found in hpGeneListRes should be in names(hpLabels)).

**clustByGene** should the heatmap be clustered according to genes (default: TRUE).

**clustByHp** should the heatmap be clustered according to HP (default: TRUE).

palFun            the palette function for the heatmap.  
 goiCol            the color used to highlight genes of interest.  
 ...                parameters for the `heatmap` function

### Value

A list of 2 matrix (invisible return):

**bmValues** For each gene and each HP of interest the best match value.

**bestMatches** The gene associated HP best matching the HP of interest.

### See Also

[hpGeneListComp](#), [hpSetCompBestMatch](#)

### Examples

```
data(geneByHp, hp_descendants, package="PCAN")
data(hp_ancestors, hpDef, package="PCAN")
data(traitDef, geneDef, package="PCAN")
data(hpByTrait, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)

#####
## Compute information content of each HP according to associated genes
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]
## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## HP Comparison
hpGeneResnik <- compareHPSets(
  hpSet1=names(ic), hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
hpMatByGene <- lapply(
  hpByGene,
  function(x){
    hpGeneResnik[x, , drop=FALSE]
  }
)
```

```

)
resnSss <- unlist(lapply(
  hpMatByGene,
  hpSetCompSummary,
  method="bma", direction="symSim"
))
candScore <- resnSss[entrez]

#####
## The pathway consensus approach
## What about genes belonging to the same pathways as the candidate
data(rPath, hsEntrezByRPath, package="PCAN")
candPath <- names(hsEntrezByRPath)[which(unlist(lapply(
  hsEntrezByRPath,
  function(x) entrez %in% x
)))]
rPath[which(rPath$Pathway %in% candPath),]
rPathRes <- hpGeneListComp(
  geneList=hsEntrezByRPath[[candPath]],
  ssMatByGene = hpMatByGene,
  geneSSScore = resnSss
)
hist(
  resnSss,
  breaks=100, col="grey",
  ylim=c(0,5),
  xlab=expression(Sim[sym]),
  ylab="Density",
  main=paste(
    "Distribution of symmetric semantic similarity scores for all the",
    length(resnSss), "genes"
  ),
  ),
  probability=TRUE
)
toAdd <- hist(
  rPathRes$scores,
  breaks=100,
  plot=FALSE
)
for(i in 1:length(toAdd$density)){
  polygon(
    x=toAdd$breaks[c(i, i+1, i+1, i)],
    y=c(0, 0, rep(toAdd$density[i], 2)),
    col="#BE00040",
    border="#80000FF"
  )
}
legend(
  "topright",
  paste0(
    "Genes belonging to the ", candPath, " pathway:\n'",
    rPath[which(rPath$Pathway %in% candPath),"Pathway_name"],
    "'\nand with a symmetric semantic similarity score ("

```

```

        sum(!is.na(rPathRes$scores)),
        "/" ,
        length(rPathRes$scores),
        ")\n",
        "p-value: ", signif(rPathRes$p.value, 2)
    ),
    pch=15,
    col="#BE0000",
    bty="n",
    cex=0.6
)
## Assessing the symmetric semantic similarity for each gene in the pathway
pathSss <- rPathRes$scores[which(!is.na(rPathRes$scores))]
names(pathSss) <- geneDef[match(names(pathSss), geneDef$entrez), "symbol"]
opar <- par(mar=c(7.1, 4.1, 4.1, 2.1))
barplot(
  sort(pathSss),
  las=2,
  ylab=expression(Sim[sym]),
  main=rPath[which(rPath$Pathway %in% candPath), "Pathway_name"]
)
p <- c(0.25, 0.5, 0.75, 0.95)
abline(
  h=quantile(resnSss, probs=p),
  col="#BE0000",
  lty=c(2, 1, 2, 2),
  lwd=c(2, 2, 2, 1)
)
text(
  rep(0,4),
  quantile(resnSss, probs=p),
  p,
  pos=3,
  offset=0,
  col="#BE0000",
  cex=0.6
)
legend(
  "topleft",
  paste0(
    "Quantiles of the distribution of symmetric semantic similarity\n",
    "scores for all the genes."
  ),
  lty=1,
  col="#BE0000",
  cex=0.6
)
par(opar)

## A heatmap showing the best HP match for each gene in the pathway
geneLabels <- geneDef$symbol[which(!duplicated(geneDef$entrez))]
names(geneLabels) <- geneDef$entrez[which(!duplicated(geneDef$entrez))]
hpLabels <- hpDef$name

