

# User Manual

<b>1. Home</b> .....	<b>1</b>
<b>2. Browse</b> .....	<b>3</b>
<b>3. Search</b> .....	<b>4</b>
<b>4. Search results</b> .....	<b>6</b>
<b>5. Detail information</b> .....	<b>7</b>
<b>6. Tool</b> .....	<b>8</b>
6.1. Aging Landscape.....	8
6.2. Differential Expression Analyzer .....	9
6.3. Data Heat Mapper .....	10
6.4. Co-Expression Network.....	11
6.5. Functional Annotation Analyzer .....	12
<b>7. Cancer &amp; Aging</b> .....	<b>14</b>
7.1. Aging Landscape.....	14
7.2. Differential Expression Analyzer .....	14
7.3. Data Heat Mapper .....	16
7.4. Co-Expression Network.....	17
7.5. Functional Annotation Analyzer .....	18
<b>8. Submit &amp; Analysis</b> .....	<b>20</b>
<b>9. Download</b> .....	<b>22</b>
<b>10. Application case</b> .....	<b>23</b>
<b>11. Search strategy</b> .....	<b>25</b>

# 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.

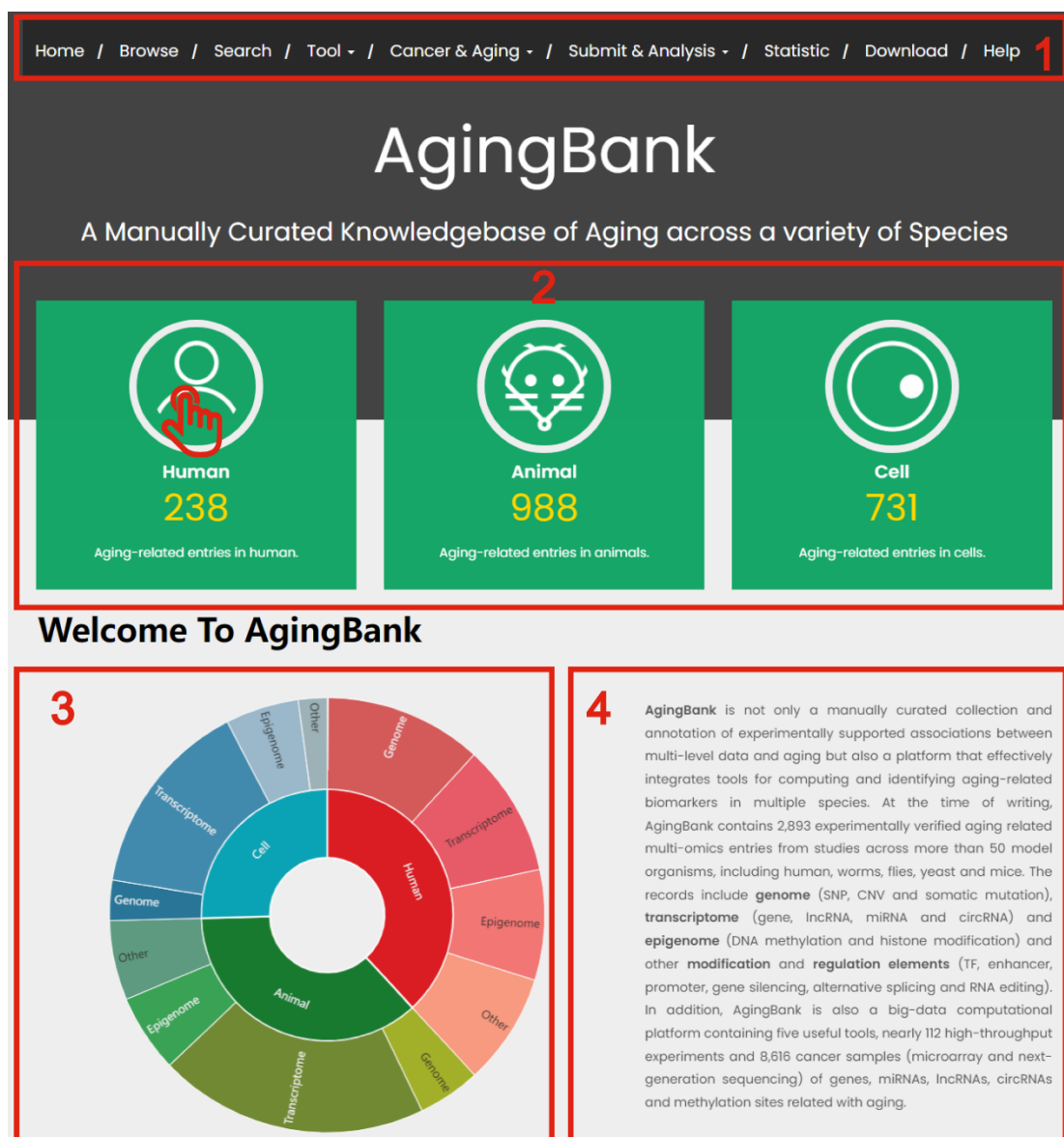


Figure 1-1

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.

