miRPathDB: The miRNA Pathway Dictionary Database

An illustrated user guide

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1 Overview

The ***miRNA Pathway Dictionary Database (miRPathDB)*** is a database that provides easy access to the information which biological pathways and categories are regulated by a certain miRNA, as well as which miRNAs target a certain pathway and how specific these regulations are. The database can be freely accessed via https://mpd.bioinf.uni-sb.de.

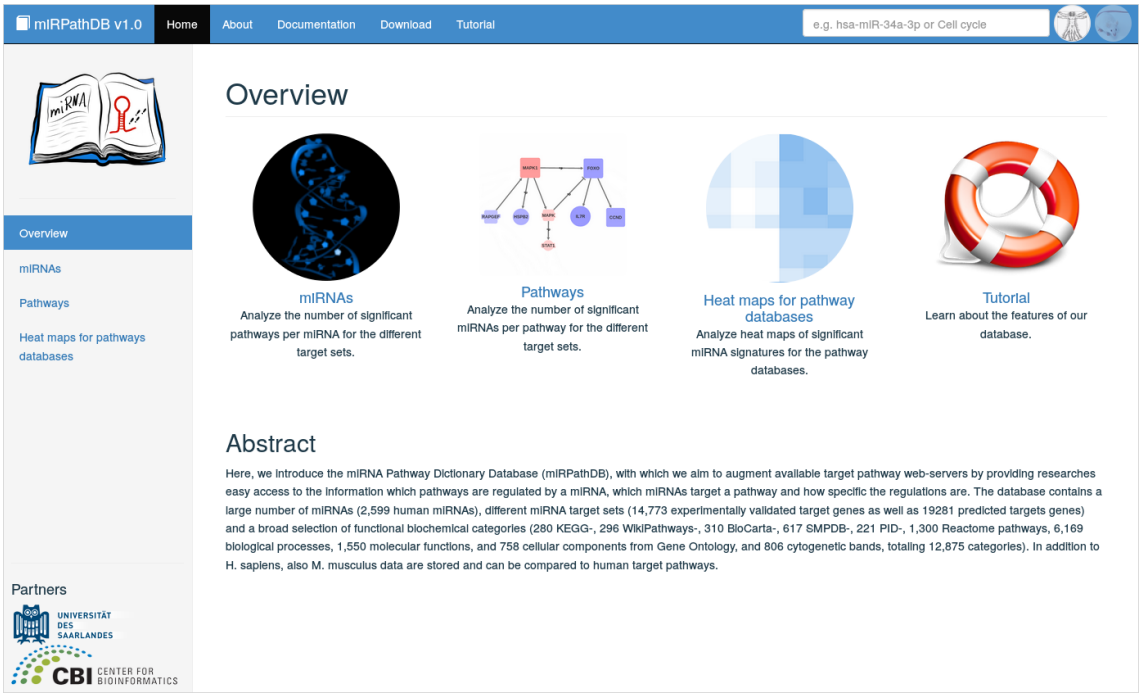


Figure 1: Start page of miRPathDB. From the start page, various analyses can be accessed and the database can be directly queried for miRNAs and pathways.

1.1 Statistics

The *miRPathDB* database contains a large number of miRNAs and miRNA target gene sets (experimentally validated and predicted) for *Homo sapiens* and *Mus musculus* (Table 2), as well as a broad collection of functional biochemical categories (Table 3).

Homo sapiens	
# miRNAs	2,599
# target genes (any experimental evidence)	14,773
# target genes (strong experimental evidence)	2,068
# target genes (weak experimental evidence)	14,595
# target genes (predicted intersection)	16197
# target genes (predicted union)	19,281

Table 1: Current statistics on human miRNA and target gene content of *miRPathDB v1.0*.

Mus musculus	
# miRNAs	1,933
# target genes (any experimental evidence)	7,011
# target genes (strong experimental evidence)	577
# target genes (weak experimental evidence)	6,786
# target genes (predicted intersection)	15,164
# target genes (predicted union)	21,238

Table 2: Current statistics on mouse miRNA and target gene content of *miRPathDB v1.0*.

Homo sapiens Resource	# categories
KEGG	280
WikiPathways	296
BioCarta	310
SMPDB	617
PID	221
Reactome	1,300
GO Biological Process	6,169
GO Molecular Function	1,550
GO Cellular Component	758
Cytogenetic bands	806
Total	**12,875**

Mus musculus Resource	# categories
KEGG	279
WikiPathways	163
BioCarta	277
Reactome	1,036
GO Biological Process	5,332
GO Molecular Function	1,124
GO Cellular Component	602
Cytogenetic bands	394
Total	**9,751**

Table 3: Current statistics on provided biochemical pathways and categories in *miRPathDB v1.0*.

2 Enrichment analyses

All *miRPathDB* database content is based on analyses performed using the gene set enrichment toolkit *GeneTrail2* [1]. Several tools and databases have been employed to identify experimentally validated and computationally predicted targets genes for all considered miRNAs. For each combination of a specific miRNA, target set category for target identification and biological pathway, an enrichment is computed using the hypergeometic test (cf. Section 2.3).

The following settings were used in *GeneTrail2*:

- Enrichment method: Hypergeometric test (ORA)
- p-value adjustment: Benjamini-Hochberg adjustment
- Significance level α: 0.05
- Minimal category size to be considered: 2
- Maximal category size to be considered: 1,000.