```

```

names(hpLabels) <- hpDef$id
hpGeneHeatmap(
  rPathRes,
  genesOfInterest=entrez,
  geneLabels=geneLabels,
  hpLabels=hpLabels,
  clustByGene=TRUE,
  clustByHp=TRUE,
  palFun=colorRampPalette(c("white", "red")),
  goiCol="blue",
  main=rPath[which(rPath$Pathway %in% candPath),"Pathway_name"]
)

#####
## What about genes interacting with the candidate (including itself)
data(hqStrNw, package="PCAN")
neighbors <- unique(c(
  hqStrNw$gene1[which(hqStrNw$gene2==entrez)],
  hqStrNw$gene2[which(hqStrNw$gene1==entrez)],
  entrez
))
neighRes <- hpGeneListComp(
  geneList=neighbors,
  ssMatByGene = hpMatByGene,
  geneSSScore = resnSss
)
hist(
  resnSss,
  breaks=100, col="grey",
  ylim=c(0,10),
  xlab=expression(Sim[sym]),
  ylab="Density",
  main=paste(
    "Distribution of symmetric semantic similarity scores for all the",
    length(resnSss), "genes"
  ),
  probability=TRUE
)
toAdd <- hist(
  neighRes$scores,
  breaks=100,
  plot=FALSE
)
for(i in 1:length(toAdd$density)){
  polygon(
    x=toAdd$breaks[c(i, i+1, i+1, i)],
    y=c(0, 0, rep(toAdd$density[i], 2)),
    col="#BE00040",
    border="#80000FF"
  )
}
legend(
  "topright",

```



```

paste0(
  "Genes interacting with ",
  geneDef[which(geneDef$entrez==entrez),"symbol"],
  " (", entrez, ")",
  "\nand with a symmetric semantic similarity score (",
  sum(!is.na(neighRes$scores)),
  "/" ,
  length(neighRes$scores),
  ")\n",
  "p-value: ", signif(neighRes$p.value, 2)
),
pch=15,
col="#BE00040",
bty="n",
cex=0.6
)

## Assessing the symmetric semantic similarity score for each interacting gene
neighSss <- neighRes$scores[which(!is.na(neighRes$scores))]
names(neighSss) <- geneDef[match(names(neighSss), geneDef$entrez), "symbol"]
opar <- par(mar=c(7.1, 4.1, 4.1, 2.1))
barplot(
  sort(neighSss),
  las=2,
  ylab=expression(Sim[sym]),
  main=paste0(
    "Genes interacting with ",
    geneDef[which(geneDef$entrez==entrez),"symbol"],
    " (", entrez, ")",
  )
)
p <- c(0.25, 0.5, 0.75, 0.95)
abline(
  h=quantile(resnSss, probs=p),
  col="#BE0000",
  lty=c(2, 1, 2, 2),
  lwd=c(2, 2, 2, 1)
)
text(
  rep(0,4),
  quantile(resnSss, probs=p),
  p,
  pos=3,
  offset=0,
  col="#BE0000",
  cex=0.6
)
legend(
  "topleft",
  paste0(
    "Quantiles of the distribution of symmetric semantic similarity\n",
    "scores for all the genes."
  ),
),

```

```

    lty=1,
    col="#BE0000",
    cex=0.6
)
par(opar)

## A heatmap showing the best HP match for each neighbor gene
hpGeneHeatmap(
  neighRes,
  genesOfInterest=entrez,
  geneLabels=geneLabels,
  hpLabels=hpLabels,
  clustByGene=TRUE,
  clustByHp=TRUE,
  palFun=colorRampPalette(c("white", "red")),
  goiCol="blue",
  main=rPath[which(rPath$Pathway %in% candPath),"Pathway_name"]
)

```

---

hpGeneListComp

*HP semantic similarity for a whole gene list.*


---

## Description

This function compare a whole gene list to a set of HP terms using a matrix of semantic similarity.

## Usage

```
hpGeneListComp(geneList, ssMatByGene, geneSSScore = NULL, ...)
```

## Arguments

geneList	a vector providing the genes of interest.
ssMatByGene	a list (one element per gene) of matrix of semantic similarity between HP terms as returned by <a href="#">compareHPSets</a> . This list has to be unbiased in order to compute p-values.
geneSSScore	a vector of semantic similarity scores for all the genes in ssMatByGene list. If not provided these scores are computed from ssMatByGene.
...	parameters for <a href="#">hpSetCompSummary</a> if geneSSScore is not provided.