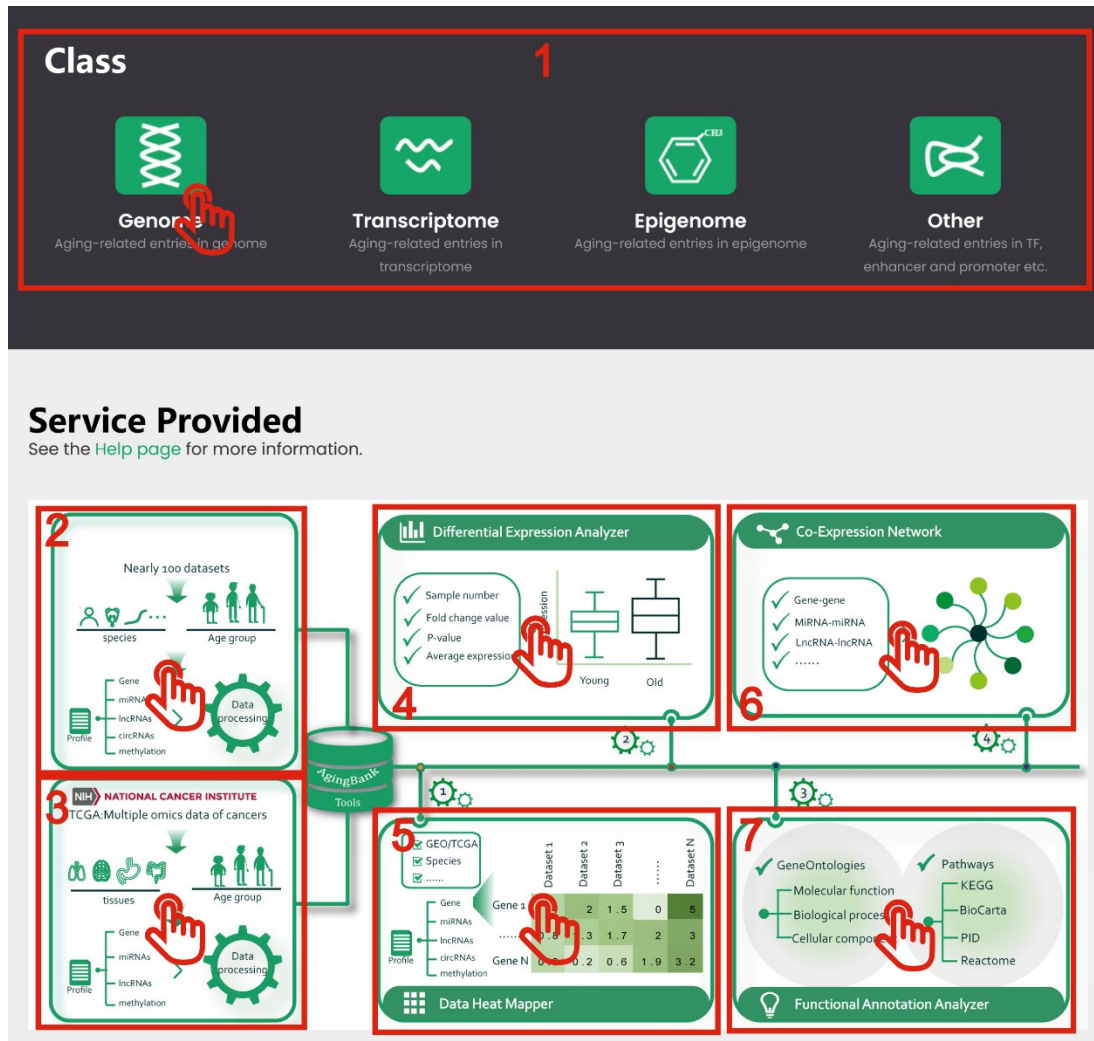


Figure 1-2

## 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.

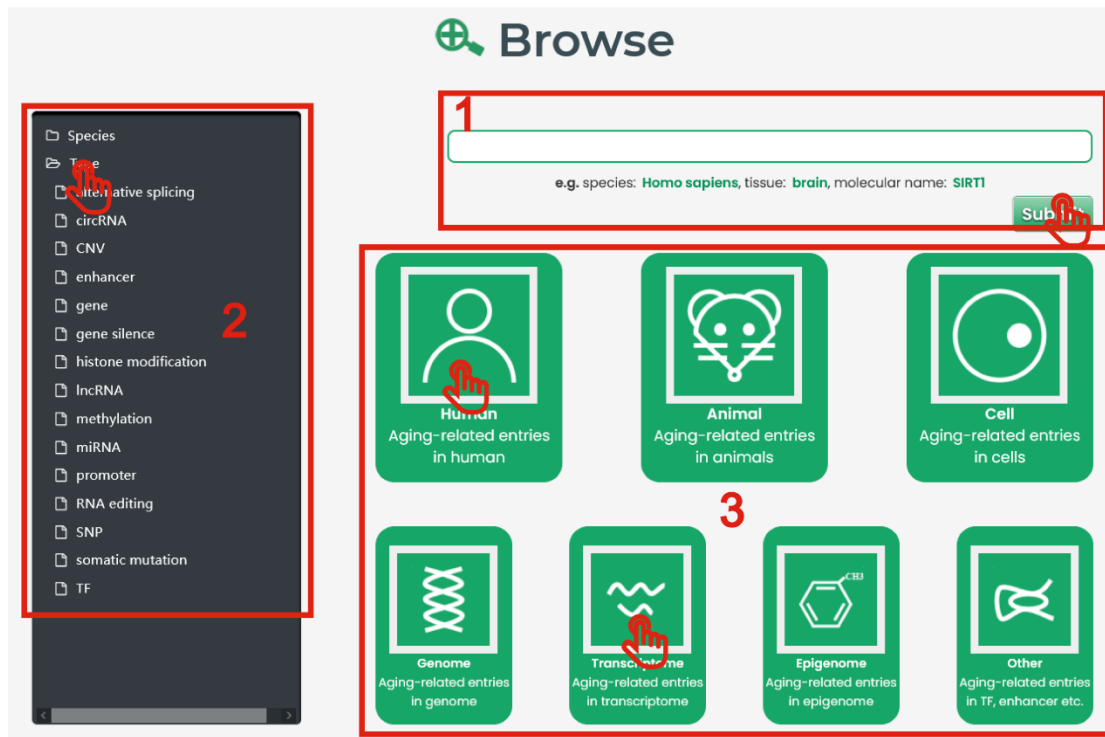


Figure 2

### 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.

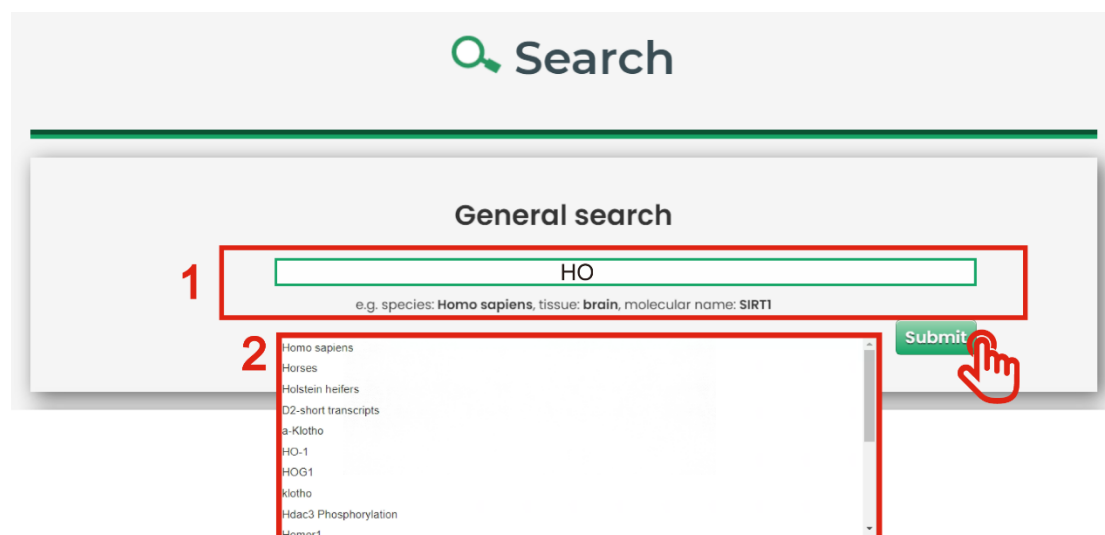


Figure 3-1

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

<b>1</b>	Species	<input type="text" value="Homo sapiens"/>
<b>2</b>	Type	<input type="text" value="gene"/>
<b>3</b>	Name	<input type="text" value="SIRT1"/>
<b>4</b>	Experiment Method	<input checked="" type="checkbox"/> qPCR <input type="checkbox"/> RNA-seq <input type="checkbox"/> Assay <input type="checkbox"/> microarray <input type="checkbox"/> ChIP-Seq <input type="checkbox"/> Immunofluorescence <input type="checkbox"/> Other
<b>5</b>	Other	<input type="checkbox"/> circulating <input type="checkbox"/> variant <input type="checkbox"/> drug <input checked="" type="checkbox"/> disease <input type="checkbox"/> environmental factor

**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.

**Result**

1 CSV Excel Copy

4 Search:

Species	Type	name	sample	Tissue	Up/Down	Pro/Anti	Pubmed ID	Details
Homo sapie...	gene	SIRT1	cell	liver	Up	Anti	29402742	details
Homo sapie...	gene	SIRT1	cell	NA	NA	Anti	16923962	details
Homo sapie...	gene	SIRT1	cell	NA	NA	Anti	16923962	details
Homo sapie...	gene	SIRT1	cell	IMR90,MEFs	Up	Anti	16939484	details
Homo sapie...	gene	SIRT1	human	Skin	Up	Anti	17180656	details
Homo sapie...	gene	SIRT1	cell	LNCaP,DU145	NA	Anti	17505061	details
Homo sapie...	gene	SIRT1	animal	C2C12 myo...	Up	Anti	17908559	details
Homo sapie...	gene	SIRT1	cell	U-2 OS	Up	Anti	17996922	details
Homo sapie...	gene	SIRT1	cell	HEK293,U3OS	Down	Anti	18203716	details
Homo sapie...	gene	SIRT1	human; ani...	embryos,ME...	Down	NA	18835033	details

Showing 1 to 10 of 15 entries


First Previous 1 2 Next Last

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.

 **Details**

---

<b>1</b>	<table border="1"><tbody><tr><td>Name</td><td>SIRT1</td></tr><tr><td>Type</td><td>gene</td></tr><tr><td>Species</td><td>Homo sapiens</td></tr><tr><td>Tissue</td><td>liver</td></tr><tr><td>Experiment Method</td><td>PCR,other</td></tr><tr><td>Up/Down</td><td>Up</td></tr><tr><td>Pro/Anti</td><td>Anti</td></tr><tr><td>Function Description</td><td>SIRT1 regulate aging-related proteins. Studies suggest that the human SIRT1 function as intracellular regulatory proteins with mono-ADP-ribosyltransferase activity. The protein encoded by this gene is included in class I of the sirtuin