User Manual

1. Home

The Home page is displayed in Figure 1-1 and Figure 1-2:

1. Main functions of the database are provided in menu bar form (boxed in red).

2. Quick browse and search experimentally verified data follow human, animal model and cell related with aging.

3. The statistics for AgingBank.

4. The brief introduction of AgingBank.

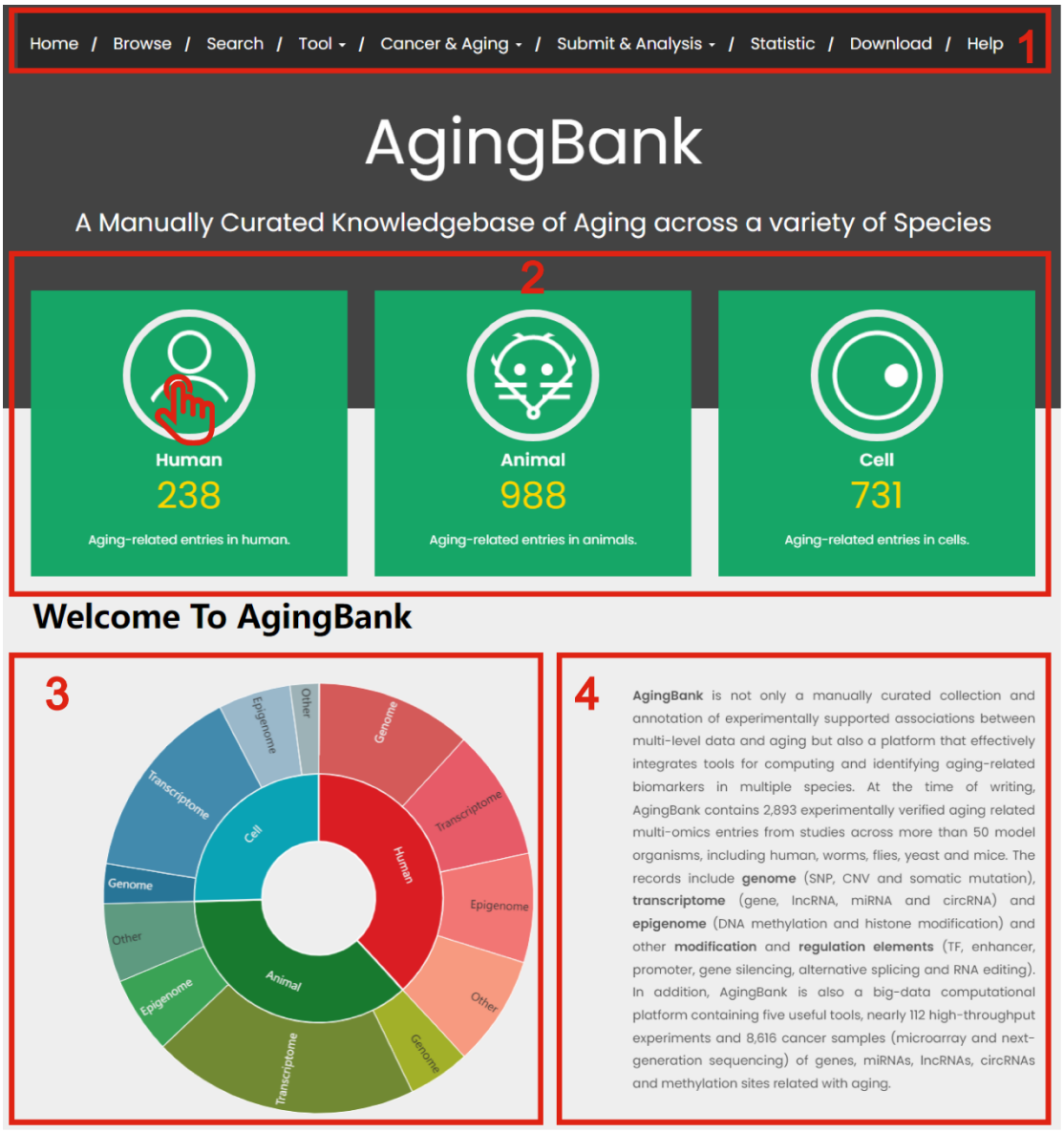

Figure 1-1

1. Quick browse and search experimentally verified data follow aging-related genome, transcriptome, epigenome and other regulatory elements.

2. Click body parts to GEO database.

3. Click body parts to TCGA database.

4. Click body parts to perform Differential Expression Analyzer module.

5. Click body parts to perform Data Heat Mapper module.

6. Click body parts to perform Co-Expression Network module.

7. Click body parts to perform Functional Annotation Analyzer module.

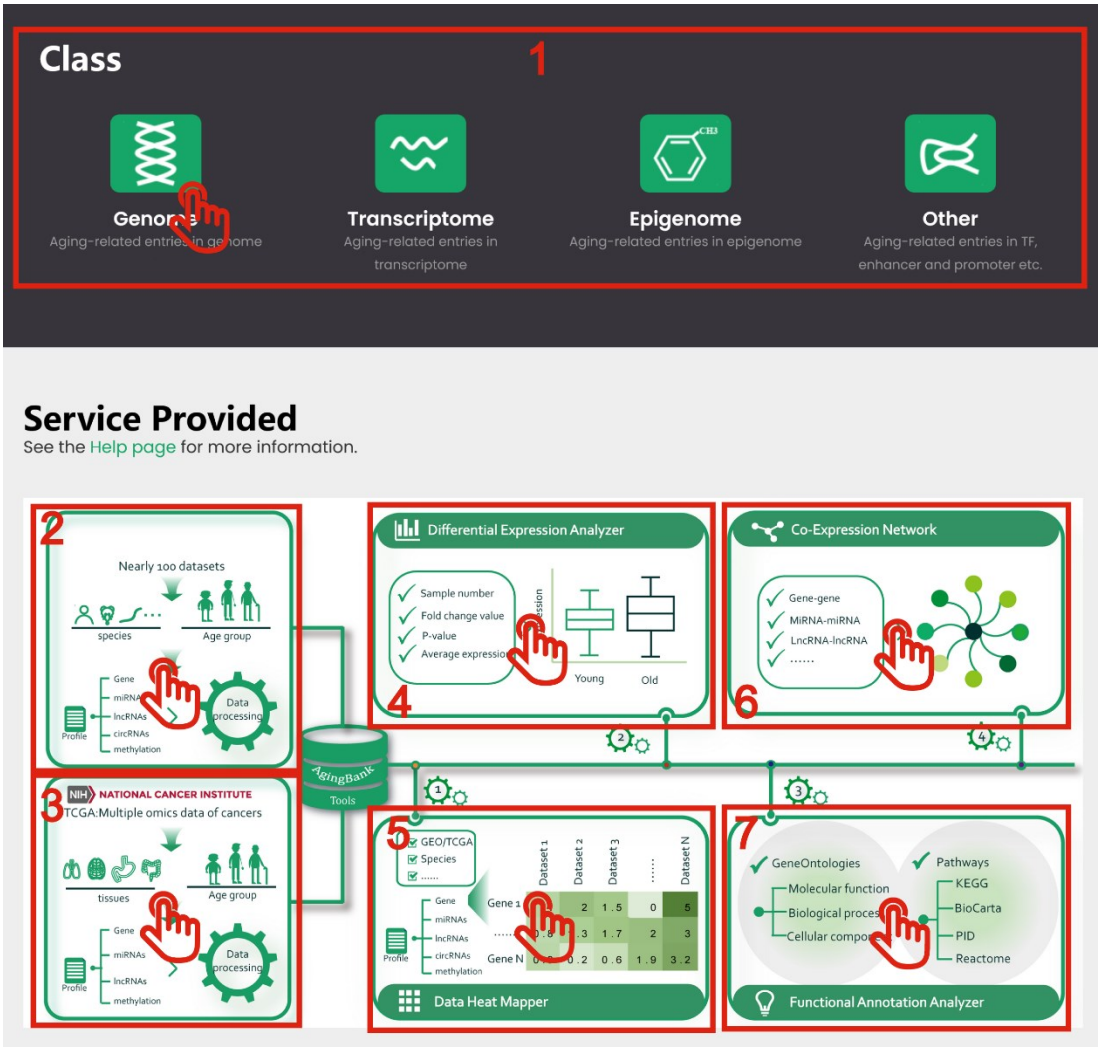

Figure 1-2

2. Browse

In the Browse page, there are three ways to search by aging-related experimentally verified data.

1. Input species, tissue and molecular name to search.

2. Browse and click to select the interested species or molecular type from the drop-down list on the left-hand side of the page.

3. Browse and click to select the interested species and molecular type.

4. After step 1, 2 or 3, you will get the result page with the target entries.

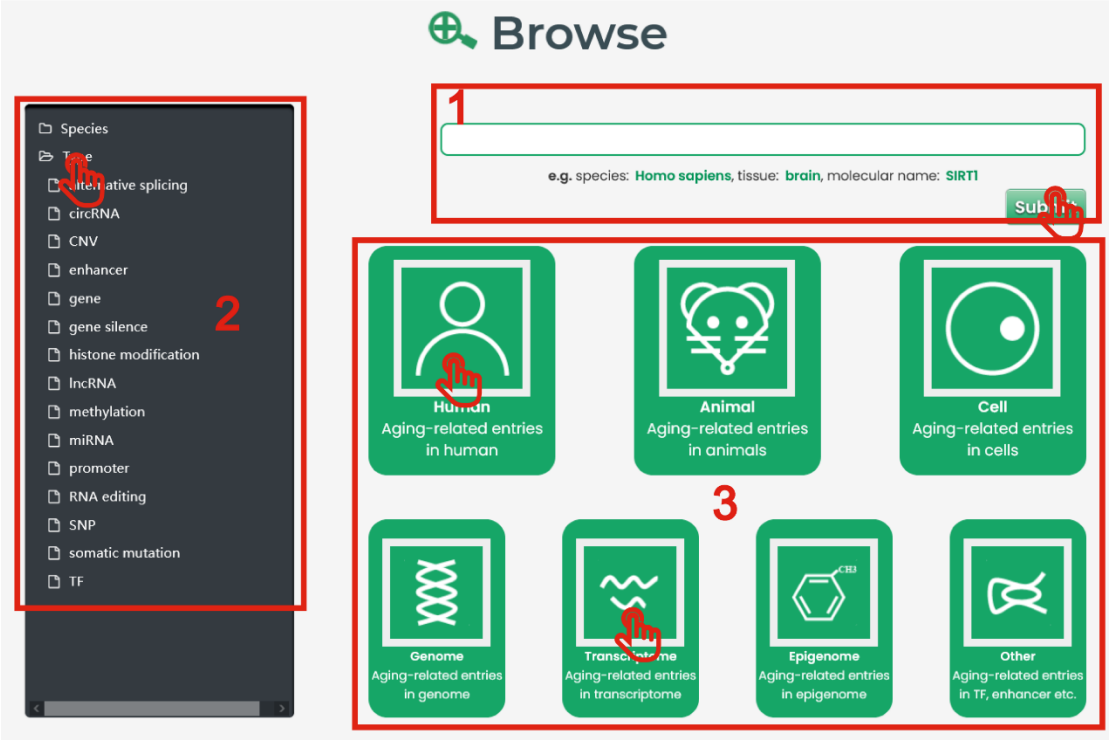

Figure 2

3. Search

Use the Search page to enter a keyword and filter results. AgingBank provides general search and advanced search.

