

Package ‘ABAEnrichment’

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Type Package

Title Gene expression enrichment in human brain regions

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Description The package ABAEnrichment is designed to test for enrichment of user defined candidate genes in the set of expressed genes in different human brain regions. The core function 'aba_enrich' integrates the expression of the candidate gene set (averaged across donors) and the structural information of the brain using an ontology, both provided by the Allen Brain Atlas project. 'aba_enrich' interfaces the ontology enrichment software FUNC to perform the statistical analyses. Additional functions provided in this package like 'get_expression' and 'plot_expression' facilitate exploring the expression data. From version 1.3.5 onwards genomic regions can be provided as input, too; and from version 1.5.9 onwards the function 'get_annotated_genes' offers an easy way to obtain annotations of genes to enriched or user-defined brain regions.

License GPL (>= 2)

Imports Rcpp (>= 0.11.5), gplots (>= 2.14.2), gtools (>= 3.5.0), ABAData (>= 0.99.2), data.table (>= 1.10.4), grDevices, stats, utils

Depends R (>= 3.4)

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aba_enrich	<i>Test genes for expression enrichment in human brain regions</i>
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Description

Tests for enrichment of user defined candidate genes in the set of expressed protein-coding genes in different human brain regions. It integrates the expression of the candidate gene set (averaged across donors) and the structural information of the brain using an ontology, both provided by the Allen Brain Atlas project [1-4]. The statistical analysis is performed using the ontology enrichment software FUNC [5].

Usage

```
aba_enrich(genes, dataset = 'adult', test = 'hyper',
           cutoff_quantiles = seq(0.1, 0.9, 0.1), n_randsets = 1000,
           gene_len = FALSE, circ_chrom = FALSE, ref_genome = 'grch37', silent = FALSE)
```

Arguments

genes	A dataframe with gene-identifiers (Entrez-ID, Ensembl-ID or gene-symbol) in the first column and test-dependent additional columns: If test='hyper' (default) a second column with 1 for candidate genes and 0 for background genes. If no background genes are defined, all remaining protein coding genes are used as background. If test='wilcoxon' a second column with the score that is associated with each gene. If test='binomial' two additional columns with two gene-associated integers. If test='contingency' four additional columns with four gene-associated integers. For test='hyper' the first column can also describe chromosomal regions ('chr:start-stop', e.g. '9:0-39200000').
dataset	'adult' for the microarray dataset of adult human brains; '5_stages' for RNA-seq expression data for different stages of the developing human brain, grouped into 5 developmental stages; 'dev_effect' for a developmental effect score. For details see <code>browseVignettes("ABADData")</code> .
test	'hyper' (default) for the hypergeometric test, 'wilcoxon' for the Wilcoxon rank test, 'binomial' for the binomial test and 'contingency' for the 2x2-contingency table test (fisher's exact test or chi-square).

cutoff_quantiles	the FUNC enrichment analyses will be performed for the sets of expressed genes at given expression quantiles defined in this vector [0,1].
n_randsets	integer defining the number of random sets created to compute the FWER.
gene_len	logical. If test='hyper' the probability of a background gene to be chosen as a candidate gene in a random set is dependent on the gene length.
circ_chrom	logical. When genes defines chromosomal regions, circ_chrom=TRUE uses background regions from the same chromosome and allows randomly chosen blocks to overlap multiple background regions. Only if test='hyper'.
ref_genome	'grch37' (default) or 'grch38'. Defines the reference genome used when genomic regions are provided as input or when gene_len=TRUE.
silent	logical. If TRUE all output to the screen except for warnings and errors is suppressed.

Details

For details please refer to `browseVignettes("ABAEnrichment")`.