family. Alternative</td></tr><tr><td>Regulation Gene</td><td>NA</td></tr></tbody></table>	Name	SIRT1	Type	gene	Species	Homo sapiens	Tissue	liver	Experiment Method	PCR,other	Up/Down	Up	Pro/Anti	Anti	Function Description	SIRT1 regulate aging-related proteins. Studies suggest that the human SIRT1 function as intracellular regulatory proteins with mono-ADP-ribosyltransferase activity. The protein encoded by this gene is included in class I of the sirtuin family. Alternative	Regulation Gene	NA
Name	SIRT1																		
Type	gene																		
Species	Homo sapiens																		
Tissue	liver																		
Experiment Method	PCR,other																		
Up/Down	Up																		
Pro/Anti	Anti																		
Function Description	SIRT1 regulate aging-related proteins. Studies suggest that the human SIRT1 function as intracellular regulatory proteins with mono-ADP-ribosyltransferase activity. The protein encoded by this gene is included in class I of the sirtuin family. Alternative																		
Regulation Gene	NA																		
<b>2</b>	<table border="1"><tbody><tr><td>Year</td><td>2018</td></tr><tr><td>Pubmed ID</td><td><a href="#">29402742</a></td></tr><tr><td>Title</td><td>Novel SIRT1 activator MHY2233 improves glucose tolerance and reduces hepatic lipid accumulation in db/db mice</td></tr></tbody></table>	Year	2018	Pubmed ID	<a href="#">29402742</a>	Title	Novel SIRT1 activator MHY2233 improves glucose tolerance and reduces hepatic lipid accumulation in db/db mice												
Year	2018																		
Pubmed ID	<a href="#">29402742</a>																		
Title	Novel SIRT1 activator MHY2233 improves glucose tolerance and reduces hepatic lipid accumulation in db/db mice																		
<b>3</b>	<table border="1"><tbody><tr><td>Drug</td><td>NA</td></tr><tr><td>Disease</td><td>NA</td></tr><tr><td>Environment Factors</td><td>NA</td></tr><tr><td>Circulating</td><td>NA</td></tr><tr><td>Variant</td><td>NA</td></tr><tr><td>High-throughput</td><td>NA</td></tr></tbody></table>	Drug	NA	Disease	NA	Environment Factors	NA	Circulating	NA	Variant	NA	High-throughput	NA						
Drug	NA																		
Disease	NA																		
Environment Factors	NA																		
Circulating	NA																		
Variant	NA																		
High-throughput	NA																		

**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.

### Aging Landscape

In this section, the samples were divided into different groups based on age for analysis. The plot shows the P-value 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.