The general search page is displayed in Figure 3-1:

1. Users can input a molecule, species or tissue name to query.

2. AgingBank also offers fuzzy keyword searching capabilities, which enables easy searching by returning the closest possible matching records.

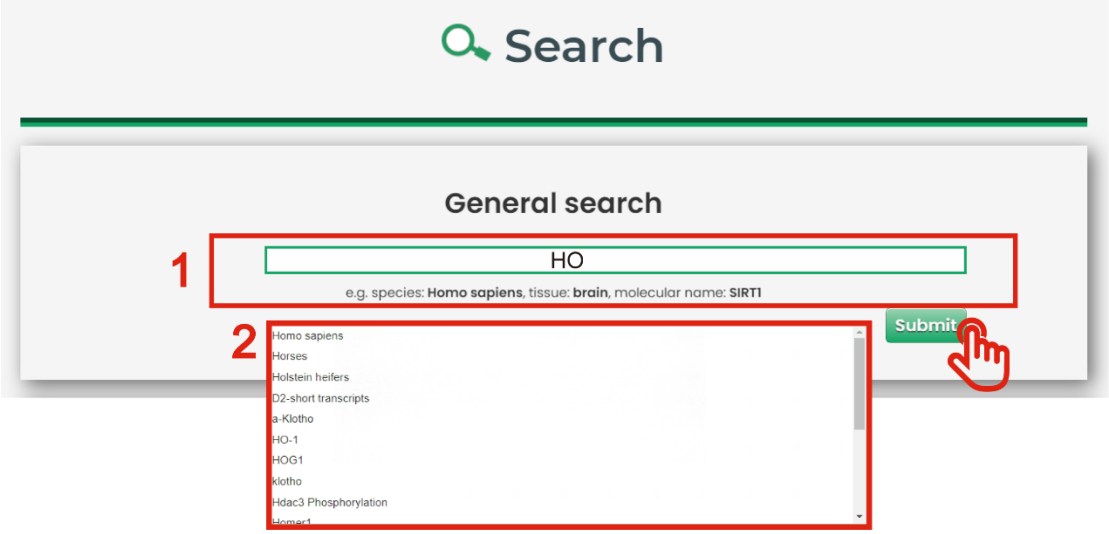

Figure 3-1

The advanced search page is displayed in Figure 3-2:

1. Input your interested species.

2. Select interested molecular types including genome (SNP, CNV and somatic mutation), transcriptome (gene, lncRNA, miRNA and circRNA) and epigenomics (DNA methylation and histone modification) and other modification and regulation elements (TF, enhancer, promoter, suppressor, gene silencing, alternative splicing and RNA editing)

3. Input interested molecular name.

4. Experiment method (RNA-seq, microarray, qPCR et al.) could filter the results.

5. Other factors including disease, environmental factor, circulating and variant could filter the results.

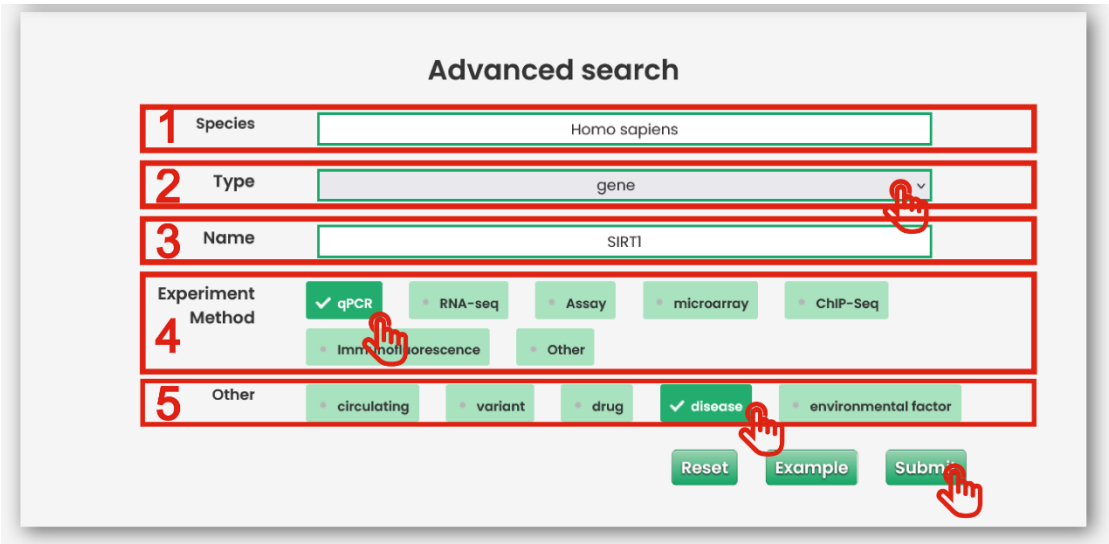
Advanced search
1
Species
Homo sapiens
2
Type
gene
3
Name
SIRT1
Experiment Method
4
qPCR
RNA-seq
Assay
microarray
ChIP-Seq
Other
5
Other
circulating
variant
drug
disease
environmental factor
Reset
Example

Figure 3-2

4. Search results

AgingBank results are organized in a data table, with a single association record on each line that contains species name, molecular type, molecular name, sample, tissue, dysregulated pattern, the associations with aging and PubMed ID.

The result page is displayed in Figure 4:

1. Click to download data.
2. Click to check the detail PubMed of the entry.
3. Click to check the detail information of the entry.
4. Users can input keywords from any column to filter the results.

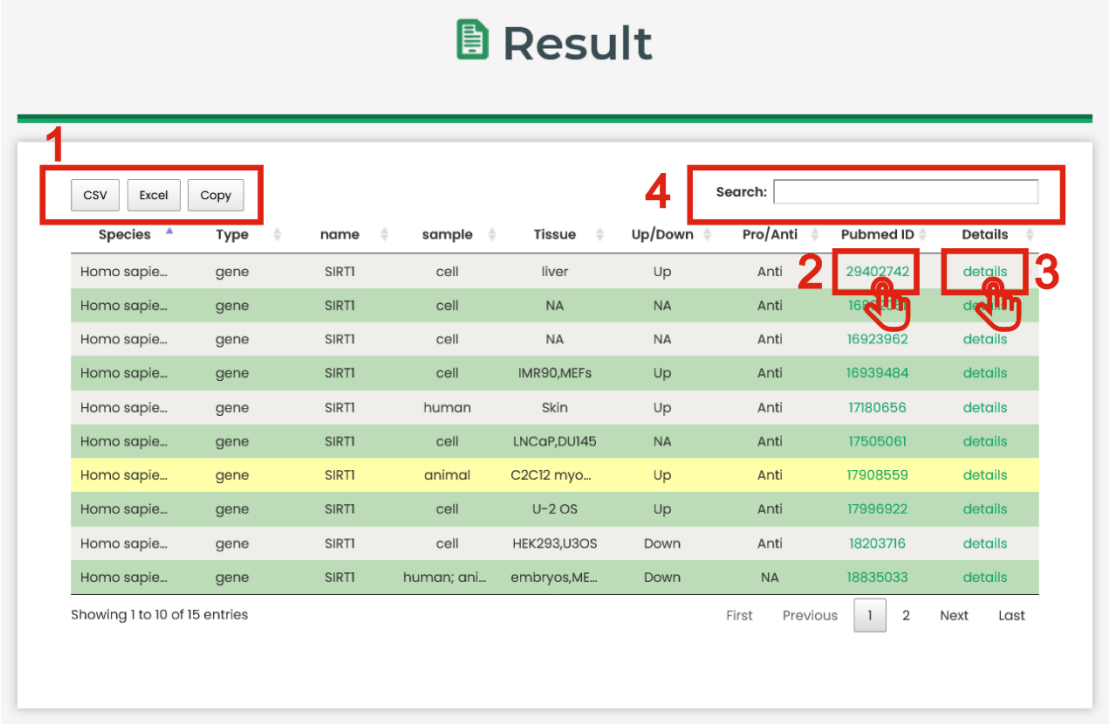

Figure 4

5. Detail information

Detailed information of the aging associations of specific molecule is displayed in Figure 5:

1. The basic information for aging-related entries.
2. The Pubmed information for aging-related entries.
3. The other information for aging-related entries.

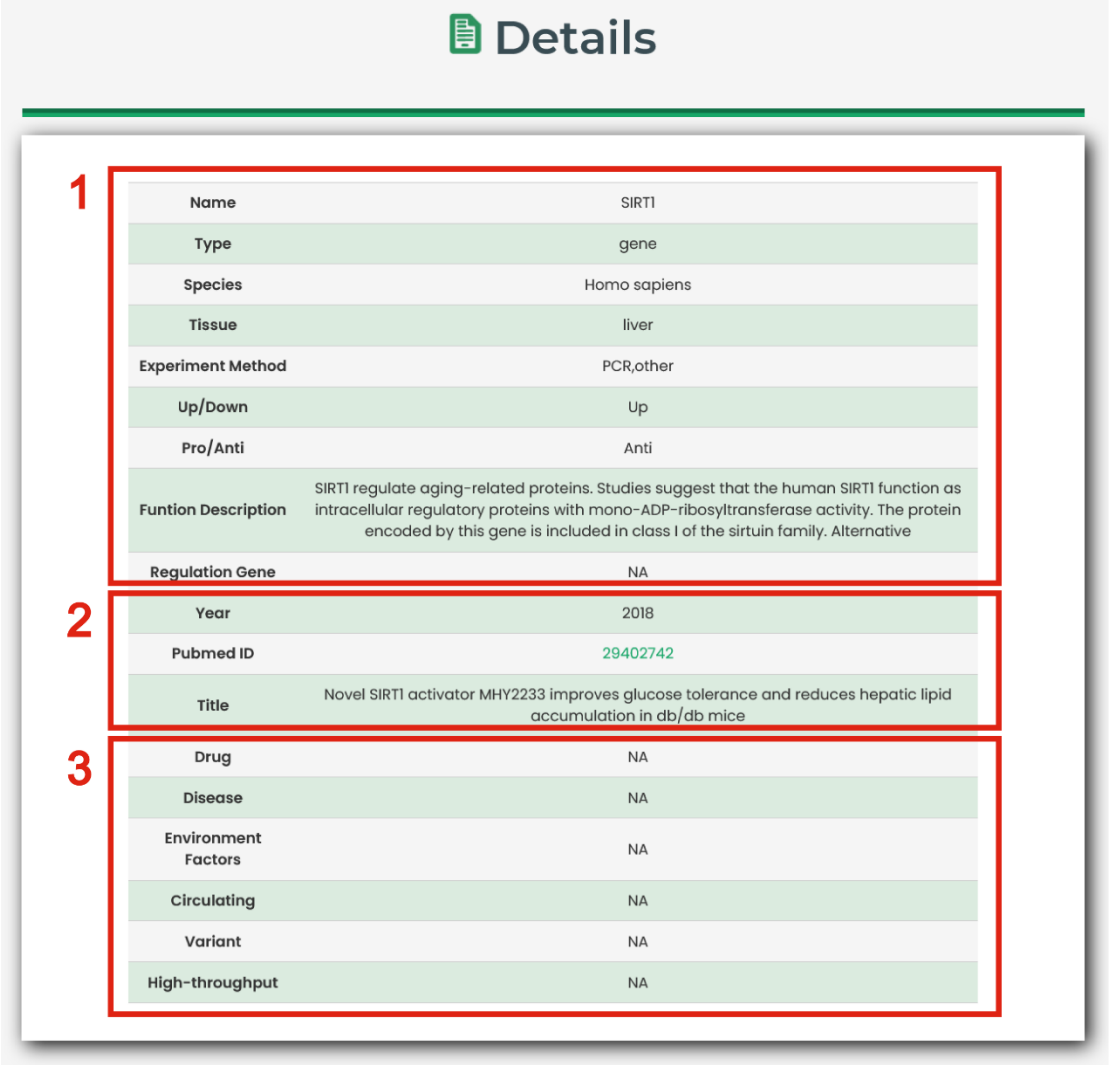

Figure 5

6. Tool

6.1. Aging Landscape

In this section, the high-throughput datasets (aging-related GEO datasets) were used to understand the whole landscape of a specific molecule.