## Value

A list with the following elements:

**hpoi** The original HP of interest.

**allScoreDist** The distribution of scores for all genes for the HP of interest.

**scores** The semantic similarity by gene.

**best.matches** For each gene which related HP terms best fits with the HP of interest (colnames of the elements of ssMatByGene).

**median** The median of scores.

**p.value** According to a [wilcox.test](#) comparing genes of interest to all the other genes.

**best.gene** Gene with the highest score among the genes of interest.

**max** Maximum score.

**score.quantiles** Quantile of the scores compared to the whole list of gene.

**adj.quant** Adjusted quantiles according Benjamini Hochberg ( $\text{link}\{p.adjust\}$ ).

### Author(s)

Patrice Godard

### See Also

[hpGeneHeatmap](#), [compareHPsets](#), [hpSetCompSummary](#) and [hpSetCompBestMatch](#)

### Examples

```
data(geneByHp, hp_descendants, package="PCAN")
data(hp_ancestors, hpDef, package="PCAN")
data(traitDef, geneDef, package="PCAN")
data(hpByTrait, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)

#####
## Compute information content of each HP according to associated genes
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]
## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## HP Comparison
hpGeneResnik <- compareHPsets(
  hpSet1=names(ic), hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
hpMatByGene <- lapply(
  hpByGene,
```

```

    function(x){
      hpGeneResnik[x, , drop=FALSE]
    }
  )
resnSss <- unlist(lapply(
  hpMatByGene,
  hpSetCompSummary,
  method="bma", direction="symSim"
))
candScore <- resnSss[entrez]

#####
## The pathway consensus approach
## What about genes belonging to the same pathways as the candidate
data(rPath, hsEntrezByRPath, package="PCAN")
candPath <- names(hsEntrezByRPath)[which(unlist(lapply(
  hsEntrezByRPath,
  function(x) entrez %in% x
)))]
rPath[which(rPath$Pathway %in% candPath),]
rPathRes <- hpGeneListComp(
  geneList=hsEntrezByRPath[[candPath]],
  ssMatByGene = hpMatByGene,
  geneSSScore = resnSss
)
hist(
  resnSss,
  breaks=100, col="grey",
  ylim=c(0,5),
  xlab=expression(Sim[sym]),
  ylab="Density",
  main=paste(
    "Distribution of symmetric semantic similarity scores for all the",
    length(resnSss), "genes"
  ),
  probability=TRUE
)
toAdd <- hist(
  rPathRes$scores,
  breaks=100,
  plot=FALSE
)
for(i in 1:length(toAdd$density)){
  polygon(
    x=toAdd$breaks[c(i, i+1, i+1, i)],
    y=c(0, 0, rep(toAdd$density[i], 2)),
    col="#BE000040",
    border="#800000FF"
  )
}
legend(
  "topright",
  paste0(

```

```

        "Genes belonging to the ", candPath, " pathway:\n'",
        rPath[which(rPath$Pathway %in% candPath), "Pathway_name"],
        "\nand with a symmetric semantic similarity score (",
        sum(!is.na(rPathRes$scores)),
        "/",
        length(rPathRes$scores),
        ")\n",
        "p-value: ", signif(rPathRes$p.value, 2)
    ),
    pch=15,
    col="#BE0000",
    bty="n",
    cex=0.6
)
## Assessing the symmetric semantic similarity for each gene in the pathway
pathSss <- rPathRes$scores[which(!is.na(rPathRes$scores))]
names(pathSss) <- geneDef[match(names(pathSss), geneDef$entrez), "symbol"]
opar <- par(mar=c(7.1, 4.1, 4.1, 2.1))
barplot(
    sort(pathSss),
    las=2,
    ylab=expression(Sim[sym]),
    main=rPath[which(rPath$Pathway %in% candPath), "Pathway_name"]
)
p <- c(0.25, 0.5, 0.75, 0.95)
abline(
    h=quantile(resnSss, probs=p),
    col="#BE0000",
    lty=c(2, 1, 2, 2),
    lwd=c(2, 2, 2, 1)
)
text(
    rep(0,4),
    quantile(resnSss, probs=p),
    p,
    pos=3,
    offset=0,
    col="#BE0000",
    cex=0.6
)
legend(
    "topleft",
    paste0(
        "Quantiles of the distribution of symmetric semantic similarity\n",
        "scores for all the genes."
    ),
    lty=1,
    col="#BE0000",
    cex=0.6
)
par(opar)

## A heatmap showing the best HP match for each gene in the pathway