- (1) You could extract the species which interest you.
- (2) Put the genes, miRNAs, lncRNAs and methylation sites which interest you.

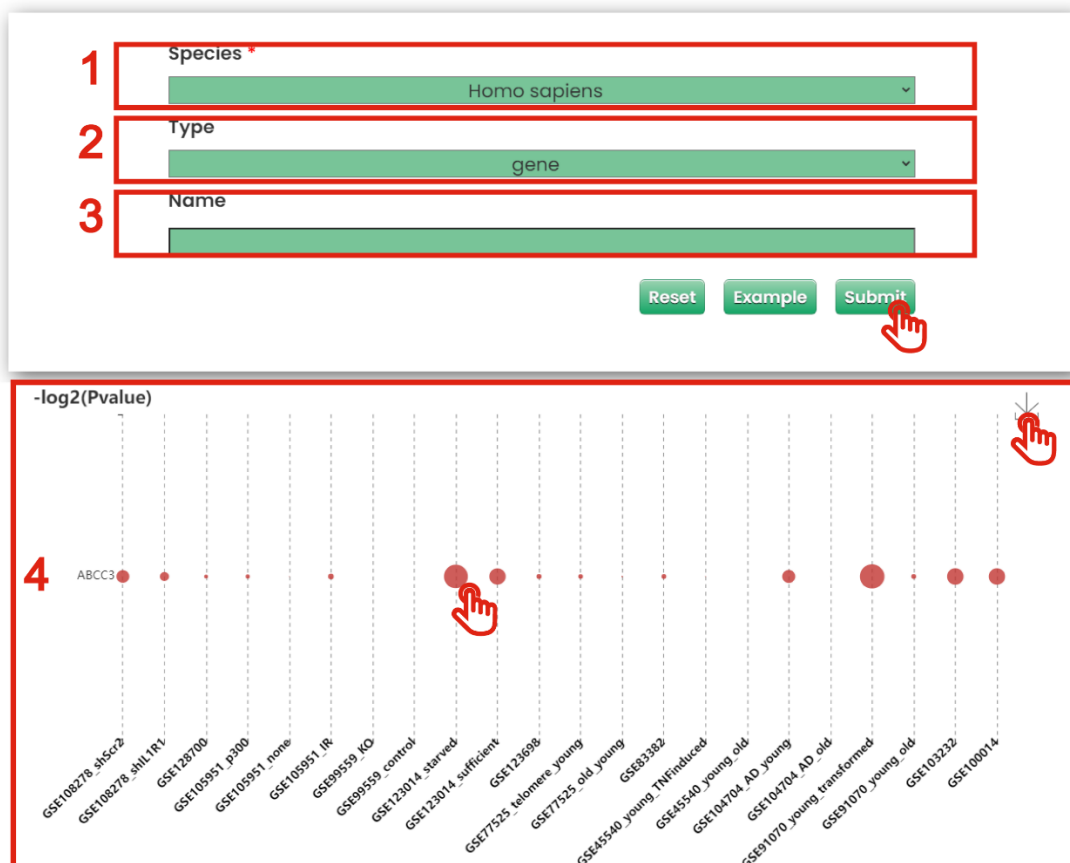


Figure 6-1

## 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  $|\log_2(\text{fold change})|$  or methylation difference of differential expression analysis.
5. You could limit interested P-values of differential expression analysis.

### Differential Expression Analyzer

In this section, the samples were divided into different groups based on age for analysis. You could identify the differential expression pattern for your interested genes, miRNAs, lncRNAs and methylation sites.

- (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.

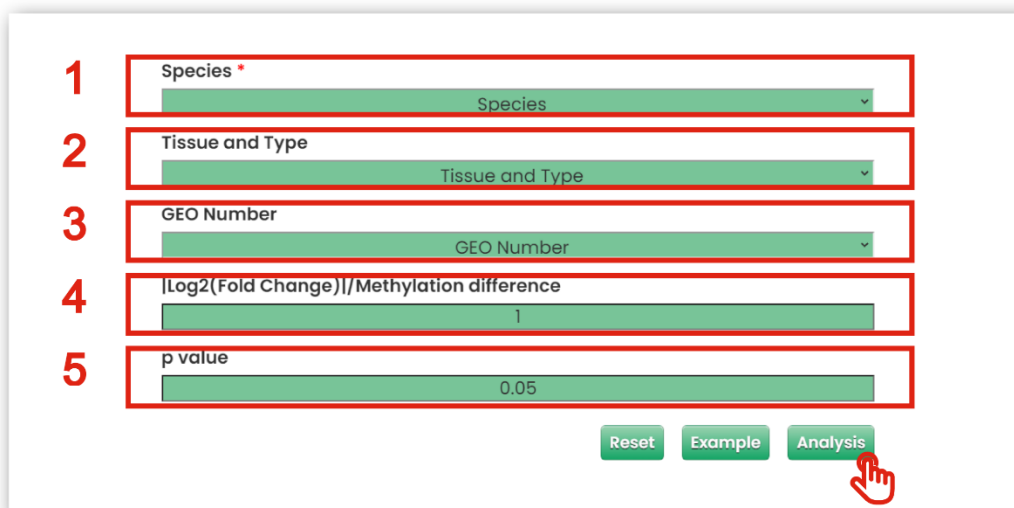
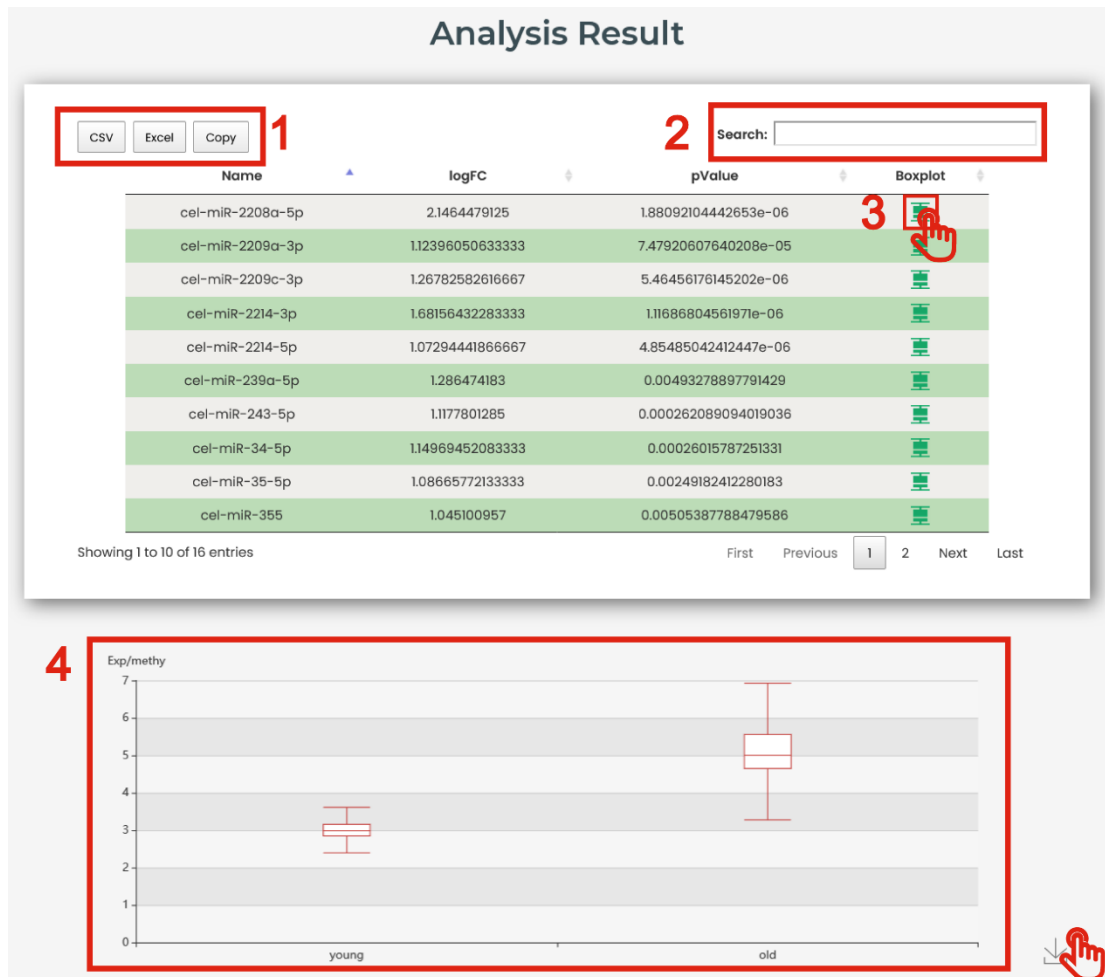