2.1 miRNA targets

Information on interactions between a miRNA and its target genes are obtained from several databases:

Database / tool	Target interaction evidence	Reference
miRTarBase, version 6	experimentally validated	[2]
DIANA microT-CDS, version 5	computationally predicted	[3]
miRDB, version 5.0	computationally predicted	[4]
TargetScan, version 7.0	computationally predicted	[5]

Table 4: Databases and tools used to obtain miRNA target genes.

2.2 miRNA target categories

Based on the used miRNA-target interaction information obtained from several databases and tools (cf. Section 2.1), we created five different target set categories:

Strong experimental evidence This target set contains miRNA-target interactions from *miRTarBase* that are experimentally validated using either Western blot, luciferase reporter assay, GFP reporter assay, or RT-PCR.

Weak experimental evidence This target set contains miRNA-target interactions from *miRTarBase* that are experimentally validated using experimental techniques that provide weak evidence like pSILAC, microarrays, branched DNA probe assay, or Northern blot.

Any experimental evidence This target set contains all experimentally validated miRNA-target interactions from *miRTarBase*.

Predicted - intersection Three different tools and databases were used to computationally predict miRNA target interactions (DIANA microT-CDS, miRDB, and TargetScan). As predictions may tremendously vary between the tools, we provide the intersection of the three predicted gene sets as gene set being targeted by a given miRNA.

Predicted - union Three different tools and databases were used to computationally predict miRNA target interactions (DIANA microT-CDS, miRDB, and TargetScan). Here, the union of the three predicted gene sets is used as gene set representing targets for a given miRNA.

2.3 Over-representation analysis

In order to assess whether a certain biological category is significantly enriched for a certain miRNA, we over-representation analysis (ORA) in the version presented by Backes et al. [6]. This approach is based on the hypergeometric distribution and can be used to test if a set of selected biological entities is significantly more or less present in a biological category than expected by chance.
Here, we use ORA to test if a biological pathway contains more targets of a certain miRNA than expected by chance. In order to caclulate this chance, ORA relies on a reference set R (background). In our case, this is the list of all miRNA targets for the corresponding confidence level.
Given a biological category C, of which k elements are contained in a list T of size n and l elements are contained in the reference set R (of size m). Based on this, we expect to find $k' = \frac{n \cdot l}{m}$ elements of category C in list T on average. The hypergeometric test is applied to compute a p-value for C:

$$P_C(k) = \begin{cases} \sum_{i=k}^{n} \frac{\binom{l}{i} \cdot \binom{m-l}{n-i}}{\binom{m}{n}}, \text{ if } k' < k \\ \sum_{i=0}^{k} \frac{\binom{l}{i} \cdot \binom{m-l}{n-i}}{\binom{m}{n}}, \text{ if } k' \geq k \end{cases}$$

Benjamini-Hochberg adjustment The Benjamini-Hochberg method [7, 8] is a step-up procedure to control the false discovery rate. It assumes all p-values to be independent. Given n p-values, sorted in

ascending order $\{p1, p2, ..., p_n\}$, the adjusted p-values can be computed using the following formula:

$$\widetilde{p}_i = \begin{cases} p_i & \text{, for } i = n \\ \min\left(\widetilde{p}_{i-1}, \frac{n}{i} p_i\right) & \text{, for } i = n-1, ..., 1 \end{cases}$$

3 miRNA-centric view

Clicking on *miRNAs* on the start page or in the side panel yields an overview of all miRNAs that are significantly over-represented in at least one category, split into the five sections of miRNA-target interaction sets described in Section 2. Per miRNA and target set category, the number of significantly enriched pathways is listed.
The displayed table is fully searchable and sortable. The number of displayed entries per page can be adjusted, as well as the number of shown columns (button *Column visibility*). Also, the (filtered) table content can be downloaded in various file formats (`.xlsx`, `.csv`, and `.pdf`) for further processing.
Additional information on a miRNA of interest can be obtained by clicking on the miRNA in the table, which forwards the user to a detailed view on this miRNA, cf. Section 3.1.