The Aging Landscape page of Tool is displayed in Figure 6-1:

1. You could extract the species which interest you.

2. Put the gene, miRNA, lncRNA and methylation which interest you.

3. The aging landscape graph for a specific molecule in all datasets.

4. The plot shows the P-values of differential expression for interested molecules in each aging-associated profiles. You could understand the whole landscape of a specific molecule in all the aging-associated datasets.

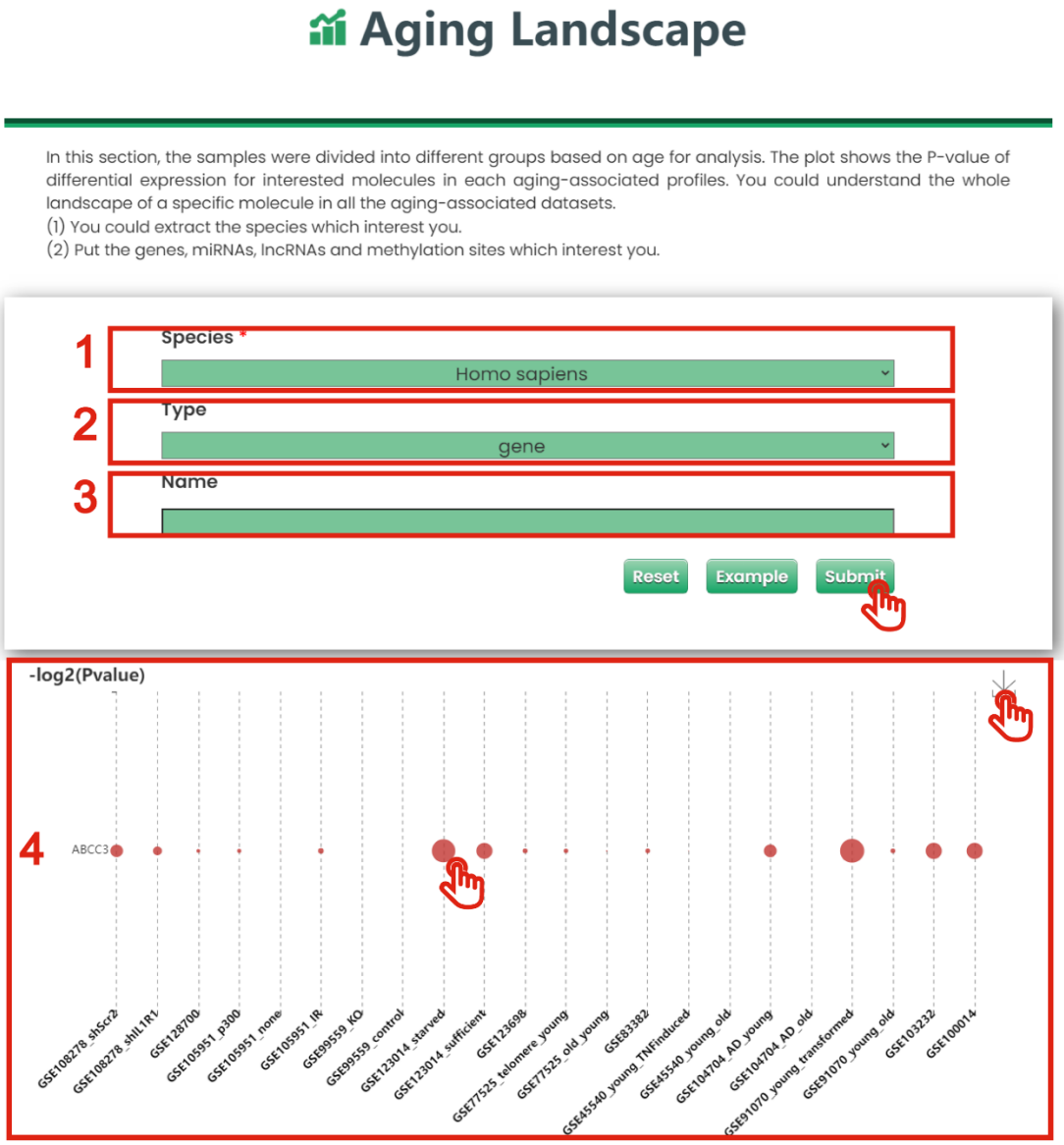

Figure 6-1

6.2. Differential Expression Analyzer

In this section, you could identify the differential expression pattern for your interested genes, miRNAs, lncRNAs and methylation sites in aging-related GEO datasets.

The Differential Expression Analyzer page of Tool is displayed in Figure 6-2:

1. You could extract the species which interest you.
2. You could extract what you are interested in from existing tissue and type.
3. You could extract what you are interested in from existing samples.
4. You could limit interested |log2 (fold change)| or methylation difference of differential expression analysis.
5. You could limit interested P-values of differential expression analysis.

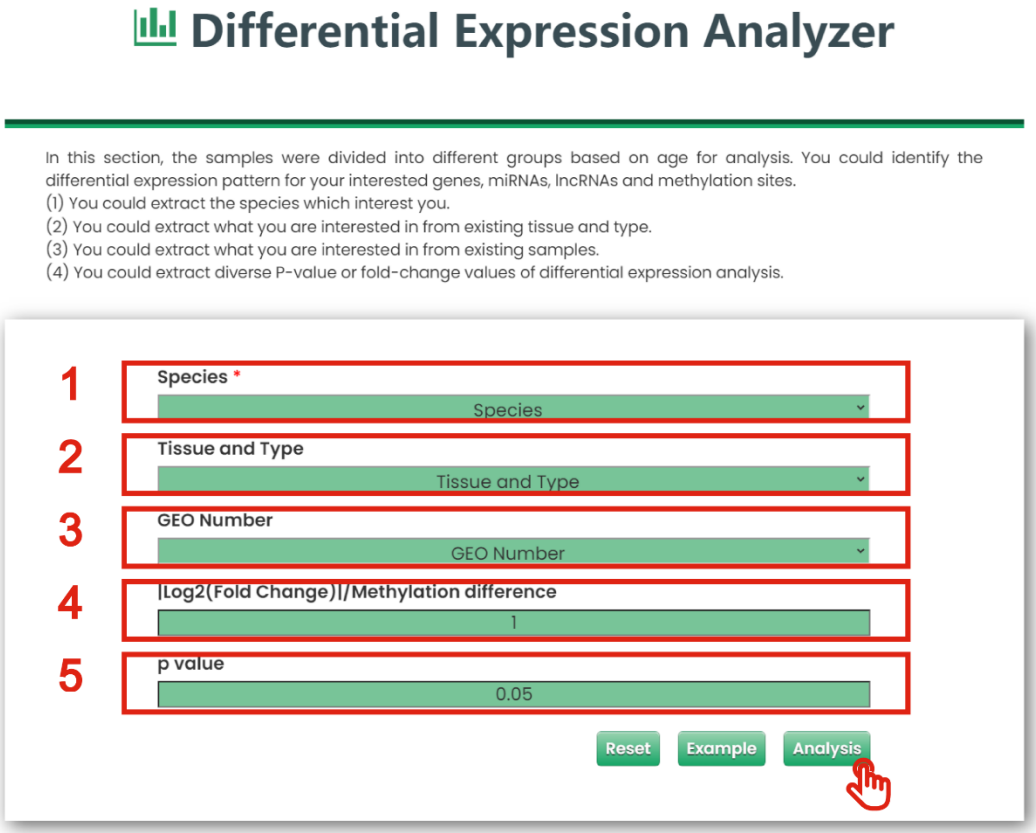

Figure 6-2

The result page is displayed in Figure 6-3:

1. Click to download data.
2. Users can input keywords from any column to filter the results.
3. Click to get a box plot graph for differential results.
4. The boxplot shows the differential expression levels of interested molecules.

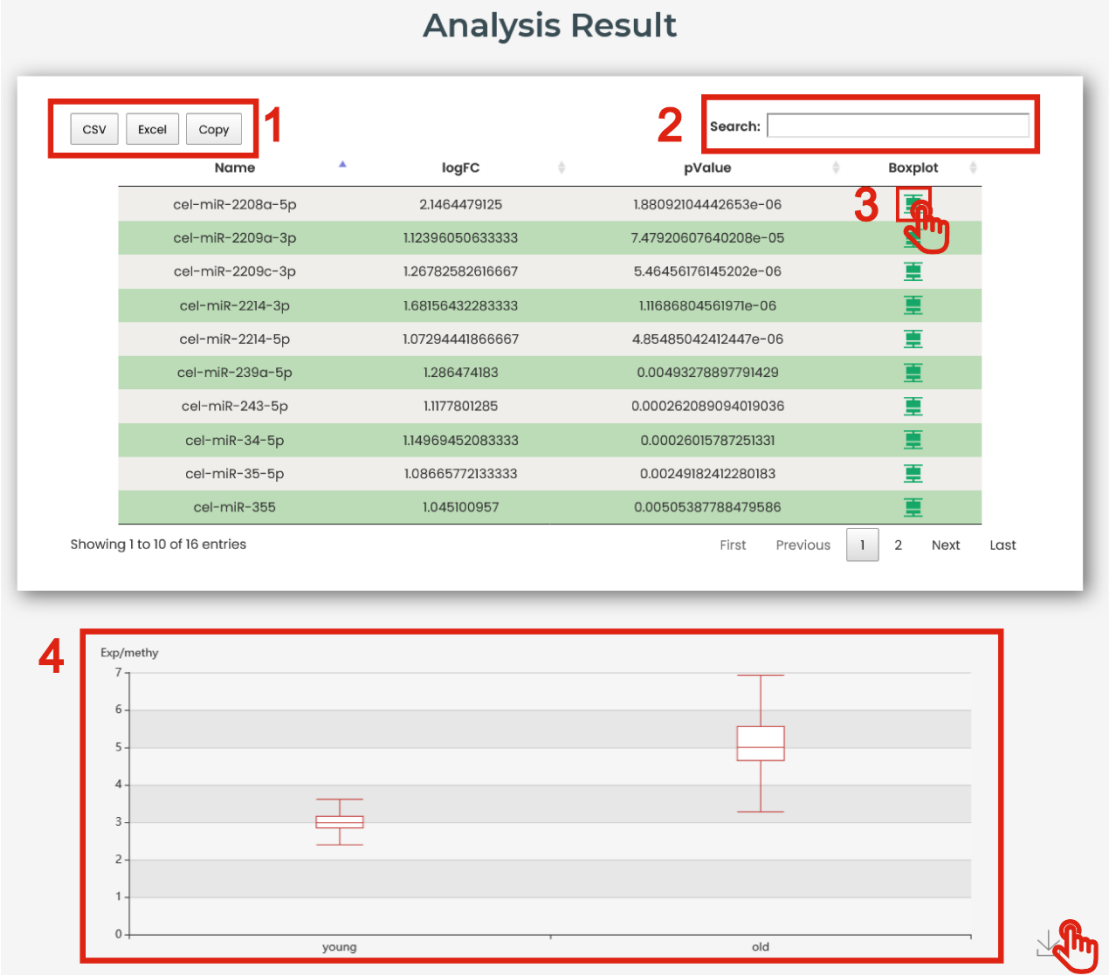

Figure 6-3

6.3. Data Heat Mapper

In this section, you will get a heatmap of the genes, miRNAs, lncRNAs and methylation sites which is related with your input based on aging-related GEO datasets.