Value

A list with components

results	a dataframe with the FWERs from the enrichment analyses per brain region and age category, ordered by 'age_category', 'n_significant', 'min_FWER' and 'mean_FWER'. 'min_FWER' for example denotes the minimum FWER for expression enrichment of the candidate genes in this brain region across all expression cutoffs. 'n_significant' reports the number of cutoffs at which the FWER was below 0.05. 'FWERs' is a semicolon separated string with the single FWERs for all cutoffs. 'equivalent_structures' is a semicolon separated string that lists structures with identical expression data due to lack of independent expression measurements in all regions.
genes	a dataframe of the input genes, excluding those genes for which no expression data is available and which therefore were not included in the enrichment analysis.
cutoffs	a dataframe with the expression values that correspond to the requested cutoff quantiles.

Author(s)

Steffi Grote

References

- [1] Hawrylycz, M.J. et al. (2012) An anatomically comprehensive atlas of the adult human brain transcriptome, Nature 489: 391-399. doi: [10.1038/nature11405](https://doi.org/10.1038/nature11405)
- [2] Miller, J.A. et al. (2014) Transcriptional landscape of the prenatal human brain, Nature 508: 199-206. doi: [10.1038/nature13185](https://doi.org/10.1038/nature13185)
- [3] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [4] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>
- [5] Pruefer, K. et al. (2007) FUNC: A package for detecting significant associations between gene sets and ontological, BMC Bioinformatics 8: 41. doi: [10.1186/14712105841](https://doi.org/10.1186/14712105841)

See Also

```

browseVignettes("ABAEnrichment")
browseVignettes("ABADData")
get_expression
plot_expression
get_name
get_id
get_sampled_substructures
get_superstructures
get_annotated_genes

```

Examples

```

#### Note that arguments 'cutoff_quantiles' and 'n_randsets' are reduced
#### to lower computational time in the examples.
#### Using the default values is recommended.

#### Perform an enrichment analysis for the developing brain
#### with defined background genes
#### and with random sets dependent on gene length
gene_ids = c('PENK', 'COCH', 'PDYN', 'CA12', 'SYNDIG1L', 'MME',
             'AN03', 'KCNJ6', 'ELAVL4', 'BEAN1', 'PVALB', 'EPN3', 'PAX2', 'FAB12')
is_candidate = rep(c(1,0),each=7)
genes = data.frame(gene_ids, is_candidate)
res = aba_enrich(genes, dataset='5_stages', cutoff_quantiles=c(0.5,0.9),
                n_randsets=100, gene_len=TRUE)
## see results for the brain regions with highest enrichment
## for children (age_category 3)
fwers = res[[1]]
head(fwers[fwers$age_category==3,])
## see the input genes dataframe (only genes with expression data available)
res[2]
## see the expression values that correspond to the requested cutoff quantiles
res[3]

# For more examples please refer to the package vignette.

```

get_annotated_genes *Get genes that are expressed in enriched or user-defined brain regions*

Description

Uses an object returned from `aba_enrich` as input and returns the brain regions that are significantly (given a FWER-threshold) enriched in expressed candidate genes (or genes with high scores if `test='wilcoxon'` in `aba_enrich`) together with the genes that are expressed in those brain regions (i.e. are 'annotated' to the brain regions). Alternatively, also user-defined brain regions, dataset and expression cutoffs can be used as input.

Usage

```
get_annotated_genes(res, fwer_threshold = 0.05, background = FALSE,
                    structure_ids = NULL, dataset = NULL, cutoff_quantiles = NULL, genes = NULL)
```