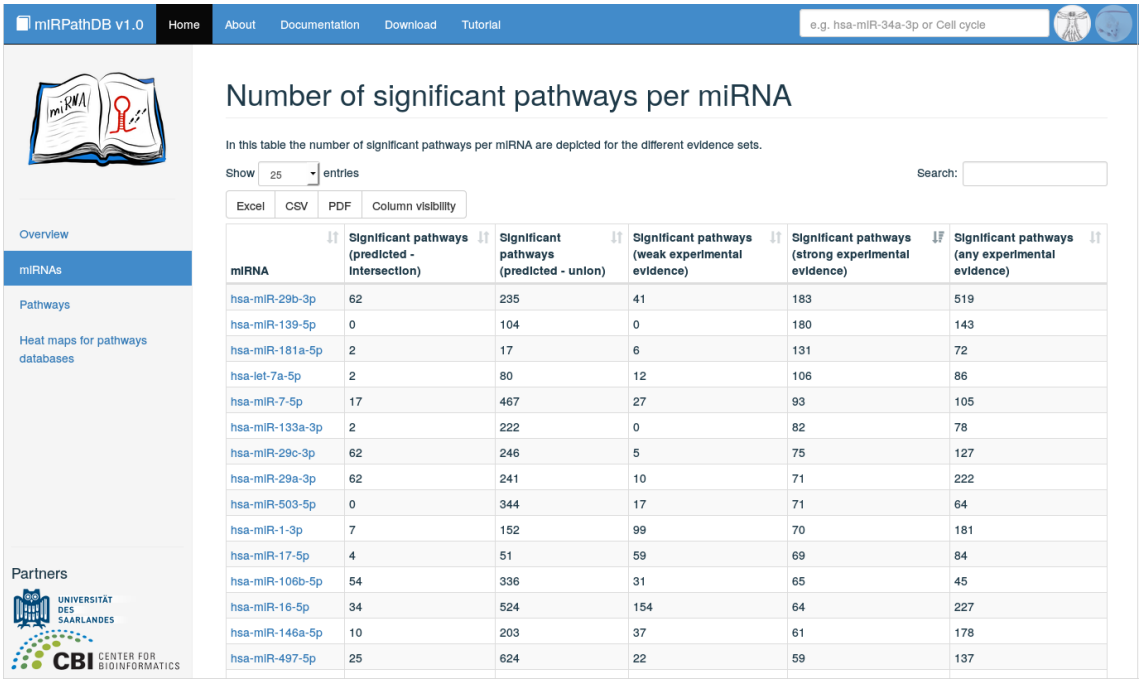


Figure 2: miRNA-centric view. The table gives an overview on the numbers of significantly over-represented pathways per miRNA, splitted by type of interaction evidence. The shown table is sorted by decreasing number of significant pathways with strong experimental evidence.

3.1 Detailed view: miRNA

In this view, detailed information on a specific miRNA can be found. It can be reached (i) by clicking on a miRNA of interest in the miRNA-centric table view or (ii) by directly querying the database for a specific miRNA via the global search field. Here, links to external databases for the considered miRNA are provided, with respect to general information (*miRBase* [9]), tissue specificity (*TissueAtlas* [10]), and target genes in network representation (*MiRTargetLink Human* [11]). Also, all validated and predicted targets of the miRNA under investigation are listed with their corresponding target set categories.
Finally, a table containing all significantly over-represented pathways are listed, i.e. all pathways that contain significantly more targets of the considered miRNA than expected by chance. This table contains information on the database, a certain pathway was obtained from, the evidence level used to map the

miRNA to the pathway genes, the considered target genes and the number of hits (mappable genes in category) and expected hits (expected number of hits by chance). This then results in a p-value that assesses the significance of over-representation for this category. Also, the pathways are linked to their pathway-centric view (cf. Section 4.1).

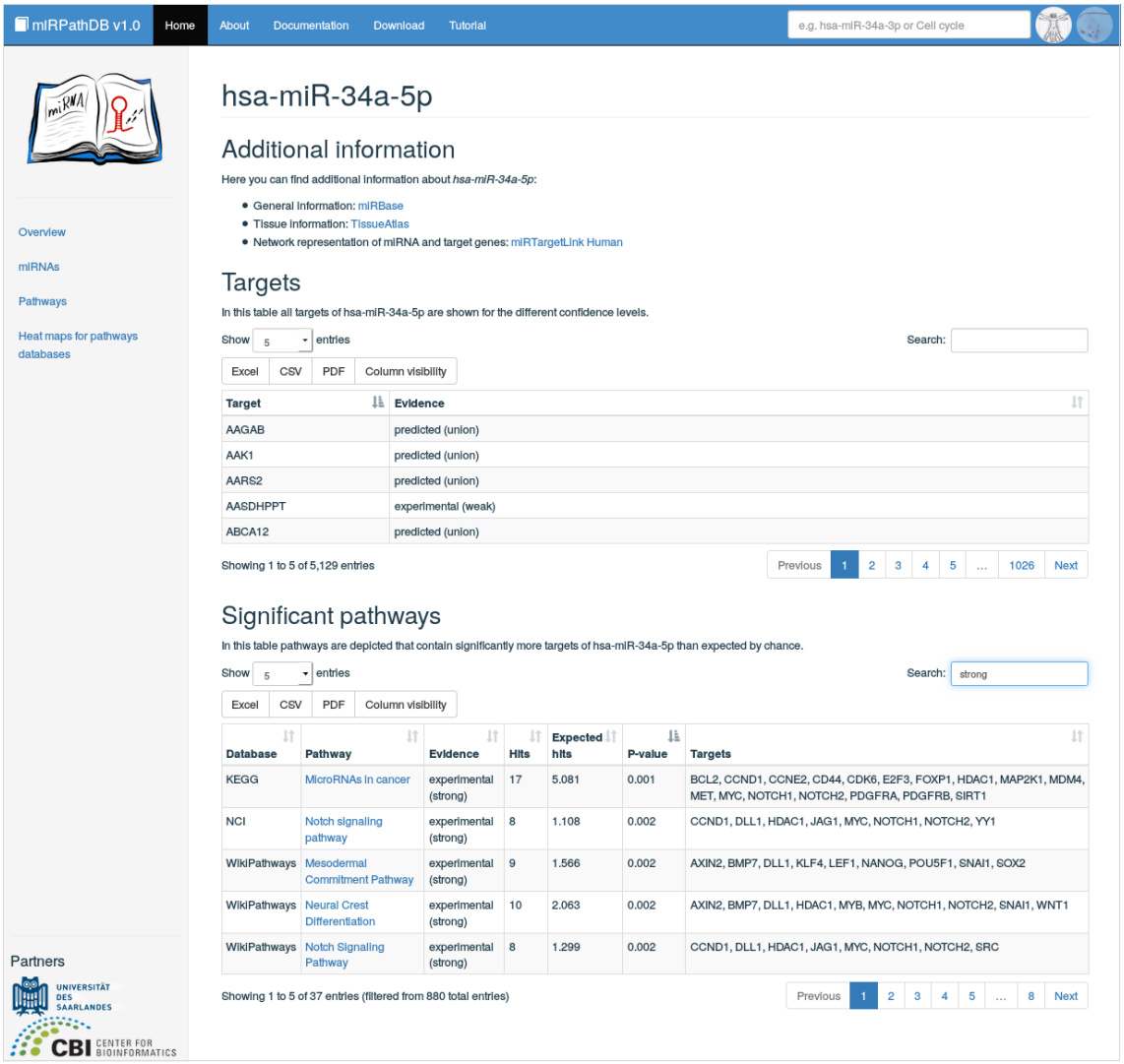


Figure 3: Detailed view of miRNA hsa-miR-34a-5p. In this figure, the pathways are filtered to display only significant enrichments on miRNA target genes that are validated using strong experimental evidence.