Figure 6-2

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  $|\log_2(\text{fold change})|$  or methylation difference.
5. You could limit interested P-values.

# ☐ Data Heat Mapper

In this section, the samples were divided into different groups based on age for analysis. You will get a heatmap of the genes, miRNAs, lncRNAs and methylation sites which is 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.

The screenshot shows the Data Heat Mapper tool interface with five input fields and three buttons. The fields are numbered 1 to 5 on the left:

1. Species \* (Dropdown menu showing "Species")
2. Tissue and Type (Dropdown menu showing "Tissue and Type")
3. GEO Number (Dropdown menu showing "GEO Number")
4. |Log2(Fold Change)|/Methylation difference (Text input field showing "1")
5. p value (Text input field showing "0.05")

Below the input fields are three buttons: "Reset", "Example", and "Analysis". A red hand cursor is pointing at the "Analysis" button.

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.

## Co-Expression Network

In this section, the samples were divided into different groups based on age for analysis. You will get a graphic illustration of the co-expression network which is 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 correlation coefficient or P-value of correlation analysis.

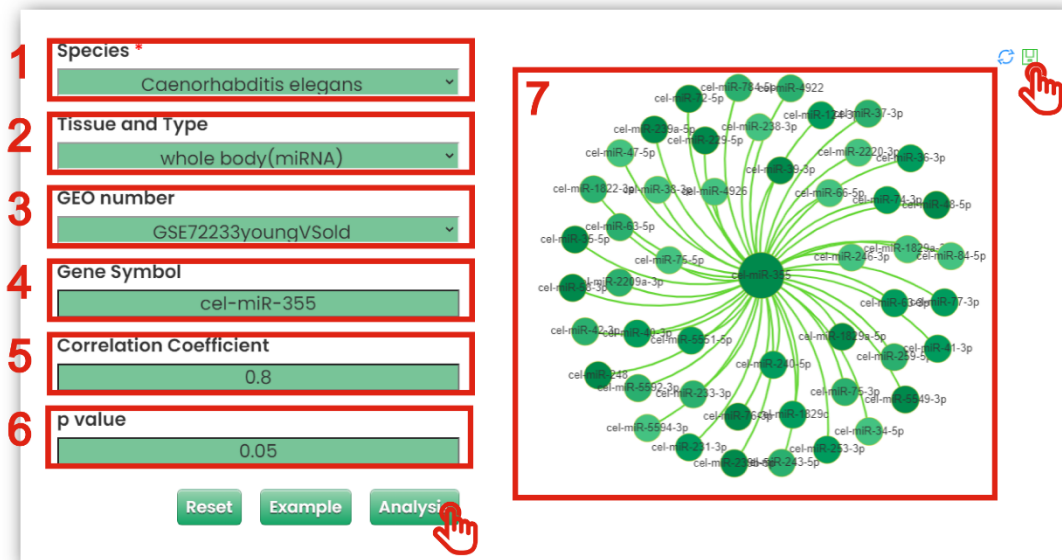


Figure 6-5

## 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  $|\log_2(\text{fold change})|$  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

6 CSV Excel Copy

7 Search:

Chromosome	Start	End	Name
chr11	63826117	63828726	Gm12289
chr11	96143219	96146639	Hoxb8
chr12	105266979	105282653	Serpina12
chr14	96280485	96281994	4921530L2IRik
chr16	16673091	16674110	Olf19
chr5	103336967	103640353	Mapk10
chr6	17147751	17160152	DB3002612Rik
chr6	90219100	90220047	Vmn1r54
chr7	126287837	126327888	Gpr139
chr7	147521742	147522719	Olf1r527

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.