Arguments

<code>res</code>	an object returned from aba_enrich (list of 3 elements). If not defined, <code>structure_ids</code> , <code>dataset</code> and <code>cutoff_quantiles</code> have to be specified.
<code>fwer_threshold</code>	numeric defining the FWER-threshold. Given <code>res</code> as input, <code>get_annotated_genes</code> extracts all brain-region/expression-cutoff combinations from <code>res</code> that have a $\text{FWER} < \text{fwer_threshold}$ and adds the (candidate) genes that are annotated to those brain regions at the given expression cutoffs.
<code>background</code>	logical indicating whether background genes should be included. Only used when <code>res</code> is defined and contains the results from a hypergeometric test (which is the default in aba_enrich).
<code>structure_ids</code>	vector of brain structure IDs, e.g. 'Allen:10208'. If <code>res</code> is not defined, <code>structure_ids</code> specifies the brain regions for which annotated genes at the given <code>cutoff_quantiles</code> will be returned.
<code>dataset</code>	'adult' for the microarray dataset of adult human brains; '5_stages' for RNA-seq expression data of the developing human brain, grouped into 5 developmental stages; 'dev_effect' for a developmental effect score. Only used when <code>res</code> is not defined.
<code>cutoff_quantiles</code>	vector of numeric values between 0 and 1. They define the expression quantiles (across all genes) which are used as cutoffs to decide whether a gene counts as expressed (and gets annotated to a brain region) or not. Only used when <code>res</code> is not defined.
<code>genes</code>	optional vector of gene identifiers, either Entrez-ID, Ensembl-ID or gene-symbol. If defined, only annotations of those genes are returned. If not defined, all expressed genes from Allen Brain Atlas are returned. Only used when <code>res</code> is not defined.

Details

Genes get annotated to a brain region when their expression value in that brain region, which is provided by the Allen Brain Atlas, exceeds a certain cutoff. Multiple cutoffs can be used. They are defined as quantiles of gene expression across all genes and brain regions. An expression cutoff of e.g. 0.8 means that only genes with expression levels higher than 80% of all measured values count as 'expressed' and get annotated to the corresponding brain region. Note that those annotations are inherited by all superstructures (parent nodes).

When the 'dev_effect' dataset is used as `dataset`-argument, the expression value is replaced by a measure of how much a gene's expression changes during the development (prenatal to adult). Genes with a developmental score higher than the cutoff then get annotated to the brain regions.

Value

A data frame with the age category, the brain region ID, the expression cutoff quantile and the annotated genes for significantly enriched or user-defined brain-region/expression-cutoff combinations. If `res` was given as input, two additional columns are added: the FWER and the score which was used for the genes in the [aba_enrich](#) input (1/0 for candidate and background genes for the hypergeometric test or scores for the wilcoxon rank sum test). Given `res` as input, the output is ordered

by the FWER, else it is ordered by the expression cutoff.

Author(s)

Steffi Grote

References

- [1] Hawrylycz, M.J. et al. (2012) An anatomically comprehensive atlas of the adult human brain transcriptome, Nature 489: 391-399. doi: [10.1038/nature11405](https://doi.org/10.1038/nature11405)
- [2] Miller, J.A. et al. (2014) Transcriptional landscape of the prenatal human brain, Nature 508: 199-206. doi: [10.1038/nature13185](https://doi.org/10.1038/nature13185)
- [3] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [4] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

```
browseVignettes("ABAEnrichment")
browseVignettes("ABADData")
aba_enrich
get_name
get_id
```

Examples

```
#### Note that arguments 'cutoff_quantiles' and 'n_randsets' are reduced
#### to lower computational time in the examples.

## perform an enrichment analysis
## for expression of 7 candidate and 7 background genes
## and get candidate genes annotated to brain regions that have a FWER < 0.05
set.seed(123)
gene_ids = c('PENK', 'COCH', 'PDYN', 'CA12', 'SYNDIG1L', 'MME',
             'AN03', 'KCNJ6', 'ELAVL4', 'BEAN1', 'PVALB', 'EPN3', 'PAX2', 'FAB12')
is_candidate = rep(c(1,0), each=7)
genes = data.frame(gene_ids, is_candidate)
res = aba_enrich(genes, dataset='5_stages', cutoff_quantiles=c(0.3,0.5,0.7,0.9),
                n_randset=100)
anno = get_annotated_genes(res, fwer_threshold=0.05)
head(anno)

## find out which of the above genes have expression above
## the 50% and 70% expression-cutoff, respectively,
## in the Cerebellar Cortex of the developing human brain (Allen:10657)
get_annotated_genes(structure_ids="Allen:10657", dataset="5_stages",
                    cutoff_quantiles=c(0.5,0.7), genes=gene_ids)
```

`get_expression`*Get expression data for given genes and brain structure IDs*

Description

Expression data obtained from the Allen Brain Atlas project [1-4].