The Data Heat Mapper page of Tool is displayed in Figure 6-4:

1. You could extract what you are interested in from existing species.
2. You could extract what you are interested in from existing tissue and type.
3. You could extract what you are interested in from existing samples.
4. You could limit interested |log2 (fold change)| or methylation difference.
5. You could limit interested P-values.

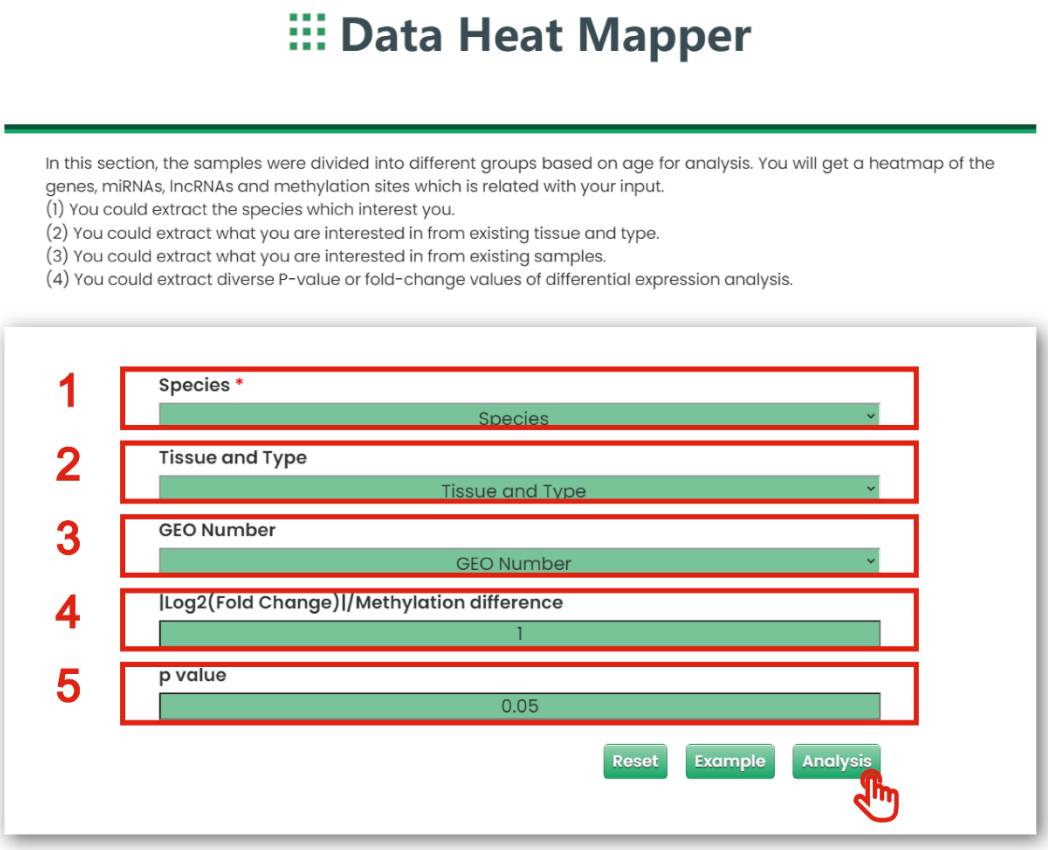

Figure 6-4

6.4. Co-Expression Network

In this section, you will get a graphic illustration of the co-expression network which is related with your input based on aging-related GEO datasets.

The Co-Expression Network page of Tool is displayed in Figure 6-5:

1. You could extract what you are interested in from existing species.
2. You could extract what you are interested in from existing tissue and type.
3. You could extract what you are interested in from existing samples.
4. You could get a table for all interested molecule.
5. You could extract diverse correlation coefficient of correlation analysis.
6. You could extract diverse P-values of correlation analysis.
7. The plot shows the co-expression network of interested molecule.

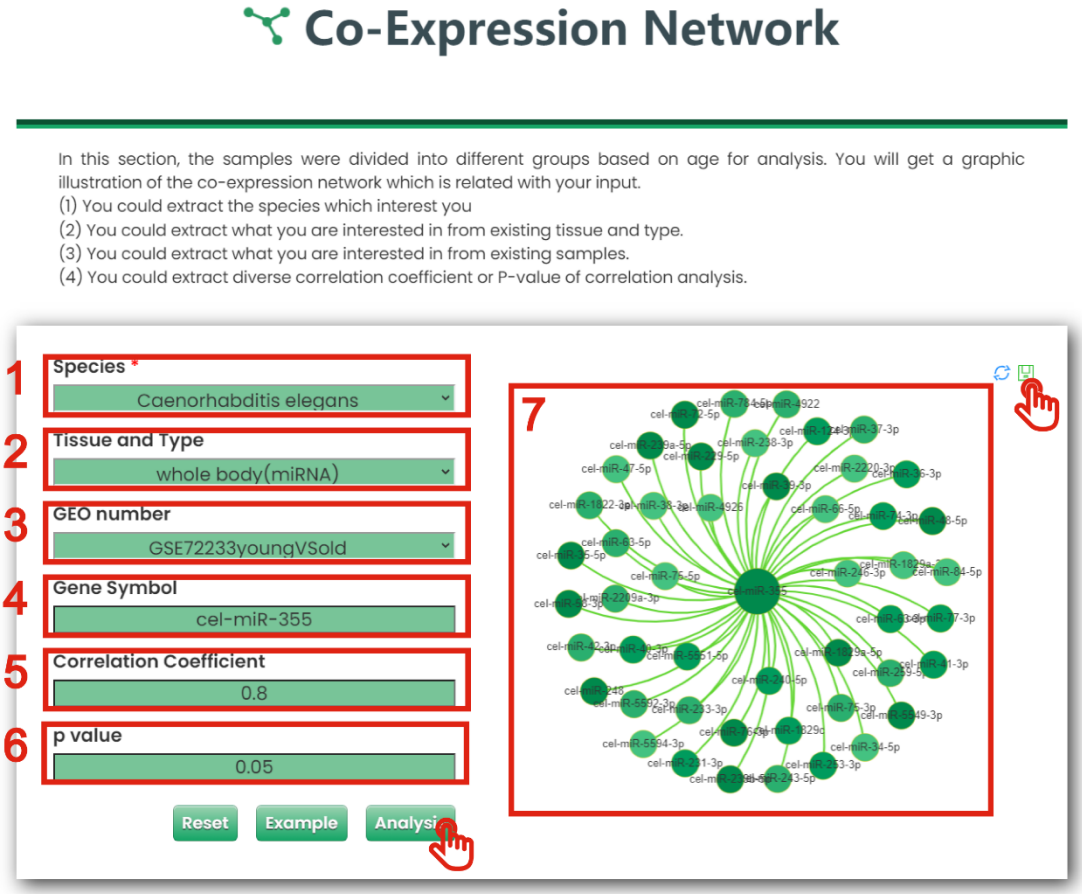

Figure 6-5

6.5. Functional Annotation Analyzer

In this section, you could extract interested genes, miRNAs and lncRNAs, and get function lists which are related with your input.

The Functional Annotation Analyzer page of Tool is displayed in Figure 6-6:

1. You could extract what you are interested in from existing species.
2. You could extract what you are interested in from existing tissue and type.
3. You could extract what you are interested in from existing samples.
4. You could extract diverse |log2 (fold change)| of differential expression analysis.
5. You could extract diverse P-values of differential expression analysis.
6. Click to download data.
7. Users can input keywords from any column to filter the results.
8. Click to get function annotation.