```

```

geneLabels <- geneDef$symbol[which(!duplicated(geneDef$entrez))]
names(geneLabels) <- geneDef$entrez[which(!duplicated(geneDef$entrez))]
hpLabels <- hpDef$name
names(hpLabels) <- hpDef$id
hpGeneHeatmap(
  rPathRes,
  genesOfInterest=entrez,
  geneLabels=geneLabels,
  hpLabels=hpLabels,
  clustByGene=TRUE,
  clustByHp=TRUE,
  palFun=colorRampPalette(c("white", "red")),
  goiCol="blue",
  main=rPath[which(rPath$Pathway %in% candPath),"Pathway_name"]
)

#####
## What about genes interacting with the candidate (including itself)
data(hqStrNw, package="PCAN")
neighbors <- unique(c(
  hqStrNw$gene1[which(hqStrNw$gene2==entrez)],
  hqStrNw$gene2[which(hqStrNw$gene1==entrez)],
  entrez
))
neighRes <- hpGeneListComp(
  geneList=neighbors,
  ssMatByGene = hpMatByGene,
  geneSSScore = resnSss
)
hist(
  resnSss,
  breaks=100, col="grey",
  ylim=c(0,10),
  xlab=expression(Sim[sym]),
  ylab="Density",
  main=paste(
    "Distribution of symmetric semantic similarity scores for all the",
    length(resnSss), "genes"
  ),
  probability=TRUE
)
toAdd <- hist(
  neighRes$scores,
  breaks=100,
  plot=FALSE
)
for(i in 1:length(toAdd$density)){
  polygon(
    x=toAdd$breaks[c(i, i+1, i+1, i)],
    y=c(0, 0, rep(toAdd$density[i], 2)),
    col="#BE00040",
    border="#80000FF"
  )
}

```

```

}
legend(
  "topright",
  paste0(
    "Genes interacting with ",
    geneDef[which(geneDef$entrez==entrez),"symbol"],
    " (", entrez, ")",
    "\nand with a symmetric semantic similarity score (",
    sum(!is.na(neighRes$scores)),
    " / ",
    length(neighRes$scores),
    ")\n",
    "p-value: ", signif(neighRes$p.value, 2)
  ),
  pch=15,
  col="#BE000040",
  bty="n",
  cex=0.6
)

## Assessing the symmetric semantic similarity score for each interacting gene
neighSss <- neighRes$scores[which(!is.na(neighRes$scores))]
names(neighSss) <- geneDef[match(names(neighSss), geneDef$entrez), "symbol"]
opar <- par(mar=c(7.1, 4.1, 4.1, 2.1))
barplot(
  sort(neighSss),
  las=2,
  ylab=expression(Sim[sym]),
  main=paste0(
    "Genes interacting with ",
    geneDef[which(geneDef$entrez==entrez),"symbol"],
    " (", entrez, ")"
  )
)
p <- c(0.25, 0.5, 0.75, 0.95)
abline(
  h=quantile(resnSss, probs=p),
  col="#BE0000",
  lty=c(2, 1, 2, 2),
  lwd=c(2, 2, 2, 1)
)
text(
  rep(0,4),
  quantile(resnSss, probs=p),
  p,
  pos=3,
  offset=0,
  col="#BE0000",
  cex=0.6
)
legend(
  "topleft",
  paste0(

```

```

        "Quantiles of the distribution of symmetric semantic similarity\n",
        "scores for all the genes."
    ),
    lty=1,
    col="#BE0000",
    cex=0.6
)
par(opar)

## A heatmap showing the best HP match for each neighbor gene
hpGeneHeatmap(
  neighRes,
  genesOfInterest=entrez,
  geneLabels=geneLabels,
  hpLabels=hpLabels,
  clustByGene=TRUE,
  clustByHp=TRUE,
  palFun=colorRampPalette(c("white", "red")),
  goiCol="blue",
  main=rPath[which(rPath$Pathway %in% candPath),"Pathway_name"]
)

```

---

hpSetCompBestMatch      *Best matches between two sets of HP terms*

---

### Description

This function returns the best matches from a semantic similarity matrix.