4 Pathway-centric view

Clicking on *Pathways* on the start page or in the side panel yields an overview of all pathways that are significantly over-represented for at least one miRNA, split into the five sections of miRNA-target sets, as described in Section 2. Per pathway and target set categories, the number of significant miRNAs are listed.
The displayed table is fully searchable and sortable. The number of displayed entries per page can be adjusted, as well as the number of shown columns (button *Column visibility*). Also, the (filtered) table content can be downloaded in various file formats (`.xlsx`, `.csv`, and `.pdf`) for further processing.
Additional information on a pathway of interest can be obtained by clicking on the pathway in the table, which forwards the user to a detailed view on this pathway, cf. Section 4.1.

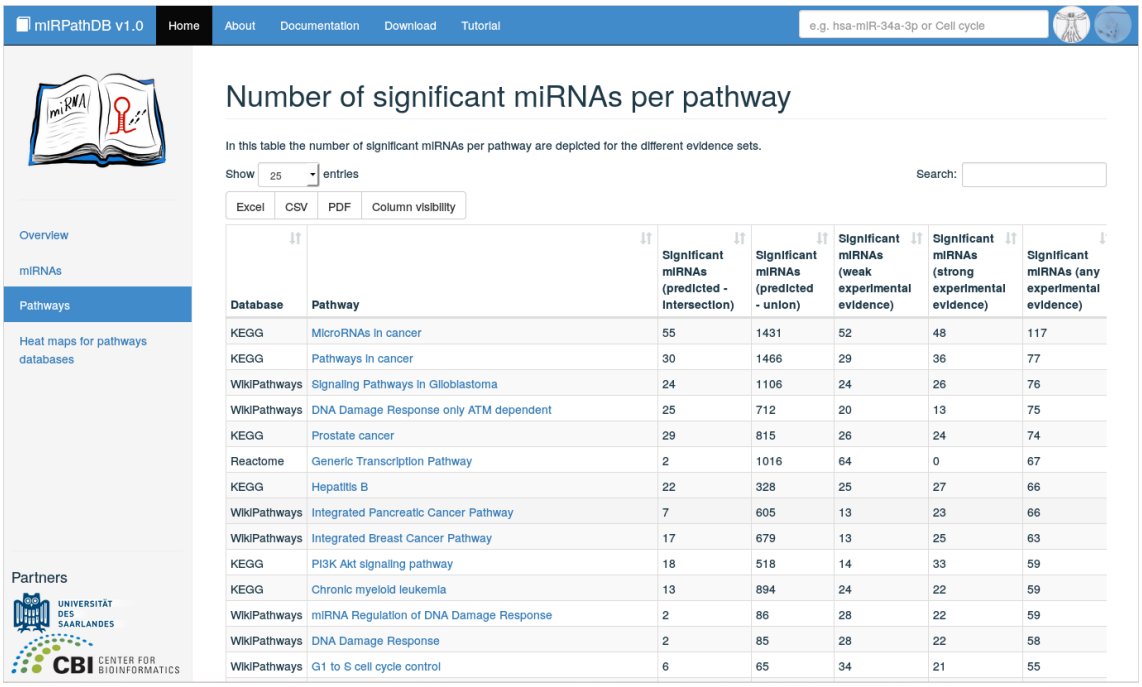
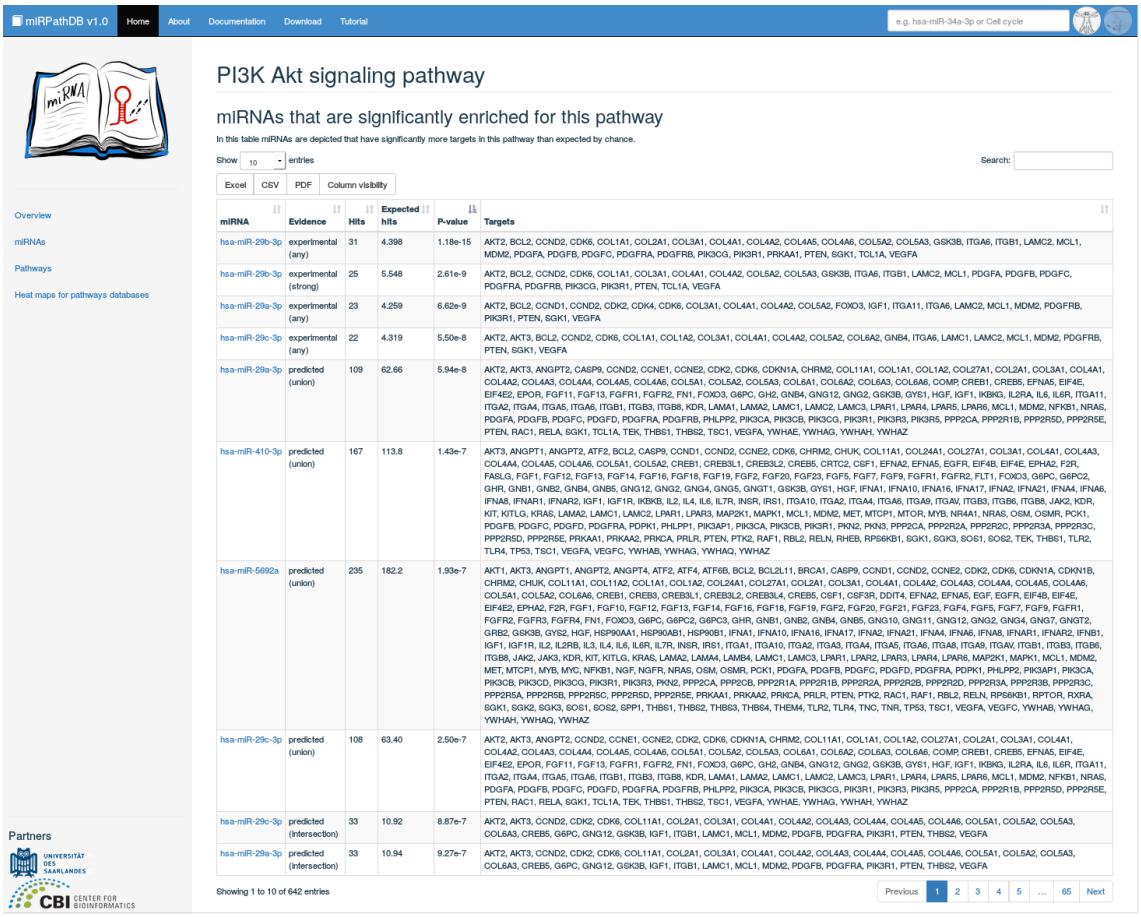