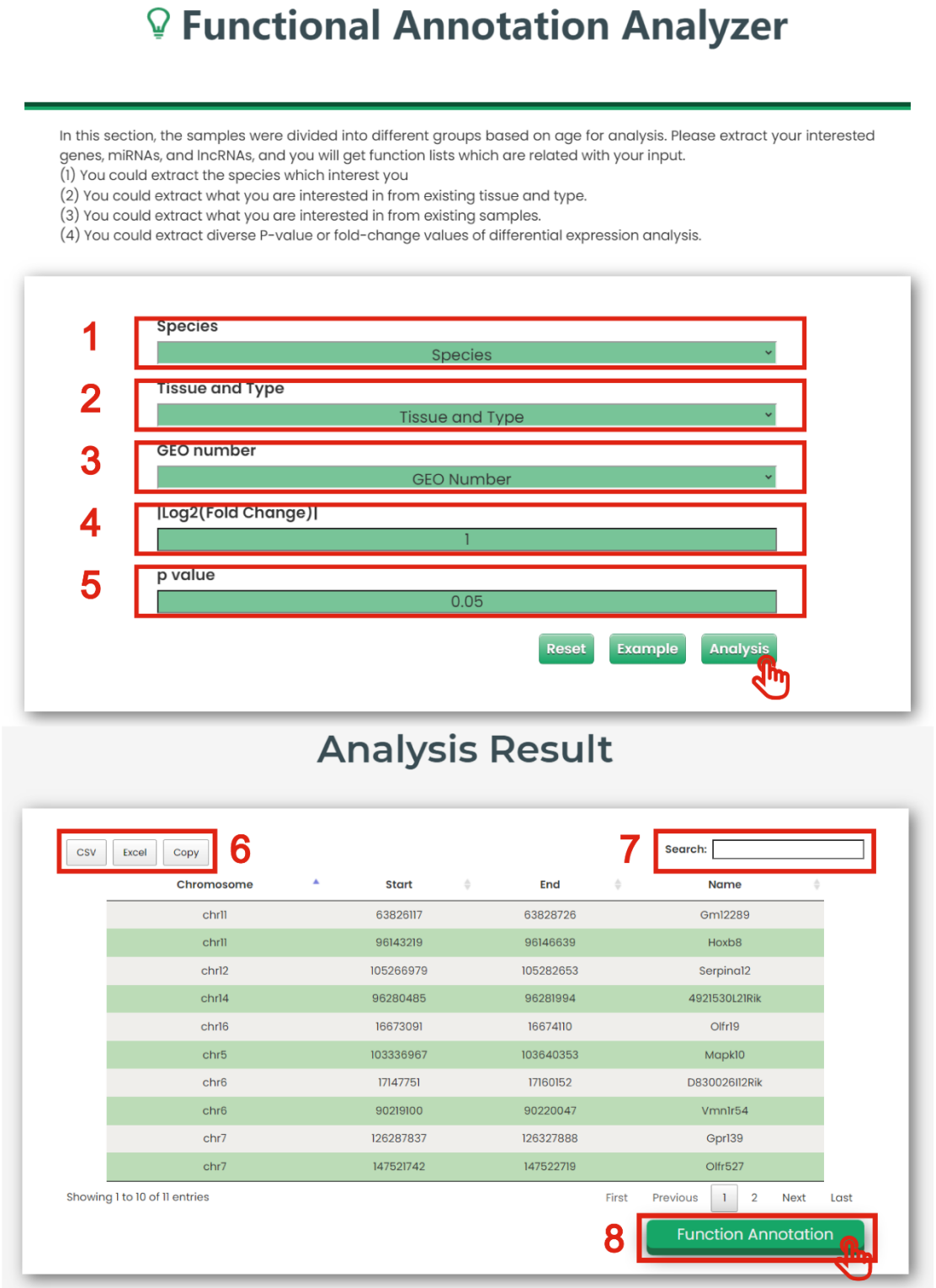
Functional Annotation Analyzer
In this section, the samples were divided into different groups based on age for analysis. Please extract your interested genes, miRNAs, and lncRNAs, and you will get function lists which are related with your input.
(1) You could extract the species which interest you
(2) You could extract what you are interested in from existing tissue and type.
(3) You could extract what you are interested in from existing samples.
(4) You could extract diverse P-value or fold-change values of differential expression analysis.
1
Species
Species
2
Tissue and Type
Tissue and Type
3
GEO number
GEO Number
4
|Log2(Fold Change)|
1
5
p value
0.05
Reset
Example
Analysis
Analysis Result
CSV
Excel
Copy
6
7
Search:
Chromosome
Start
End
Name
chr11 63826117 63828726 Gm12289
chr11 96143219 96146639 Hoxb8
chr12 105266979 105282653 Serpina12
chr14 96280485 96281994 4921530L21Rik
chr16 16673091 16674110 Olfr19
chr5 103336967 103640353 Mapkl0
chr6 17147751 17160152 D830026I12Rik
chr6 90219100 90220047 Vmn1r54
chr7 126287837 126327888 Gpr139
chr7 147521742 147522719 Olfr527
Showing 1 to 10 of 11 entries
First
Previous
1
2
Next
Last
8
Function Annotation

Figure 6-6

7. Cancer & Aging

7.1. Aging Landscape

In this section, the high-throughput datasets (age-grouped cancer datasets of TCGA) were used to understand the whole landscape of a specific molecule in all aging-related datasets.

The Aging Landscape page of Cancer & Aging is displayed in Figure 7-1:

1. Put the gene, miRNA and lncRNA which interest you.
2. The aging landscape graph for a specific molecule in all datasets.
3. The plot shows the P-values of differential expression for interested molecules in each aging-associated profiles. You could understand the whole landscape of a specific molecule in all the aging-associated datasets.

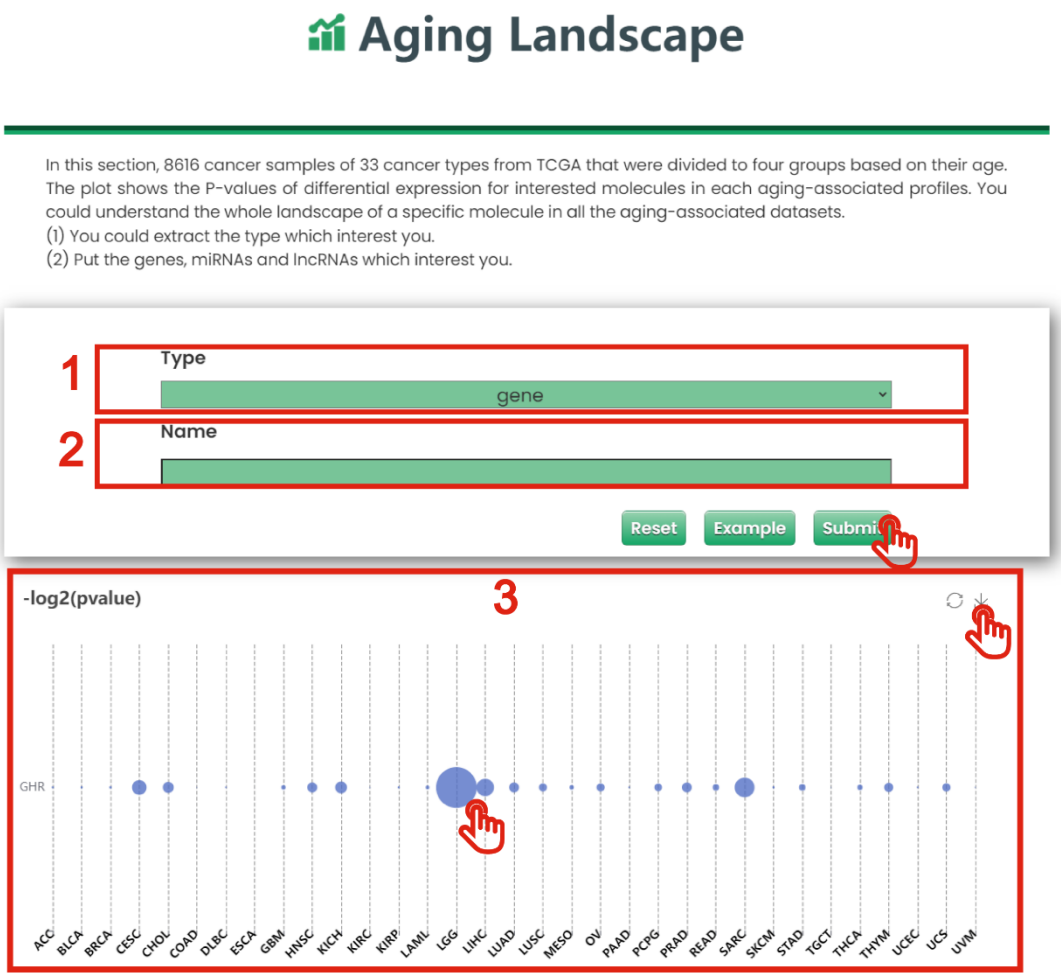

Figure 7-1

7.2. Differential Expression Analyzer

In this section, you could identify the differential expression pattern for your

interested genes, miRNAs and lncRNAs in age-grouped cancer datasets of TCGA. The Differential Expression Analyzer page of Cancer & Aging is displayed in Figure 7-2:

1. You could extract what you are interested in from existing tissue (TCGA Cancers).
2. You could put the gene, miRNA and lncRNA which interest you.
3. You could limit interested P-values of differential expression analysis.

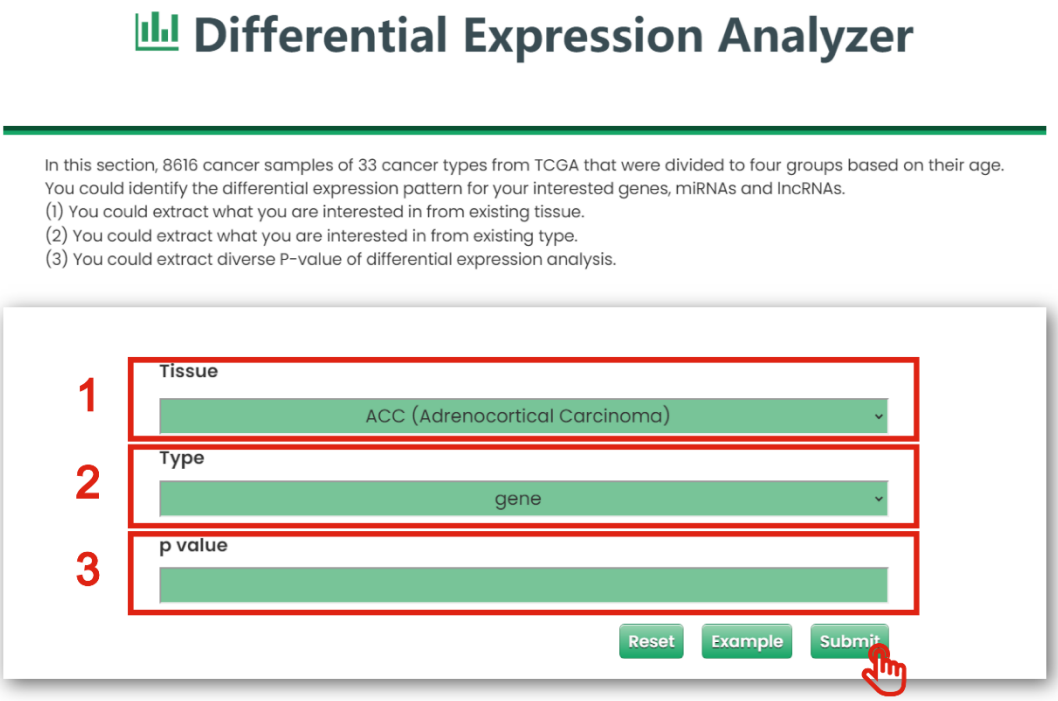

Figure 7-2

The result page is displayed in Figure 7-3:

1. Click to download data.
2. Users can input keywords from any column to filter the results.
3. Click to get a box plot graph for differential results.
4. The boxplot shows the differential expression levels of interested molecules.