### Usage

```
hpSetCompBestMatch(hpSetComp, direction = c("b", "r", "c"))
```

### Arguments

hpSetComp	a matrix of semantic similarities between couples of HP terms
direction	taken into account. "r": best match per row. "c": best match per column. "b" (symetric): best match for the whole matrix

### Value

A data frame with the compared term, the best match and the value of the match.

### Author(s)

Patrice Godard

### See Also

[compareHPsets](#) and [hpSetCompSummary](#)



**Examples**

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPSets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
## Get the symmetric semantic similarity score
hpSetCompSummary(compMat, method="bma", direction="symSim")
bm <- hpSetCompBestMatch(compMat, "b")
hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]
```

---

hpSetCompSummary

*Global semantic similarity between 2 HP sets*


---

**Description**

This function summarize the comparison of 2 sets of HP terms

**Usage**

```
hpSetCompSummary(hpSetComp, method = c("bma", "bm", "average"),
  direction = c("symSim", "r", "c"))
```

**Arguments**

hpSetComp      a matrix of semantic similarities between couples of HP terms

method	"bma" (Best Match Average): the average of the best matches on rows or columns (see direction param). "bm": the maximum value. "average": the average of the whole matrix.
direction	taken into account only if method="bma". "r": best match per row. "c": best match per column. "symSim" (symmetric semantic similarity): average of calls with "r" and "c"

**Value**

A numeric value corresponding to the semantic similarity of the 2 HP sets

**Author(s)**

Patrice Godard

**See Also**

[compareHPSets](#)

**Examples**

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPSets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
  IC=ic,
  ancestors=hp_ancestors,
  method="Resnik",
  BPPARAM=SerialParam()
)
## Get the symmetric semantic similarity score
hpSetCompSummary(compMat, method="bma", direction="symSim")
bm <- hpSetCompBestMatch(compMat, "b")
hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]
```

---

hp_ancestors	<i>HP ancestors (Example data)</i>
--------------	------------------------------------

---

## Description

HP terms which are ancestors of each HP term (including itself) in the Human Phenotype Ontology (<http://www.human-phenotype-ontology.org/>). Only descendants of 'Phenotypic abnormality' were taken into account.

## Format

A named list of 10962 character vectors.

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

<http://compbio.charite.de/hudson/job/hpo/1529/artifact/hp/hp.obo>

## Examples

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

## Compute similarity between different couples of HP terms
data(hp_ancestors, hpDef, package="PCAN")
hp1 <- "HP:0000518"
hp2 <- "HP:0030084"
hp3 <- "HP:0002119"
hp4 <- "HP:0001305"
hpDef[which(hpDef$id %in% c(hp1, hp2)), 1:2]
calcHpSim(hp1, hp2, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp3)), 1:2]
calcHpSim(hp2, hp3, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp2, hp4)), 1:2]
calcHpSim(hp2, hp4, IC=ic, ancestors=hp_ancestors)
hpDef[which(hpDef$id %in% c(hp3, hp4)), 1:2]
calcHpSim(hp3, hp4, IC=ic, ancestors=hp_ancestors)
```

---

hp_class	<i>HP class (Example data)</i>
----------	--------------------------------

---

### Description

Each HP term can be of one or several classes. Classes are HP terms direct descendants of the 'Phenotypic abnormality' term.

### Format

A named list of 10962 character vectors.

### Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

### Source

<http://compbio.charite.de/hudson/job/hpo/1529/artifact/hp/hp.obo>

### Examples

```
data(hpDef, hp_class, package="PCAN")
hp <- "HP:0100089"
hpDef[which(hpDef$id==hp),]
# This term has 2 classes:
hpDef[which(hpDef$id %in% hp_class[[hp]]),]
```

---

hp_descendants	<i>HP descendants (Example data)</i>
----------------	--------------------------------------

---

### Description

HP terms which are descendants of each HP term (including itself) in the Human Phenotype Ontology (<http://www.human-phenotype-ontology.org/>). Only descendants of 'Phenotypic abnormality' were taken into account.

### Format

A named list of 10962 character vectors.

### Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

**Source**

<http://compbio.charite.de/hudson/job/hpo/1529/artifact/hp/hp.obo>

**Examples**