Usage

```
get_expression(structure_ids, gene_ids = NA, dataset = NA, background = FALSE)
```

Arguments

- | | |
|----------------------------|---|
| <code>structure_ids</code> | vector of brain structure IDs, e.g. 'Allen:10208'. |
| <code>gene_ids</code> | vector of gene identifiers, either Entrez-ID, Ensembl-ID or gene-symbol. If not defined, genes from previous enrichment analysis with aba_enrich are used. |
| <code>dataset</code> | 'adult' for the microarray dataset of adult human brains; '5_stages' for RNA-seq expression data of the developing human brain, grouped into 5 developmental stages; 'dev_effect' for a developmental effect score. If not defined, dataset from last enrichment analysis with aba_enrich are used. |
| <code>background</code> | logical indicating whether expression from background genes should be included. Only used when <code>gene_ids</code> and <code>dataset</code> are NA and test from preceding aba_enrich call is 'hyper'. |

Details

Get gene expression in defined brain regions from adult or developing humans, or a developmental effect score for the developing human brain. Expression data is obtained from the Allen Brain Atlas project [1-4], averaged across donors, and for the developing human brain divided into five major age categories. The developmental effect score is based on expression data of the developing human brain. If `gene_ids` and `dataset` are not specified, the genes and dataset from the last enrichment analysis with [aba_enrich](#) are used, since it may be a common case to first run the enrichment analysis and then look at the expression data. If a requested brain region has no expression data annotated, data from sampled substructures of this region is returned.

Please refer to the `ABADa` package vignette for details on the datasets.

Value

A matrix with expression values or developmental effect scores per brain region (rows) and gene (columns).

For expression data from the developing human brain ('5_stages') it is a list with an expression matrix for each of the 5 developmental stages.

Author(s)

Steffi Grote

References

- [1] Hawrylycz, M.J. et al. (2012) An anatomically comprehensive atlas of the adult human brain transcriptome, Nature 489: 391-399. doi: [10.1038/nature11405](https://doi.org/10.1038/nature11405)
- [2] Miller, J.A. et al. (2014) Transcriptional landscape of the prenatal human brain, Nature 508: 199-206. doi: [10.1038/nature13185](https://doi.org/10.1038/nature13185)
- [3] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [4] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

```
browseVignettes("ABAEnrichment")
browseVignettes("ABADData")
plot_expression
aba_enrich
get_name
get_id
get_sampled_substructures
get_annotated_genes
```

Examples

```
## get expression data of six genes in two brain regions
## from the developing human brain,
## each of the five list elements corresponds to an age category
get_expression(structure_ids=c('Allen:10657', 'Allen:10208'),
  gene_ids=c('ENSG00000168036', 'ENSG00000157764', 'ENSG00000182158',
    'ENSG00000147889'), dataset='5_stages')

## see the package vignette for more examples
```

get_id

Get the structure ID of a brain region given its name

Description

Returns brain regions given (part of) their name, together with their structure IDs from the ontologies for the adult and for the developing brain (e.g. 'Allen:10657' as used throughout the ABAEnrichment package).

Usage

```
get_id(structure_name)
```

Arguments

structure_name (partial) name of a brain structure, e.g. 'telencephalon'

Value

a data frame with the full names of the brain structures that contain structure_name; together with the ontology ('developmental' or 'adult') and the structure IDs.