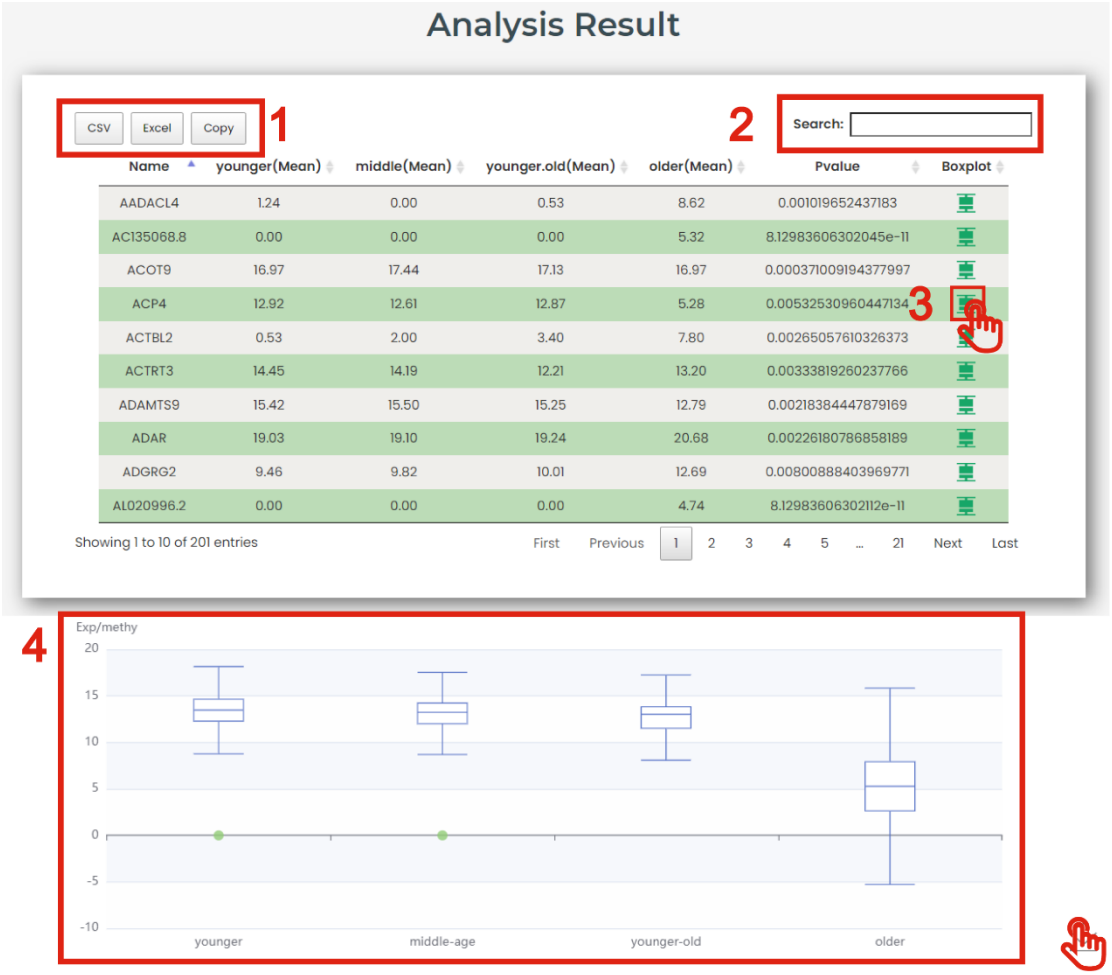

Figure 7-3

7.3. Data Heat Mapper

In this section, you will get a heatmap of the genes, miRNAs and lncRNAs which is related with your input based on age-grouped cancer datasets of TCGA.

The Data Heat Mapper page of Cancer & Aging is displayed in Figure 7-4:

1. You could extract what you are interested in from existing tissue (TCGA Cancers).
2. You could put the gene, miRNA and lncRNA which interest you.
3. You could limit interested P-values of differential expression analysis.

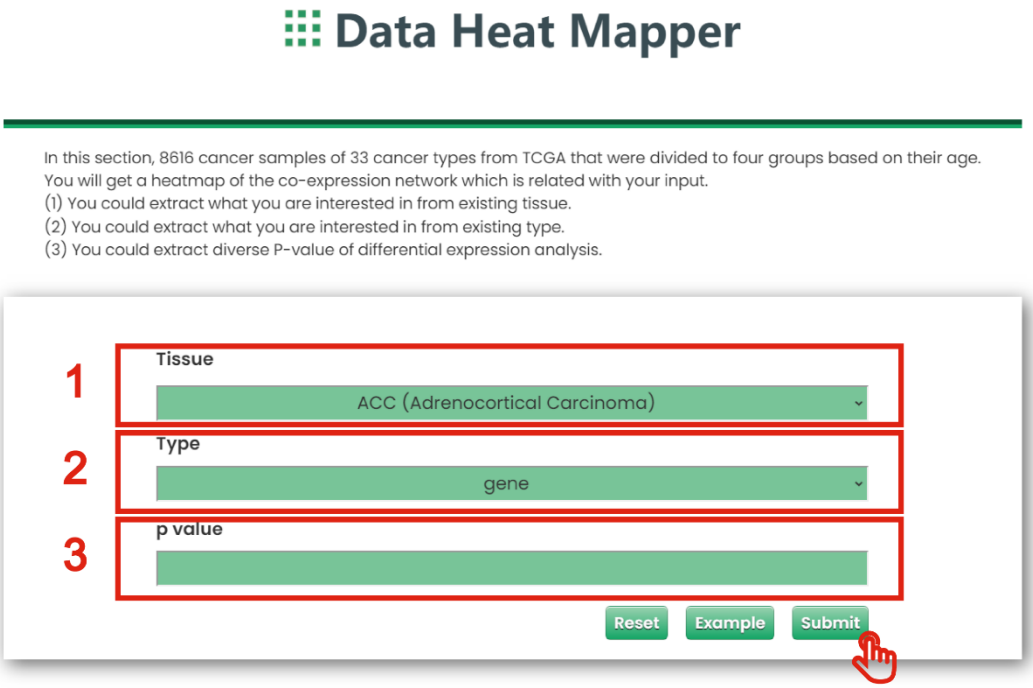

Figure 7-4

7.4. Co-Expression Network

In this section, you will get a graphic illustration of the co-expression network which is related with your input based on age-grouped cancer datasets of TCGA.

The Co-Expression Network page of Cancer & Aging is displayed in Figure 7-5:

1. You could extract what you are interested in from existing tissue (TCGA Cancers).
2. You could extract what you are interested in from type (gene, miRNA and lncRNA).
3. You could get a table for all interested molecule.
4. You could extract diverse correlation coefficient of correlation analysis.
5. You could extract diverse P-values of correlation analysis.
6. The plot shows the co-expression network of interested molecule.

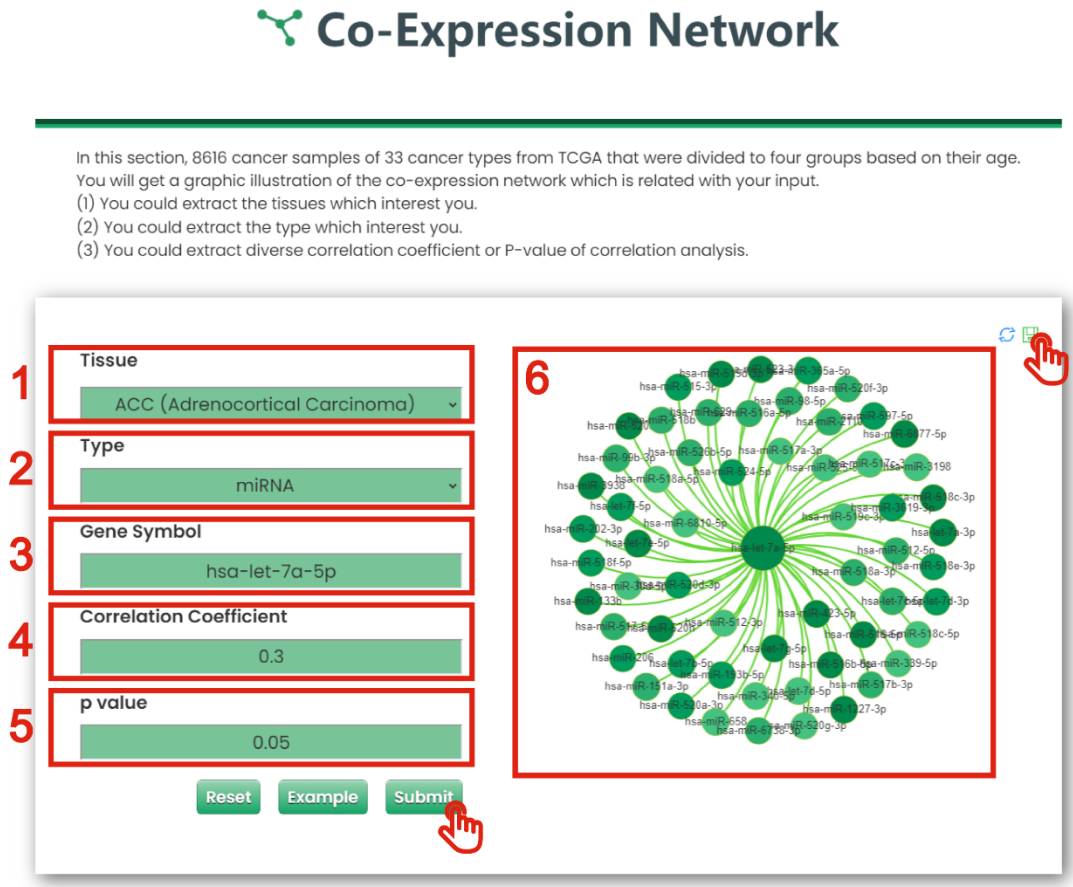

Figure 7-5

7.5. Functional Annotation Analyzer

In this section, you could extract interested genes, miRNAs and lncRNAs, and get function lists which are related with your input.

The Functional Annotation Analyzer page of Cancer & Aging is displayed in Figure 7-6:

1. You could extract what you are interested in from existing tissue (TCGA Cancers).
2. You could extract what you are interested in from existing type (gene, miRNA and lncRNA).
3. You could extract diverse P-values of differential expression analysis.
4. Click to download data.
5. Users can input keywords from any column to filter the results.
6. Click to get function annotation.