```
#####
## Compute information content of each HP according to associated genes
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)
hist(
  ic,
  breaks=100, col="grey",
  main="Distribution of Information Content",
  xlab="IC base on genes associated to HP"
)
```

---

hqStrNw

*STRIND database network of Homo sapiens genes (Example data)*

---

**Description**

A network of human entrez gene IDs taken from the STRING database.

**Format**

A data frame of 643683 and 3 columns:

**gene1** Entrez gene IDs.

**gene2** Entrez gene IDs.

**upstream** TRUE if the directionality of the interaction between the 2 genes is known. In this case gene1 is upstream gene 2.

**Source**

Different resources were used in June 2 2015:

- [http://string-db.org/newstring\\_download/protein.actions.v10/9606.protein.actions.v10.txt.gz](http://string-db.org/newstring_download/protein.actions.v10/9606.protein.actions.v10.txt.gz) was used to get the network of Ensembl protein IDs. Only interaction with a score greater or equal to 500 were kept.
- BioMart from <http://jan2013.archive.ensembl.org/index.html> was used to map Ensembl protein IDs to Ensembl gene IDs. Ensembl gene IDs were mapped to Entrez gene IDs using this resource in addition to <ftp://ftp.ncbi.nih.gov/gene/DATA/gene2ensembl.gz>

**Examples**

```
## Not run: example(hpGeneListComp)
```

---

hsEntrezByRPath	<i>Homo sapiens entrez gene ID by Reactome pathway (Example data)</i>
-----------------	---

---

**Description**

The human genes coding for proteins involved in the different Reactome pathways.

**Format**

A named list of 1345 character vectors.

**Source**

Two resources were used in June 2 2015:

- <http://www.reactome.org/download/current/UniProt2Reactome.txt> was used to get list of Uniprot ID associated to each pathway.
- [ftp://ftp.uniprot.org/pub/databases/uniprot/current\\_release/knowledgebase/idmapping/by\\_organism/HUMAN\\_9606\\_idmapping.dat.gz](ftp://ftp.uniprot.org/pub/databases/uniprot/current_release/knowledgebase/idmapping/by_organism/HUMAN_9606_idmapping.dat.gz) was used to map Uniprot ID to Entrez gene IDs

**Examples**

```
## Not run: example(hpGeneListComp)
```

---

rPath	<i>Reactome pathways (Example data)</i>
-------	---

---

**Description**

Pathways taken from the Reactome database.

**Format**

A data frame with 1345 rows and 2 columns:

**Pathway** Reactome ID.

**Pathway\_name** The name of the pathway.

**Source**

<http://www.reactome.org/download/current/UniProt2Reactome.txt>

**Examples**

```
## Not run: example(hpGeneListComp)
```

---

traitDef	<i>Description of Traits (Example data)</i>
----------	---

---

## Description

Basic information about traits. Only OMIM diseases associated to at least one gene are taken into account.

## Format

A data frame with 3675 rows and 3 columns:

**db** Always "OMIM" here.

**id** The trait ID (OMIM IDs here).

**name** The name of the trait.

## Details

These data are used to exemplify the different functions of the package. More data are available in the MultiHumanPhenoDB package.

## Source

[ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease\\_2015-05.xml.gz](ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/xml/ClinVarFullRelease_2015-05.xml.gz)

## Examples

```
## Prerequisite
data(geneByHp, hp_descendants, package="PCAN")
geneByHp <- unstack(geneByHp, entrez~hp)
ic <- computeHpIC(geneByHp, hp_descendants)

#####
## Use case: comparing a gene and a disease
data(traitDef, geneDef, hp_ancestors, hpDef, package="PCAN")
omim <- "612285"
traitDef[which(traitDef$id==omim),]
entrez <- "57545"
geneDef[which(geneDef$entrez==entrez),]
## Get HP terms associated to the disease
data(hpByTrait, package="PCAN")
hpOfInterest <- hpByTrait$hp[which(hpByTrait$id==omim)]

## Get HP terms associated to the gene
hpByGene <- unstack(stack(geneByHp), ind~values)
geneHps <- hpByGene[[entrez]]
## Comparison of the two sets of HP terms
compMat <- compareHPsets(
  hpSet1=geneHps, hpSet2=hpOfInterest,
```

```
    IC=ic,
    ancestors=hp_ancestors,
    method="Resnik",
    BPPARAM=SerialParam()
)
## Get the symmetric semantic similarity score
hpSetCompSummary(compMat, method="bma", direction="symSim")
bm <- hpSetCompBestMatch(compMat, "b")
hpDef[match(c(bm$compared, bm$candidate), hpDef$id),]
```



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