Author(s)

Steffi Grote

References

[1] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>

[2] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

[get_name](#)
[get_sampled_substructures](#)
[get_superstructures](#)
`browseVignettes("ABADData")`

Examples

```
## get structure IDs of brain regions that contain 'accumbens' in their names
get_id('accumbens')
## get structure IDs of brain regions that contain 'telencephalon' in their name
get_id('telencephalon')
## get all brain regions that have direct or indirect expression data
all_regions = get_id('')
head(all_regions)
```

get_name

Get the full name of a brain region given structure IDs

Description

Returns the full name of brain regions given the structure IDs, e.g. 'Allen:10657' as used throughout the ABAEnrichment package. The full name is composed of an acronym and the name as used by the Allen Brain Atlas project [1-2].

Usage

```
get_name(structure_ids)
```

Arguments

structure_ids a vector of brain structure IDs, e.g. c('Allen:10657','Allen:10173') or c(10657,10173)

Value

vector of the full names of the brain structures; composed of acronym, underscore and name.

Note

The acronym is added because the names alone are not unique.

Author(s)

Steffi Grote

References

- [1] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [2] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

[get_id](#)
[get_sampled_substructures](#)
[get_superstructures](#)

Examples

```
## get the full names of the brain structures 'Allen:10657' and 'Allen:10225'  
get_name(c('Allen:10657', 'Allen:10225'))
```

get_sampled_substructures

Return sampled substructures of a given brain region

Description

The function returns for a given brain structure ID all its substructures with available expression data, potentially including the structure itself.

Usage

```
get_sampled_substructures(structure_id)
```

Arguments

structure_id a brain structure ID, e.g. 'Allen:10657' or '10657'

Details

The ontology enrichment analysis in [aba_enrich](#) tests all brain regions for which data is available, although the region might not have been sampled directly. In this case the region inherits the expression data from its substructures with available expression data. The function `get_sampled_substructures` helps to explore where the expression data for a brain region came from.

Value

vector of brain structure IDs that contains all substructures of the requested brain region that were sampled.

Author(s)

Steffi Grote

References

- [1] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [2] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

`browseVignettes("ABAEnrichment")`
`browseVignettes("ABAData")`
[aba_enrich](#)
[get_name](#)
[get_superstructures](#)

Examples

```
## get the brain structures from which the brain structures
## 'Allen:4010' and 'Allen:10208' inherit their expression data
get_sampled_substructures('Allen:4010')
get_sampled_substructures('Allen:10208')
```

`get_superstructures` *Returns all superstructures of a brain region using the Allen Brain Atlas ontology*

Description

Returns all superstructures of a brain region and the brain region itself given a structure ID, e.g. 'Allen:10657' as used throughout the ABAEnrichment package. The output vector contains the superstructures according to the hierarchy provided by the Allen Brain Atlas ontology [1,2] beginning with the root ('brain' or 'neural plate') and ending with the requested brain region.

Usage

```
get_superstructures(structure_id)
```

Arguments

`structure_id` a brain structure ID, e.g. 'Allen:10657' or '10657'

Value

vector of brain structure IDs that contains all superstructures of the requested brain region and the brain region itself. The order of the brain regions follows the hierarchical organization of the brain.

Note

The ontologies for the adult and the developing human brain are different.

Author(s)

Steffi Grote

References

- [1] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [2] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

[get_name](#)
[get_id](#)
[get_sampled_substructures](#)

Examples

```
## Get the IDs of the superstructures of the precentral gyrus
## (adult brain ontology)
get_superstructures('Allen:4010')

## Get the IDs and the names of the superstructures
## of the dorsolateral prefrontal cortex
## (developing brain ontology)
data.frame(superstructure=get_name(get_superstructures("Allen:10173")))
```

plot_expression

Plot expression data for given genes and brain structure IDs

Description

The function produces a heatmap ([heatmap.2](#) from package `gplots`) of gene expression in defined brain regions from adult or developing humans, or a developmental effect score for the developing human brain. Expression data is obtained from the Allen Brain Atlas project [1-4], averaged across donors, and for the developing human brain divided into five major age categories. If `gene_ids` and `dataset` are not specified, the genes and dataset from the last enrichment analysis with [aba_enrich](#) are used, since it may be a common case to first run the enrichment analysis and then look at the expression data. If a requested brain region has no expression data annotated, data from sampled substructures of this region is returned.