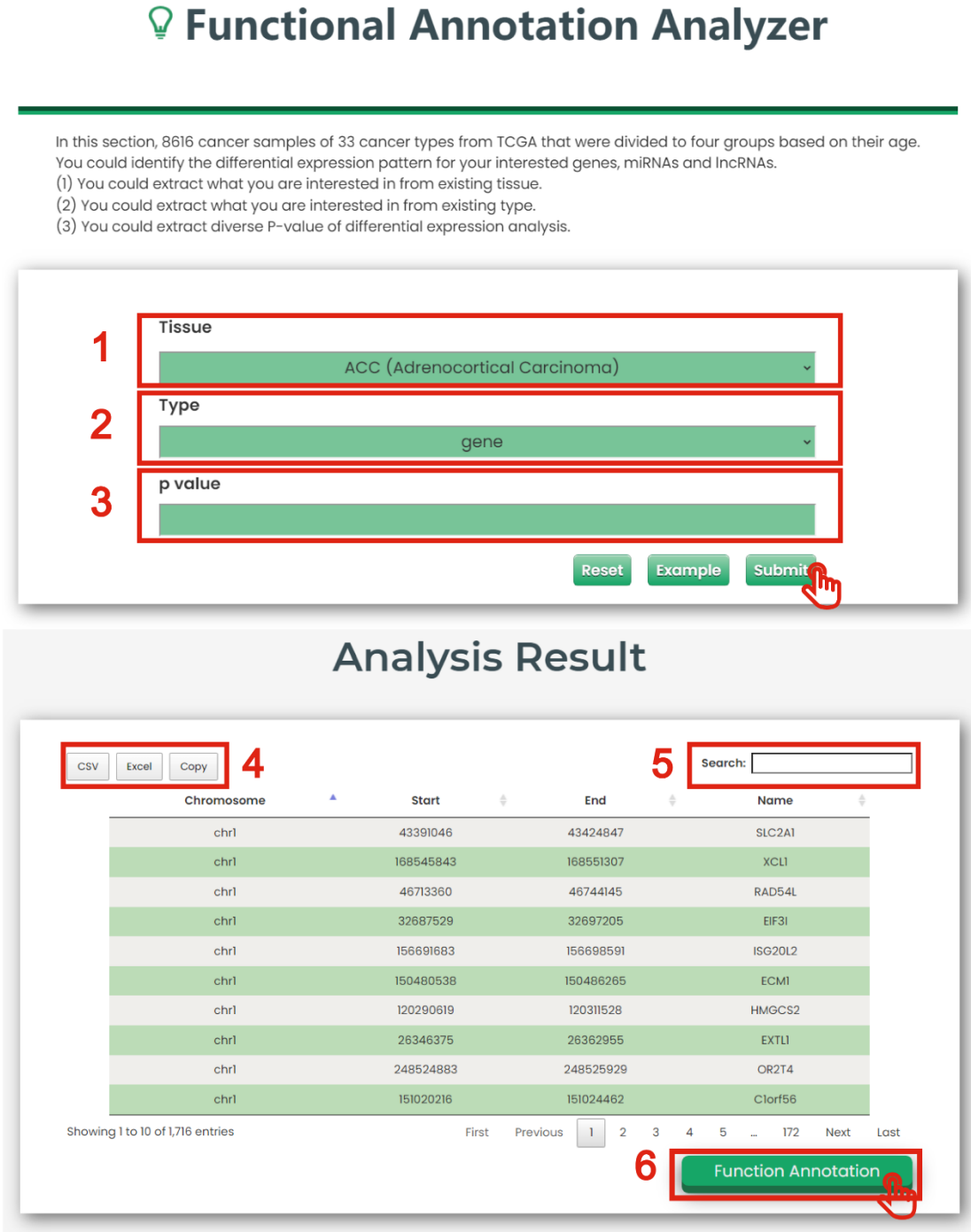
Functional Annotation Analyzer
In this section, 8616 cancer samples of 33 cancer types from TCGA that were divided to four groups based on their age.
You could identify the differential expression pattern for your interested genes, miRNAs and lncRNAs.
(1) You could extract what you are interested in from existing tissue.
(2) You could extract what you are interested in from existing type.
(3) You could extract diverse P-value of differential expression analysis.
1
Tissue
ACC (Adrenocortical Carcinoma)
2
Type
gene
3
p value
Reset
Example
Submit
Analysis Result
CSV
Excel
Copy
4
5
Search:
Chromosome
Start
End
Name
chr1 43391046 43424847 SLC2A1
chr1 168545843 168551307 XCL1
chr1 46713360 46744145 RAD54L
chr1 32687529 32697205 EIF3I
chr1 156691683 156698591 ISG20L2
chr1 150480538 150486265 ECM1
chr1 120290619 120311528 HMGCS2
chr1 26346375 26362955 EXTL1
chr1 248524883 248525929 OR2T4
chr1 151020216 151024462 C1orf56
Showing 1 to 10 of 1,716 entries
First
Previous
1
2
3
4
5
...
172
Next
Last
6
Function Annotation

Figure 7-6

8. Submit & Analysis

In this section, users could upload data for correlation analysis of interested molecules with age, and visualize them with heatmaps and correlation scatter plots.

The Submit & Analysis page is displayed in Figure 8-1:

1. You could upload dataset for correlation analysis.
2. You could extract diverse correlation coefficient of correlation analysis.
3. You could extract diverse P-values of correlation analysis.

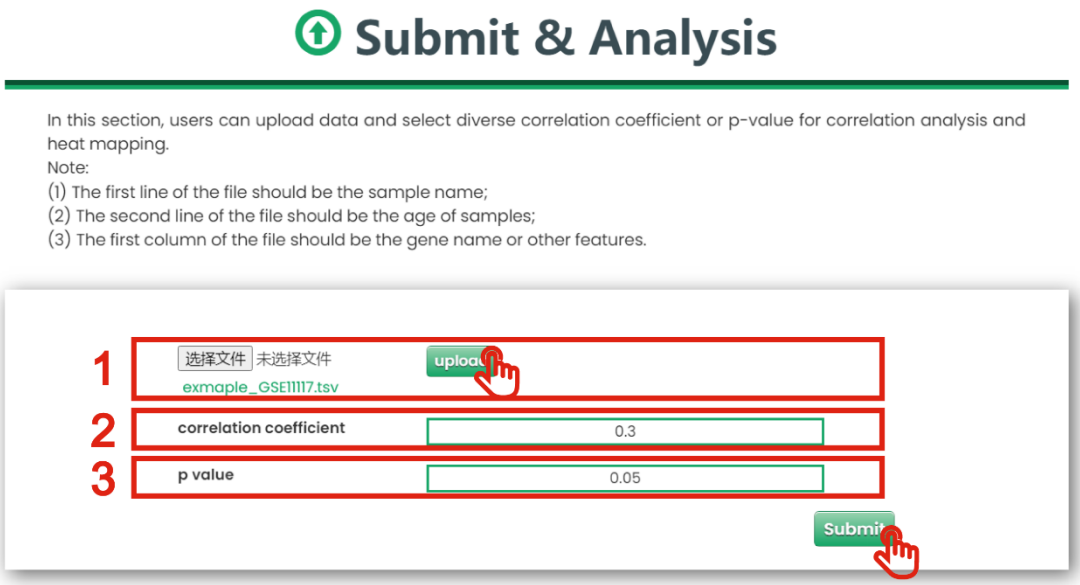

Figure 8-1

The analysis result page is displayed in Figure 8-2:

1. Click to download data.
2. Users can input keywords from any column to filter the results.

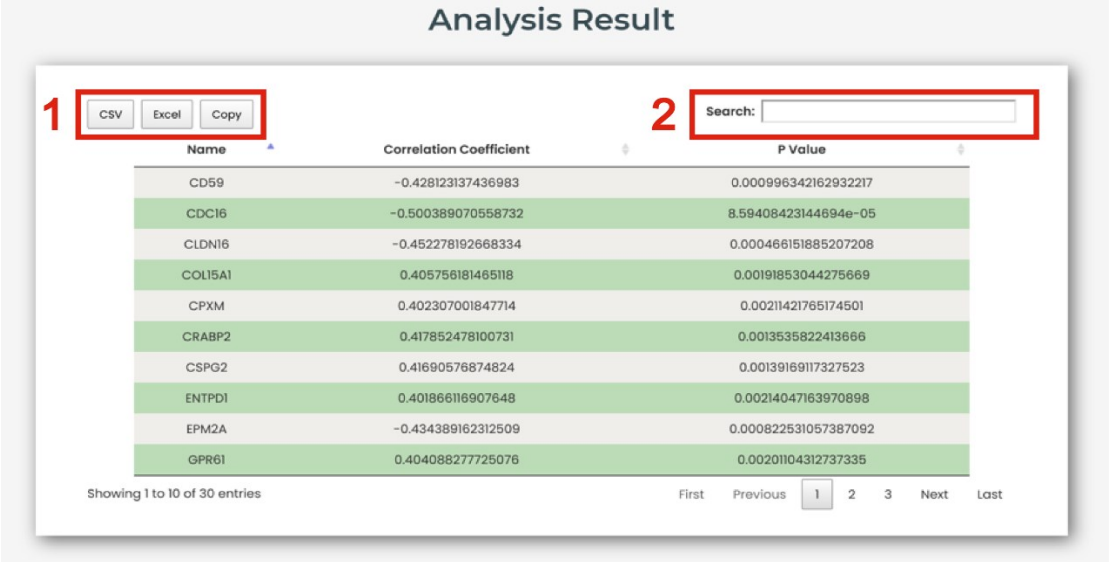

Figure 8-2

The page of heatmap or correlation scatter plot is displayed in Figure 8-3:

1. The correlation scatter plot shows the correlation between interested molecule and age.

2. The heatmap shows the association of interested molecules and age.

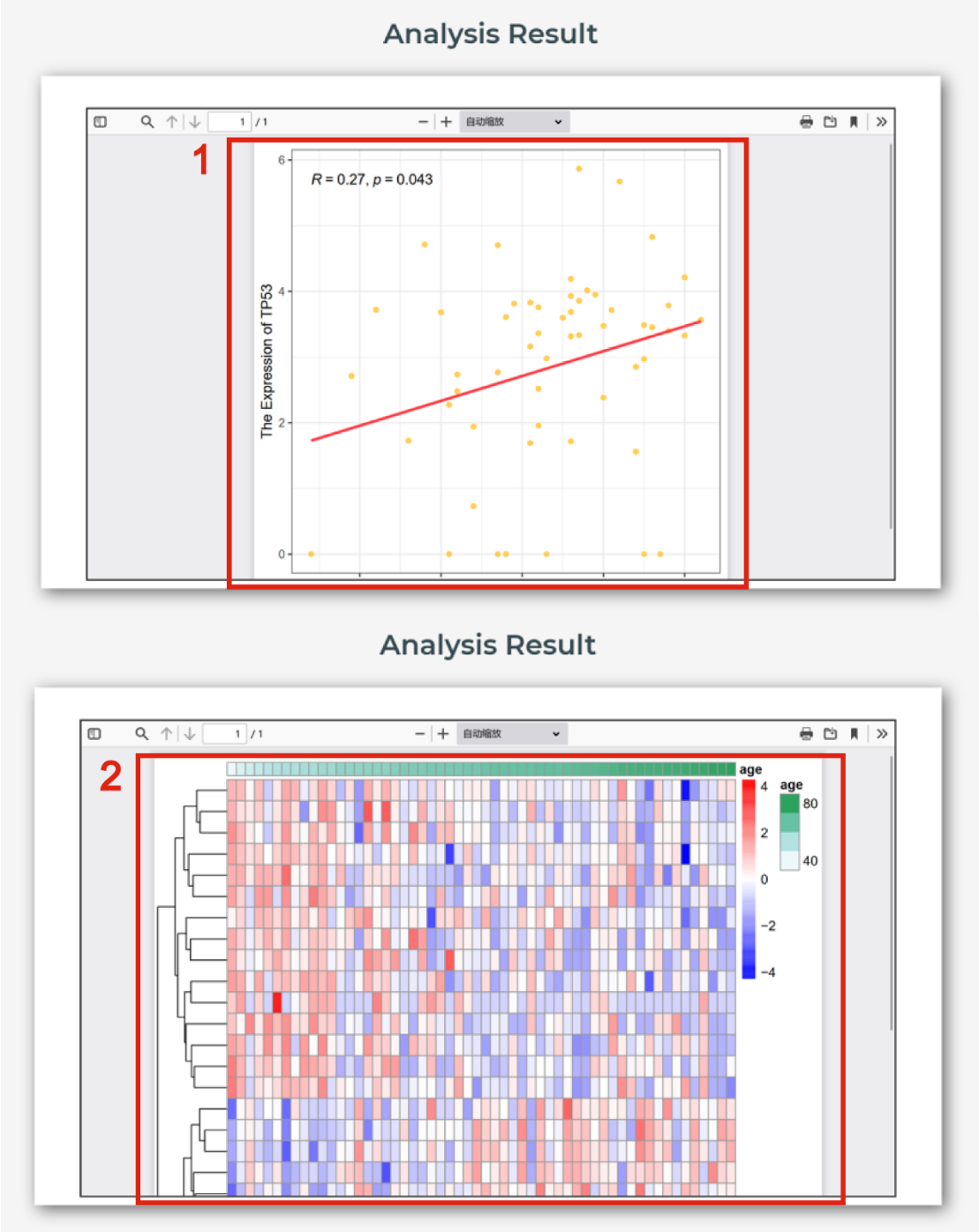

Figure 8-3

9. Download

Users could download experimentally supported diverse biomarker types and regulatory mechanisms for aging associations.