### Aging Landscape

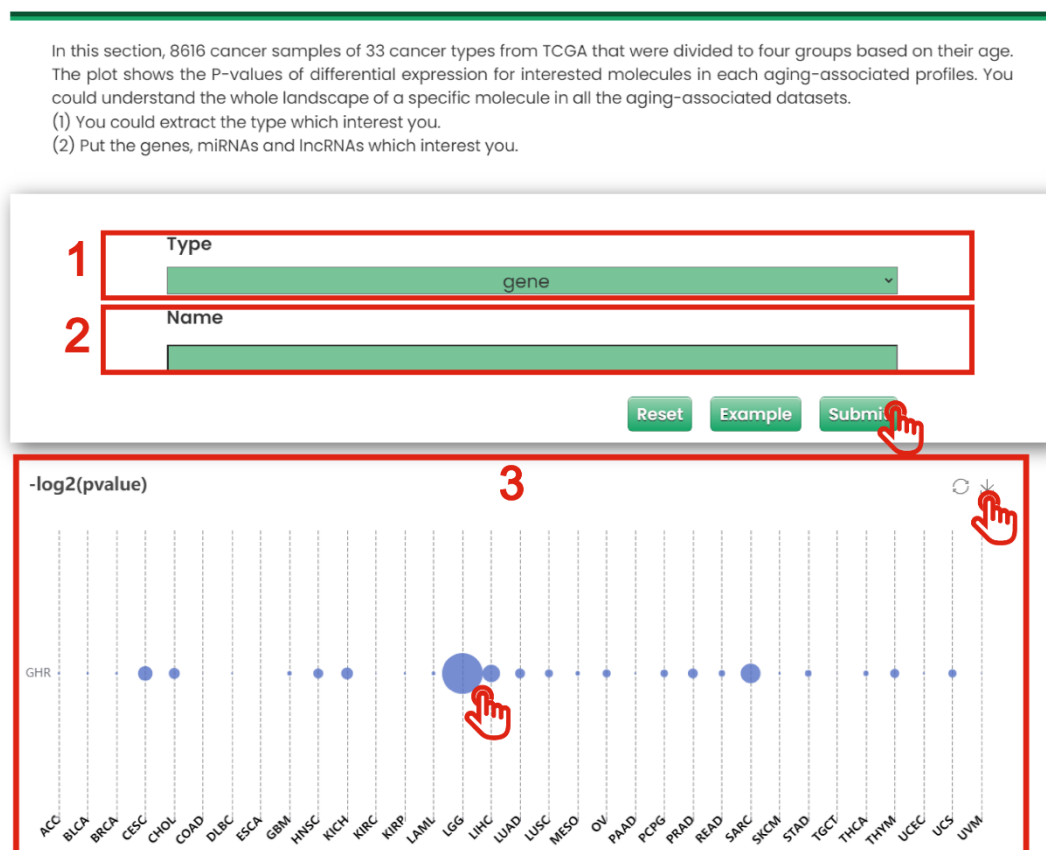


Figure 7-1

### 7.2. Differential Expression Analyzer

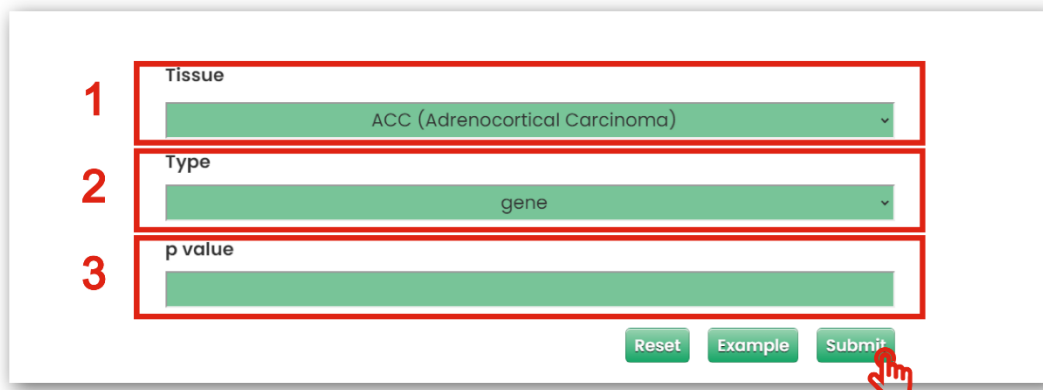
In this section, you could identify the differential expression pattern for your