Figure 4: Pathway-centric view. The table gives an overview on the numbers of significantly enriched miRNAs per pathway, splitted by type of interaction evidence. The shown table is sorted by decreasing number of significant miRNAs with strong experimental evidence.

4.1 Detailed view: pathway

In this view, detailed information on a specific pathway can be found. It can be reached (i) by clicking on a pathway of interest in the pathway-centric table view or (ii) by directly querying the database for a specific pathway via the global search field. Here, a table containing all significant miRNAs targeting the considered pathway are listed, i.e. all miRNAs that have significantly more targets in this pathway than expected by chance. This table contains information on the targeting miRNA and its target genes based on a certain target set category. Also the number of hits (mappable genes in category) and expected hits (exprected number of this by chance) are listed. These then result in a p-value that assesses the significance of over-representation for this miRNA and the considered pathway. Also, the miRNAs are linked to their miRNA-centric view (cf. Section 3.1).



miRNA	Evidence	Hits	Expected hits	P-value	Targets
hsa-miR-29b-3p	experimental (any)	31	4.398	1.18e-15	AKT2, BCL2, CCND2, CDK6, COL1A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A5, COL4A6, COL5A2, COL5A3, GSK3B, ITGA6, ITGB1, LAMC2, MCL1, MDM2, PDGFA, PDGFB, PDGFC, PDGFRA, PDGFRB, PIK3CG, PIK3R1, PRKAA1, PTEN, SGK1, TCL1A, VEGFA
hsa-miR-29b-3p	experimental (strong)	25	5.548	2.61e-9	AKT2, BCL2, CCND2, CDK6, COL1A1, COL3A1, COL4A1, COL4A2, COL5A2, COL5A3, GSK3B, ITGA6, ITGB1, LAMC2, MCL1, PDGFA, PDGFB, PDGFC, PDGFRA, PDGFRB, PIK3CG, PIK3R1, PTEN, TCL1A, VEGFA
hsa-miR-29a-3p	experimental (any)	23	4.259	6.62e-9	AKT2, BCL2, CCND1, CCND2, CDK2, CDK4, CDK6, COL3A1, COL4A1, COL4A2, COL5A2, FOXO3, IGF1, ITGA11, ITGA6, LAMC2, MCL1, MDM2, PDGFRB, PIK3R1, PTEN, SGK1, VEGFA
hsa-miR-29c-3p	experimental (any)	22	4.319	5.50e-8	AKT2, AKT3, BCL2, CCND2, CDK6, COL1A1, COL1A2, COL3A1, COL4A1, COL4A2, COL5A2, COL6A2, GNB4, ITGA6, LAMC1, LAMC2, MCL1, MDM2, PDGFRB, PTEN, SGK1, VEGFA
hsa-miR-29a-3p	predicted (union)	109	62.66	5.94e-8	AKT2, AKT3, ANGPT2, CASP9, CCND2, CCNE1, CCNE2, CDK2, CDK6, CDKN1A, CHRM2, COL11A1, COL1A1, COL1A2, COL27A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL5A3, COL6A1, COL6A2, COL6A3, COL6A6, COMP, CREB1, CREB5, EFNA5, EIF4E, EIF4E2, EPOR, FGF11, FGF13, FGFR1, FGFR2, FN1, FOXO3, G6PC, GH2, GNB4, GNG12, GNG2, GSK3B, GYS1, HGF, IGF1, IKBKG, IL2RA, IL6, IL6R, ITGA11, ITGA2, ITGA4, ITGA5, ITGA6, ITGB1, ITGB3, ITGB8, KDR, LAMA1, LAMA2, LAMC1, LAMC2, LAMC3, LPAR1, LPAR4, LPAR5, LPAR6, MCL1, MDM2, NFKB1, NRAS, PDGFA, PDGFB, PDGFC, PDGFD, PDGFRA, PDGFRB, PHLPP2, PIK3CA, PIK3CB, PIK3CG, PIK3R1, PIK3R3, PIK3R5, PPP2CA, PPP2R1B, PPP2R5D, PPP2R5E, PTEN, RAC1, RELA, SGK1, TCL1A, TEK, THBS1, THBS2, TSC1, VEGFA, YWHAE, YWHAG, YWHAH, YWHAZ
hsa-miR-410-3p	predicted (union)	167	113.8	1.43e-7	AKT3, ANGPT1, ANGPT2, ATF2, BCL2, CASP9, CCND1, CCND2, CCNE2, CDK6, CHRM2, CHUK, COL11A1, COL24A1, COL27A1, COL3A1, COL4A1, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, CREB1, CREB3L1, CREB3L2, CREB5, CRTC2, CSF1, EFNA2, EFNA5, EGFR, EIF4B, EIF4E, EPHA2, F2R, FASLG, FGF1, FGF12, FGF13, FGF14, FGF16, FGF18, FGF19, FGF2, FGF20, FGF23, FGF5, FGF7, FGF9, FGFR1, FGFR2, FLT1, FOXD3, G6PC, G6PC2, GHR, GNB1, GNB2, GNB4, GNB5, GNG12, GNG2, GNG4, GNG5, GNGT1, GSK3B, GYS1, HGF, IFNA1, IFNA10, IFNA16, IFNA17, IFNA2, IFNA21, IFNA4, IFNA6, IFNA8, IFNAR1, IFNAR2, IGF1, IGF1R, IKBKB, IL2, IL4, IL6, IL7R, INSR, IRS1, ITGA10, ITGA2, ITGA4, ITGA6, ITGA9, ITGAV, ITGB3, ITGB6, ITGB8, JAK2, KDR, KIT, KITLG, KRAS, LAMA2, LAMC1, LAMC2, LPAR1, LPAR3, MAP2K1, MAPK1, MCL1, MDM2, MET, MTCP1, MTOR, MYB, NR4A1, NRAS, OSM, OSMR, PCK1, PDGFB, PDGFC, PDGFD, PDGFRA, PDPK1, PHLPP1, PIK3AP1, PIK3CA, PIK3CB, PIK3R1, PKN2, PKN3, PPP2CA, PPP2R2A, PPP2R2C, PPP2R3A, PPP2R3C, PPP2R5D, PPP2R5E, PRKAA1, PRKAA2, PRKCA, PRLR, PTEN, PTK2, RAF1, RBL2, RELN, RHEB, RPS6KB1, SGK1, SGK3, SOS1, SOS2, TEK, THBS1, TLR2, TLR4, TP53, TSC1, VEGFA, VEGFC, YWHAB, YWHAG, YWHAQ, YWHAZ
hsa-miR-5692a	predicted (union)	235	182.2	1.93e-7	AKT1, AKT3, ANGPT1, ANGPT2, ANGPT4, ATF2, ATF4, ATF6B, BCL2, BCL2L11, BRCA1, CASP9, CCND1, CCND2, CCNE2, CDK2, CDK6, CDKN1A, CDKN1B, CHRM2, CHUK, COL11A1, COL11A2, COL1A1, COL1A2, COL24A1, COL27A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL6A6, CREB1, CREB3, CREB3L1, CREB3L2, CREB3L4, CREB5, CSF1, CSF3R, DDIT4, EFNA2, EFNA5, EGF, EGFR, EIF4B, EIF4E, EIF4E2, EPHA2, F2R, FGF1, FGF10, FGF12, FGF13, FGF14, FGF16, FGF18, FGF19, FGF2, FGF20, FGF21, FGF23, FGF4, FGF5, FGF7, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FN1, FOXO3, G6PC, G6PC2, G6PC3, GHR, GNB1, GNB2, GNB4, GNB5, GNG10, GNG11, GNG12, GNG2, GNG4, GNG7, GNGT2, GRB2, GSK3B, GYS2, HGF, HSP90AA1, HSP90AB1, HSP90B1, IFNA1, IFNA10, IFNA16, IFNA17, IFNA2, IFNA21, IFNA4, IFNA6, IFNA8, IFNAR1, IFNAR2, IFNB1, IGF1, IGF1R, IL2, IL2RB, IL3, IL4, IL6, IL6R, IL7R, INSR, IRS1, ITGA1, ITGA10, ITGA2, ITGA3, ITGA4, ITGA5, ITGA6, ITGA8, ITGA9, ITGAV, ITGB1, ITGB3, ITGB6, ITGB8, JAK2, JAK3, KDR, KIT, KITLG, KRAS, LAMA2, LAMA4, LAMB4, LAMC1, LAMC3, LPAR1, LPAR2, LPAR3, LPAR4, LPAR6, MAP2K1, MAPK1, MCL1, MDM2, MET, MTCP1, MYB, MYC, NFKB1, NGF, NGFR, NRAS, OSM, OSMR, PCK1, PDGFA, PDGFB, PDGFC, PDGFD, PDGFRA, PDPK1, PHLPP2, PIK3AP1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R3, PKN2, PPP2CA, PPP2CB, PPP2R1A, PPP2R1B, PPP2R2A, PPP2R2B, PPP2R2D, PPP2R3A, PPP2R3B, PPP2R3C, PPP2R5A, PPP2R5B, PPP2R5C, PPP2R5D, PPP2R5E, PRKAA1, PRKAA2, PRKCA, PRLR, PTEN, PTK2, RAC1, RAF1, RBL2, RELN, RPS6KB1, RPTOR, RXRA, SGK1, SGK2, SGK3, SOS1, SOS2, SPP1, THBS1, THBS2, THBS3, THBS4, THEM4, TLR2, TLR4, TNC, TNR, TP53, TSC1, VEGFA, VEGFC, YWHAB, YWHAG, YWHAH, YWHAQ, YWHAZ
hsa-miR-29c-3p	predicted (union)	108	63.40	2.50e-7	AKT2, AKT3, ANGPT2, CCND2, CCNE1, CCNE2, CDK2, CDK6, CDKN1A, CHRM2, COL11A1, COL1A1, COL1A2, COL27A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL5A3, COL6A1, COL6A2, COL6A3, COL6A6, COMP, CREB1, CREB5, EFNA5, EIF4E, EIF4E2, EPOR, FGF11, FGF13, FGFR1, FGFR2, FN1, FOXO3, G6PC, GH2, GNB4, GNG12, GNG2, GSK3B, GYS1, HGF, IGF1, IKBKG, IL2RA, IL6, IL6R, ITGA11, ITGA2, ITGA4, ITGA5, ITGA6, ITGB1, ITGB3, ITGB8, KDR, LAMA1, LAMA2, LAMC1, LAMC2, LAMC3, LPAR1, LPAR4, LPAR5, LPAR6, MCL1, MDM2, NFKB1, NRAS, PDGFA, PDGFB, PDGFC, PDGFD, PDGFRA, PDGFRB, PHLPP2, PIK3CA, PIK3CB, PIK3CG, PIK3R1, PIK3R3, PIK3R5, PPP2CA, PPP2R1B, PPP2R5D, PPP2R5E, PTEN, RAC1, RELA, SGK1, TCL1A, TEK, THBS1, THBS2, TSC1, VEGFA, YWHAE, YWHAG, YWHAH, YWHAZ
hsa-miR-29c-3p	predicted (intersection)	33	10.92	8.87e-7	AKT2, AKT3, CCND2, CDK2, CDK6, COL11A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL5A3, COL6A3, CREB5, G6PC, GNG12, GSK3B, IGF1, ITGB1, LAMC1, MCL1, MDM2, PDGFB, PDGFRA, PIK3R1, PTEN, THBS2, VEGFA
hsa-miR-29a-3p	predicted (intersection)	33	10.94	9.27e-7	AKT2, AKT3, CCND2, CDK2, CDK6, COL11A1, COL2A1, COL3A1, COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6, COL5A1, COL5A2, COL5A3, COL6A3, CREB5, G6PC, GNG12, GSK3B, IGF1, ITGB1, LAMC1, MCL1, MDM2, PDGFB, PDGFRA, PIK3R1, PTEN, THBS2, VEGFA