The Download page is displayed in Figure 9:

1. Click to download all aging-related experimental validated dataset.
2. Click to download aging-related experimental validated dataset in human.
3. Click to download aging-related experimental validated dataset in animal model.
4. Click to download aging-related experimental validated dataset in cell senescence.
5. Click to download aging-related experimental validated genes.
6. Click to download aging-related experimental validated non-coding RNAs.
7. Click to download aging-related experimental validated epigenomes.
8. Click to download aging-related experimental validated other regulatory elements.

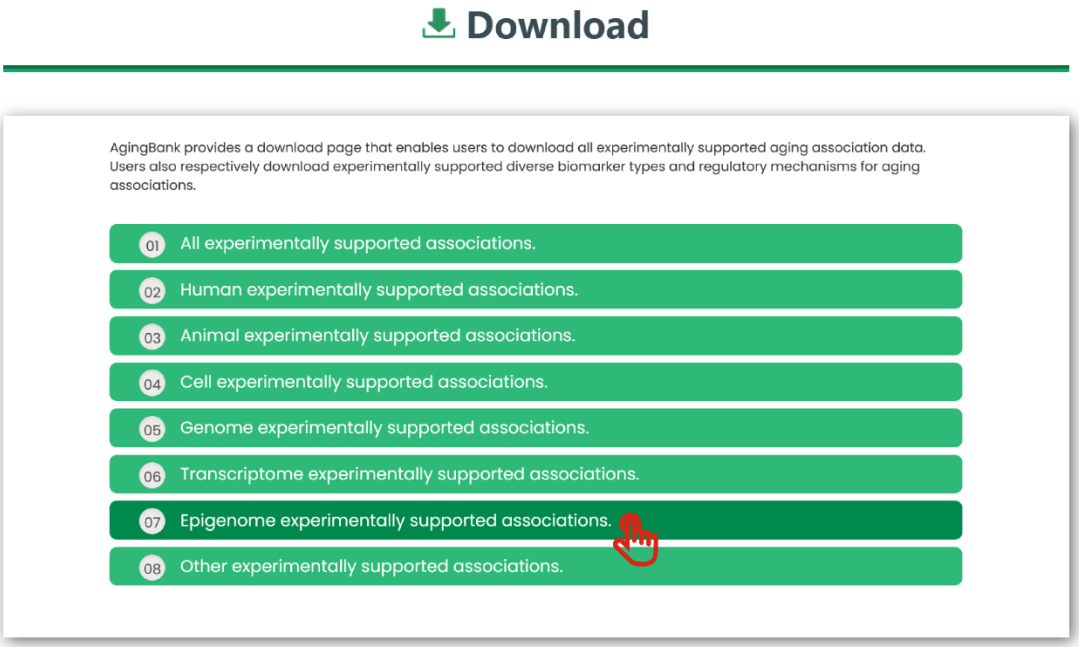

Figure 9

10. Application case

To allow a more comprehensive understanding for the functionality of AgingBank, we present the results of a case study of human-brain aging-related genes/miRNAs using AgingBank (Figure 10A). Aging could induce a variety of brain degenerative diseases and brain cancers. Thus, identifying aging-related biomarkers in brain tissues could provide references for study and treatment of brain diseases and cancers. AgingBank could become a useful tool for identifying aging-related biomarkers by integrating experimentally verified data, high-throughput experiment data and multi-omics data. First, we applied the Differential Expression Analyzer of AgingBank's Cancer & Aging and Tools modules for high-throughput datasets (TCGA-HNSC and GEO-GSE104704 gene expression profiles) and obtained gene biomarkers associated with aging. We also screened interested species (Homo sapiens), molecular types (gene), and other factors (disease) in AgingBank's Search module to obtain experimentally supported aging-related gene biomarkers. Then, based on the characteristics of the above three genesets, we obtained the common genes and selected the interested gene from them. In addition, we searched and gained interested miRNAs, including miRNAs obtained by Differential Expression Analyzer in Cancer & Aging modules (TCGA-HNSC miRNA) and miRNAs in gene-miRNA pairs. Finally, we constructed gene-miRNA regulatory network for the interested gene.

Based on brain-related high-throughput datasets, we used Agingbank to identify 2524 and 987 differentially expressed aging-related genes in the TCGA-HNSC and GEO-GSE104704 datasets, respectively (p-values < 0.05, Figure 10B). We also collected 97 experimentally supported aging-related genes associated with human diseases (Figure 10B). Notably, RBM38 appeared in the above genesets as the interested gene. RBM38 is involved in DNA damage response, signal transduction by p53-like mediators, negative regulation of cell population proliferation and regulation of RNA metabolic processes. Current study has shown that ectopic expression of RBM38 induced apoptosis and senescence in hepatocellular carcinoma cells, inhibited proliferation and colony growth, and suppressed migration and invasion in vitro[1]. However, the association of RBM38 aberrant expression with brain aging still unknown and further exploration is needed. In addition, 121 differentially expressed aging-associated miRNAs (TCGA-HNSC miRNA) and 190 RBM38-miRNA pairs were obtained, respectively. Fifteen miRNAs were included as interested miRNAs for further

study (Figure 10C). Finally, we constructed the regulatory network of RBM38-miRNA based on gene-miRNA pairs. Notably, we found three experimentally supported aging-related miRNAs (miR-449a, miRNA-15b and miRNA-106a) in the regulatory network (Figure 10D). And, other miRNAs in the network may become potential aging-related biomarkers. The users could use Agingbank to identify candidate aging-related biomarkers, or explore the potential link between biological aging and the risk of many age-related diseases.

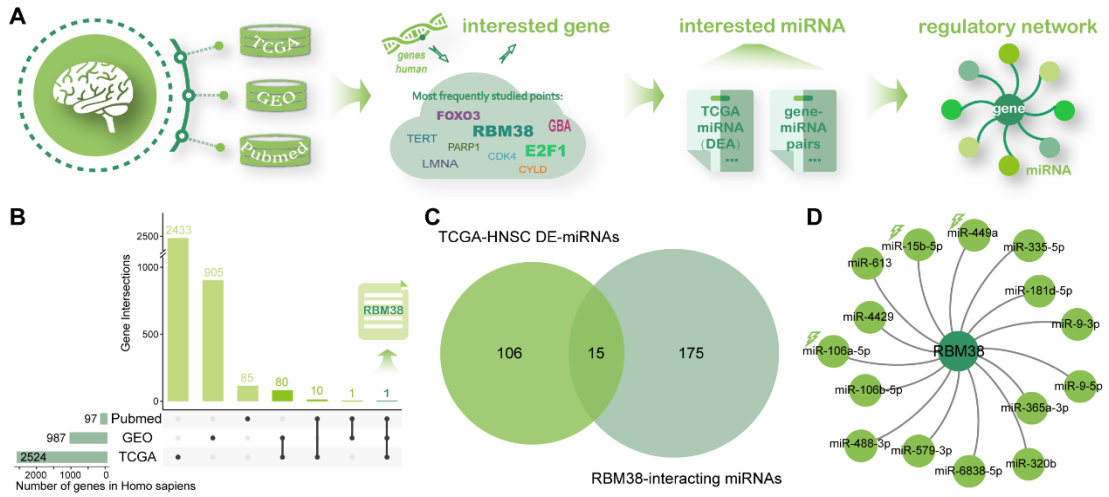

Figure 10

11. Search strategy

We searched the PubMed database as follows:

1. ((((aging[Title/Abstract])) OR (ageing[Title/Abstract])) OR (senescence[Title/Abstract]) OR (age[Title]) OR (longevity[Title/Abstract]) OR (age-[Title])) AND (lncRNA[Title/Abstract] OR lncRNAs[Title/Abstract] OR long non-coding RNA[Title/Abstract] OR long non-coding RNAs[Title/Abstract] OR lincRNA[Title/Abstract] OR lincRNAs[Title/Abstract] OR miRNAs[Title/Abstract] OR miRNA[Title/Abstract] OR microRNA[Title/Abstract] OR microRNAs[Title/Abstract] OR circRNA[Title/Abstract] OR circRNAs[Title/Abstract] OR circular RNA[Title/Abstract] OR circular RNAs[Title/Abstract]OR circular RNAs[Title/Abstract] OR non-coding RNAs[Title/Abstract] OR non-coding RNA[Title/Abstract] OR non coding[Title/Abstract] OR pseudogene[Title/Abstract] OR linRNA[Title/Abstract] OR linRNAs[Title/Abstract] OR SAL-RNAs[Title/Abstract] OR SAL-RNA[Title/Abstract] OR piRNA[Title/Abstract] OR piRNAs[Title/Abstract] OR snRNA[Title/Abstract]).

2. ((((aging[Title/Abstract])) OR (ageing[Title/Abstract])) OR (senescence[Title/Abstract]) OR (OR (age[Title]) OR (age-[Title] OR (longevity[Title/Abstract])) AND (methylation[Title/Abstract] OR methylations[Title/Abstract] OR histone[Title/Abstract] OR histone modification[Title/Abstract]).

3. (aging[Title] OR (ageing[Title]) OR (senescence[Title]) OR (age[Title]) OR (age-[Title]) OR longevity[Title]) AND (impringting[Title/Abstract] OR RNA editing[Title/Abstract] OR gene silencing[Title/Abstract] OR alternative splicing[Title/Abstract] OR enhancer[Title/Abstract] OR transcription factor[Title/Abstract] OR TF[Title/Abstract] OR silencer[Title/Abstract] OR terminator[Title/Abstract] OR insulator[Title/Abstract] OR variant[Title/Abstract] OR SNP[Title/Abstract] OR mutation[Title/Abstract] OR CNV[Title/Abstract] OR copy number variation[Title/Abstract] OR variation[Title/Abstract]).

4. (aging[Title] OR (ageing[Title]) OR (senescence[Title]) OR (age[Title]) OR (age-[Title]) OR longevity[Title]) AND (impringting[Title/Abstract] OR RNA editing[Title/Abstract] OR gene silencing[Title/Abstract] OR alternative splicing[Title/Abstract] OR enhancer[Title/Abstract] OR transcription factor[Title/Abstract] OR TF[Title/Abstract] OR silencer[Title/Abstract] OR

terminator[Title/Abstract] OR insulator[Title/Abstract] OR SNP[Title/Abstract] OR mutation[Title/Abstract] OR CNV[Title/Abstract] OR copy number variation[Title/Abstract] OR variant[Title/Abstract] OR regulatory element[Title/Abstract]).

Reference

1 Ye, J. *et al.* RBM38 plays a tumor-suppressor role via stabilizing the p53-mdm2 loop function in hepatocellular carcinoma. *J Exp Clin Cancer Res* **37**, 212, doi:10.1186/s13046-018-0852-x (2018).