**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.

## Differential Expression 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

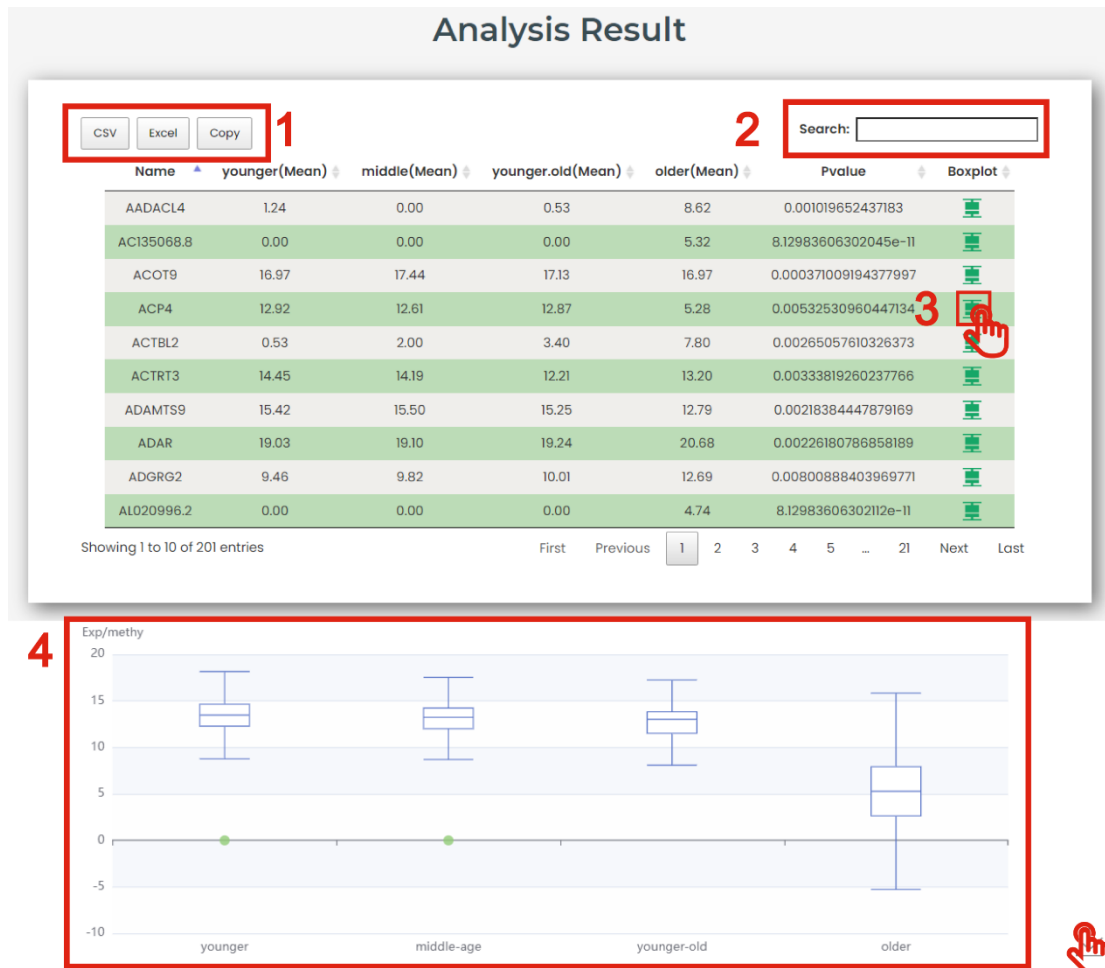
3 p value

Reset Example Submit

**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.

# ☐☐☐ Data Heat Mapper

In this section, 8616 cancer samples of 33 cancer types from TCGA that were divided to four groups based on their age. You will get a heatmap of the co-expression network which is related with your input.

- (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.

The screenshot shows a web interface with three input fields, each highlighted with a red box and a red number: 1. 'Tissue' dropdown menu with 'ACC (Adrenocortical Carcinoma)' selected. 2. 'Type' dropdown menu with 'gene' selected. 3. 'p value' text input field. Below the fields are three buttons: 'Reset', 'Example', and 'Submit'. A red hand cursor is pointing at the 'Submit' button.

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.

## Co-Expression Network

In this section, 8616 cancer samples of 33 cancer types from TCGA that were divided to four groups based on their age. You will get a graphic illustration of the co-expression network which is related with your input.

- (1) You could extract the tissues which interest you.
- (2) You could extract the type which interest you.
- (3) You could extract diverse correlation coefficient or P-value of correlation analysis.

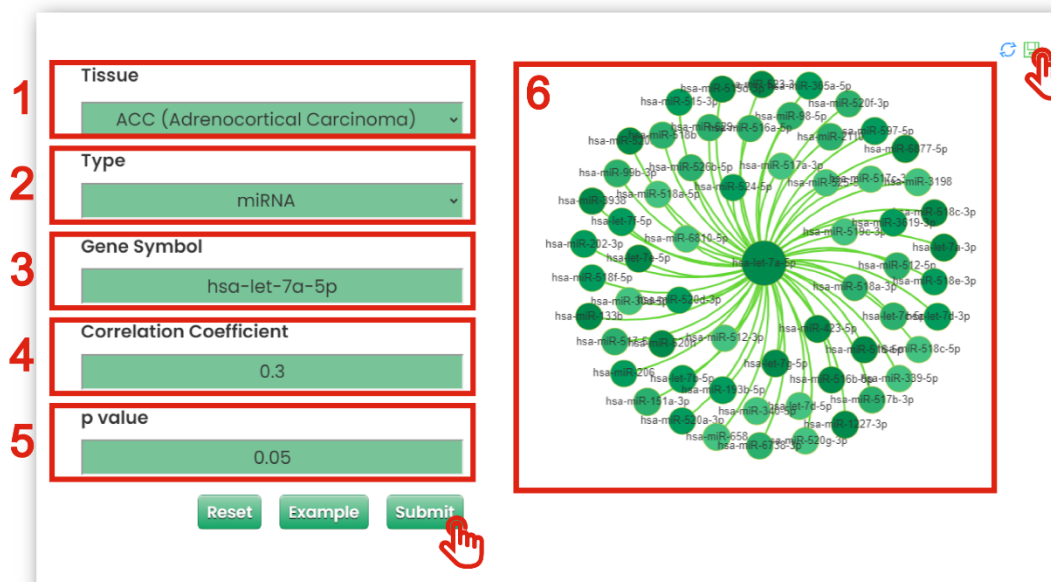


Figure 7-5

## 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

4 CSV Excel Copy

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	Clorf56

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:

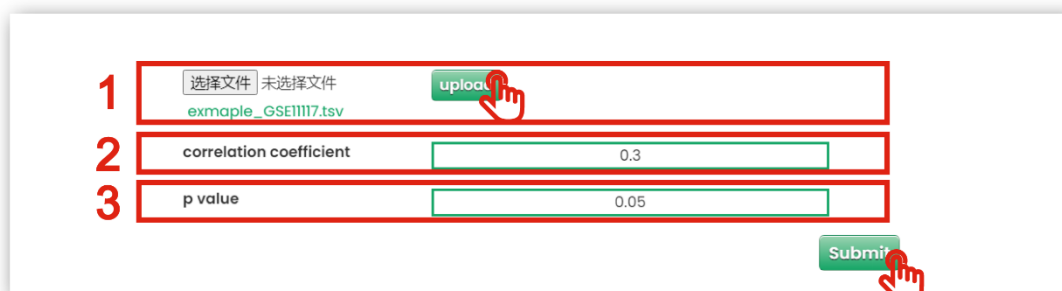
1. You could upload dataset for correlation analysis.
2. You could extract diverse correlation coefficient of correlation analysis.
3. You could extract diverse P-values of correlation analysis.

### Submit & Analysis

In this section, users can upload data and select diverse correlation coefficient or p-value for correlation analysis and heat mapping.

Note:

- (1) The first line of the file should be the sample name;
- (2) The second line of the file should be the age of samples;
- (3) The first column of the file should be the gene name or other features.