Figure 5: Detailed view of pathway. The table contains all miRNAs that have significantly more targets in the considered pathway than expected by chance.

5 Heat maps for pathway databases

Clicking on *Heat maps for pathway databases* on the start page or in the side panel yields an interactive heat map displaying scores of enrichment for a selected set of miRNAs and pathways originating from a specified database. The considered database and confidence level for the mRNA-target interactions, can be selected from drop-down menus. The displayed enrichment scores are computed from the respective p-values as

$$\text{Enrichment score (category, miRNA, confidence)} = -\log_{10}(\text{p-value(category, miRNA, confidence)}).$$

Hence, the larger the enrichment score (and the 'bluer' the cell), the more significant is the enrichment of the respective miRNA in the respective pathway. Hovering over the cells of the heat map indicates the corresponding miRNAs and pathways withr their respective score. The heat maps are clustered using the `hclust` method from the R-package `stats`.
Using this representation, the user can immediately see whether miRNAs targeting pathways are rather specific or whether a miRNA is targeting almost all categories. In the latter case the significant results may e.g. be the result of a bias in the enrichment analysis.

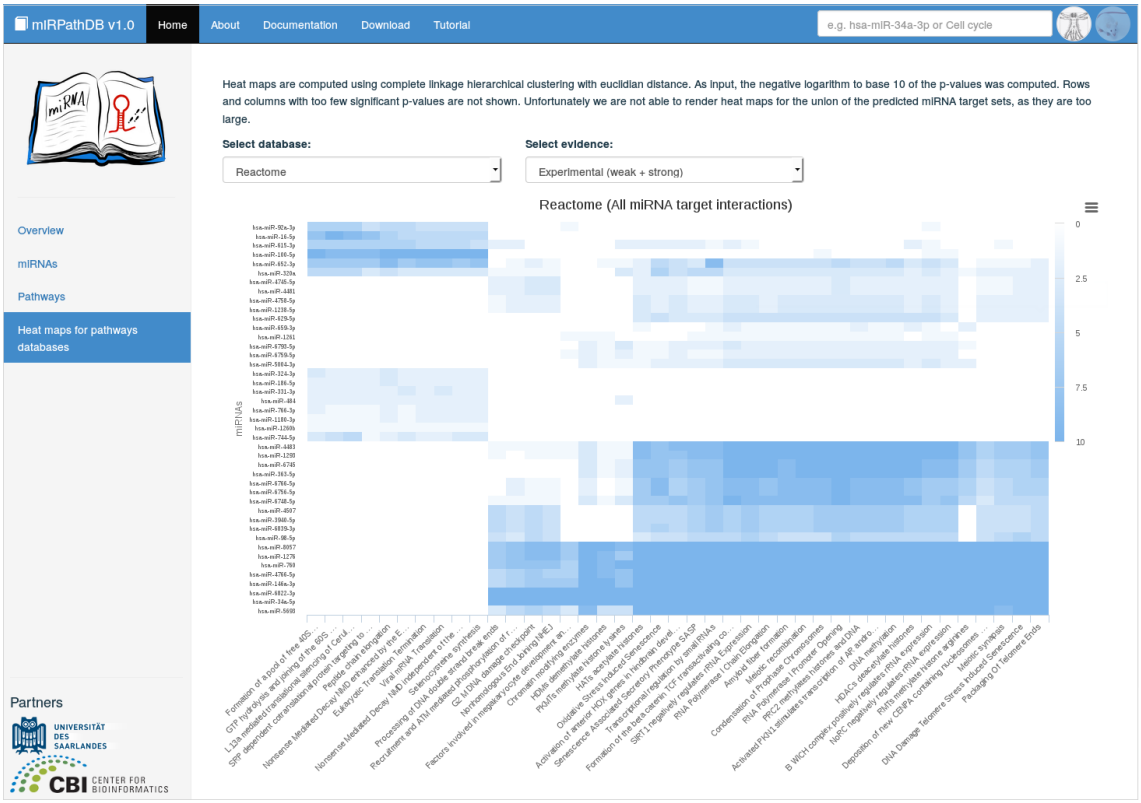


Figure 6: Heat map. Heat map displaying enrichment scores for Reactome and all experimentally validated targets.

6 Data download

The database content can either be downloaded as flat files for access of the complete database, or via the miRNA- and pathway-centric, as well as the detailed views. Clicking on *Download* in the top panel forwards the user to the download page, where current and former versions of miRPathDB content can be obtained. Per release, two types of data are provided:

- The *GeneTrail2 enrichment results* archive, which contains a directory for each miRNA that holds the enrichment results for the individual databases.
- The *Pathway* × *miRNA p-value matrix* archive, which contains a matrix for each database and confidence level. Each matrix (`.csv` file) contains the FDR-adjusted p-value for each miRNA-pathway pair. Rows represent miRNAs and columns individual pathways.

All archives ar provided in `.tar.gz` and `.zip` format for *Homo sapiens* and *Mus musculus* respectively.

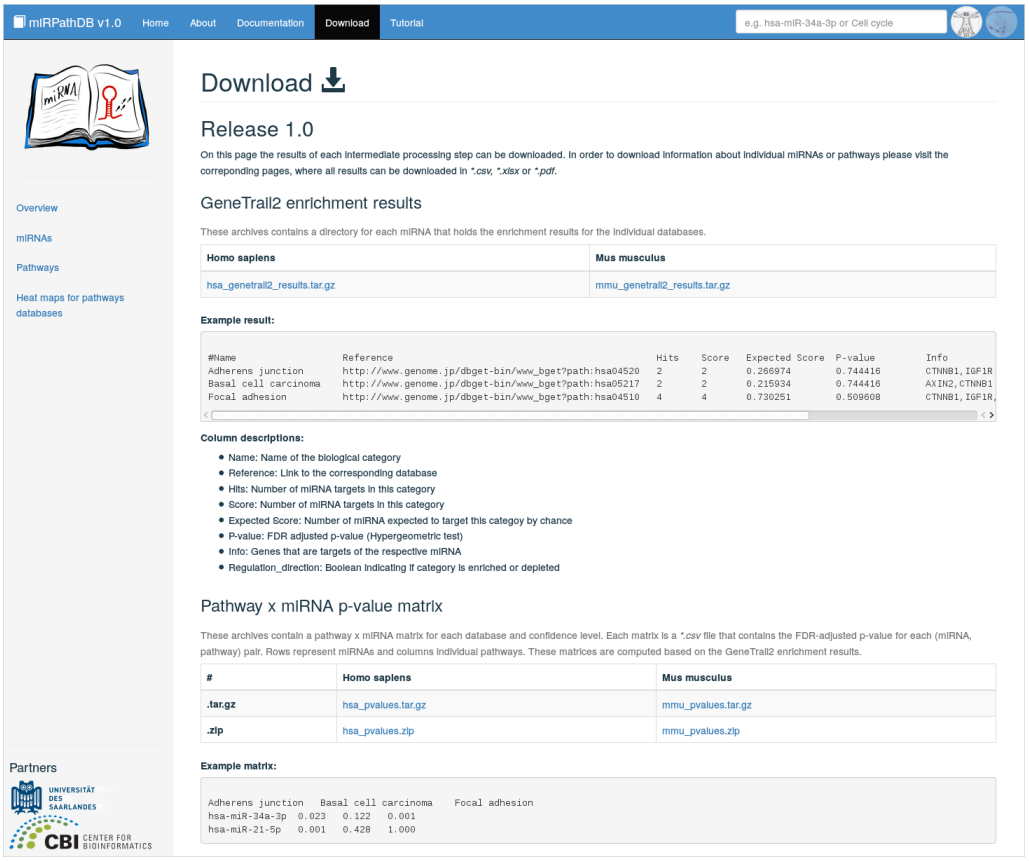


Figure 7: Download flat files. Overview of *miRPathDB*'s download page.

7 Disclaimer

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