Usage

```
plot_expression(structure_ids, gene_ids = NA, dataset = NA, background = FALSE,
               dendro = TRUE, age_category = 1)
```

Arguments

structure_ids	vector of brain structure ids, e.g. "Allen:10208".
gene_ids	vector of gene identifiers, either Entrez-ID, Ensembl-ID or gene-symbol. If not defined, genes from previous enrichment analysis with aba_enrich are used.
dataset	'adult' for the microarray dataset of adult human brains; '5_stages' for RNA-seq expression data of the developing human brain, grouped into 5 developmental stages; 'dev_effect' for a developmental effect score. If not defined, dataset from last enrichment analysis with aba_enrich are used.
background	logical indicating whether expression from background genes should be included. Only used when gene_ids and dataset are NA so that genes from the last enrichment analysis with aba_enrich are used and when this analysis was performed using the hypergeometric test.
dendro	logical indicating whether rows and columns should be rearranged with a dendrogram based on row/column means (using hclust). If FALSE and if gene_ids and dataset are NA so that genes from the last enrichment analysis with aba_enrich are used, a side bar indicates the gene-associated variables from the enrichment analysis: for a hypergeometric test the genes are grouped into candidate (red) and background genes (black); for the Wilcoxon rank-sum test, the side bar indicates the user-defined scores; for the binomial test the side bar shows $*A/(A+B)*$ and for the 2x2 contingency table test $*((A+1)/(B+1)) / ((C+1)/(D+1))*$ (+1 added to prevent division by 0, this is just a visual indication of the proportion of the ratios and not the real odds ratio from the 2x2 contingency table test)
age_category	an integer between 1 and 5 indicating the age category if dataset='5_stages'.

Value

Invisibly, a list with components

rowInd	row index permutation vector as returned by order.dendrogram
colInd	column index permutation vector.
call	the matched call
carpet	reordered 'x' values used to generate the main 'carpet'
rowDendrogram	row dendrogram, if present
colDendrogram	column dendrogram, if present
breaks	values used for color break points
col	colors used
colorTable	A three-column data frame providing the lower and upper bound and color for each bin

Author(s)

Steffi Grote

References

- [1] Hawrylycz, M.J. et al. (2012) An anatomically comprehensive atlas of the adult human brain transcriptome, Nature 489: 391-399. doi: [10.1038/nature11405](https://doi.org/10.1038/nature11405)
- [2] Miller, J.A. et al. (2014) Transcriptional landscape of the prenatal human brain, Nature 508: 199-206. doi: [10.1038/nature13185](https://doi.org/10.1038/nature13185)
- [3] Allen Institute for Brain Science. Allen Human Brain Atlas. Available from: <http://human.brain-map.org/>
- [4] Allen Institute for Brain Science. BrainSpan Atlas of the Developing Human Brain. Available from: <http://brainspan.org/>

See Also

```
browseVignettes("ABAEnrichment")
browseVignettes("ABAData")
get_expression
aba_enrich
get_name
get_id
get_sampled_substructures
get_annotated_genes
heatmap.2
hclust
```

Examples

```
## plot expression data of six genes in two brain regions
## from children (age_category 3) without dendrogram
plot_expression(structure_ids=c("Allen:10657", "Allen:10208"),
  gene_ids=c("ENSG00000168036", "ENSG00000157764", "ENSG00000182158",
    "ENSG00000147889"), dataset="5_stages", dendro=FALSE, age_category=3)

## see the package vignette for more examples
```

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