1   exmaple\_GSE11117.tsv

2 correlation coefficient

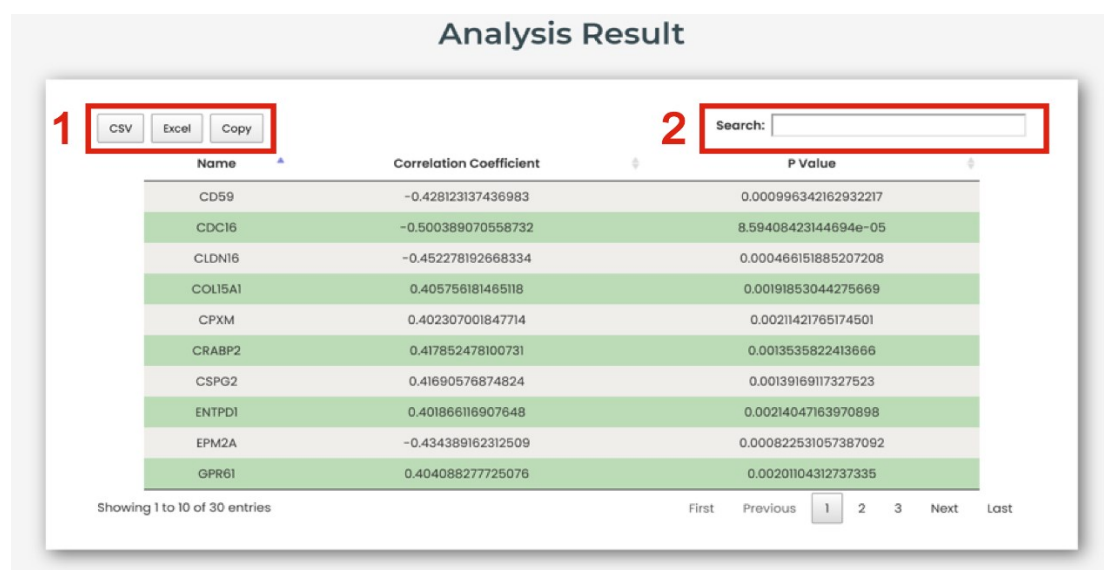
3 p value

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.

### Analysis Result



1

2 Search:

Name	Correlation Coefficient	P Value
CD59	-0.428123137436983	0.000996342162932217
CDC16	-0.500389070558732	8.59408423144694e-05
CLDN16	-0.452278192668334	0.000466151885207208
COL15A1	0.405756181465118	0.00191853044275669
CPXM	0.402307001847714	0.00211421765174501
CRABP2	0.417852478100731	0.0013535822413666
CSPG2	0.41690576874824	0.00139169117327523
ENTPD1	0.401866116907648	0.00214047163970898
EPM2A	-0.434389162312509	0.000822531057387092
GPR61	0.404088277725076	0.00201104312737335

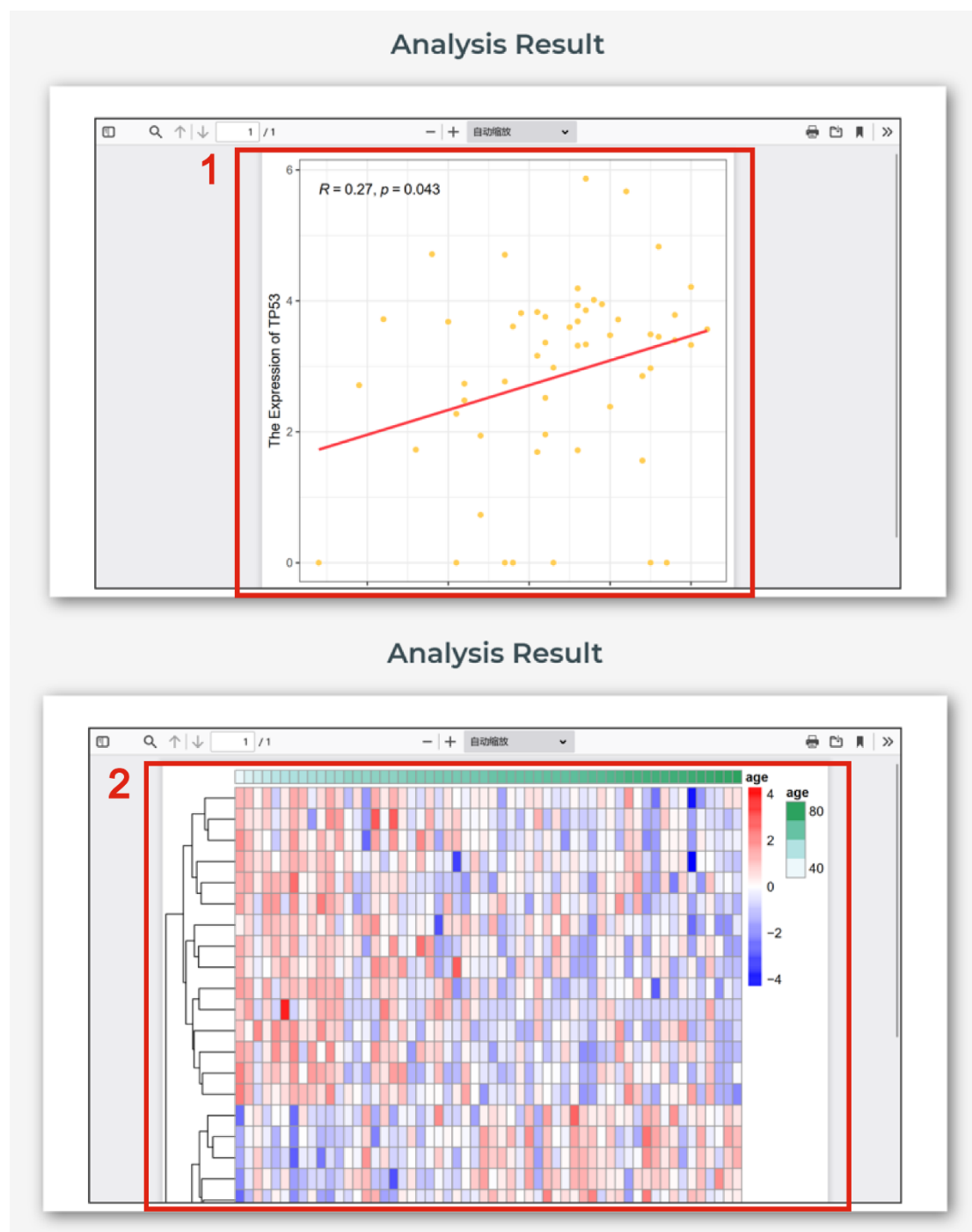
Showing 1 to 10 of 30 entries

First Previous    Next Last

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.



## 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.

### Download



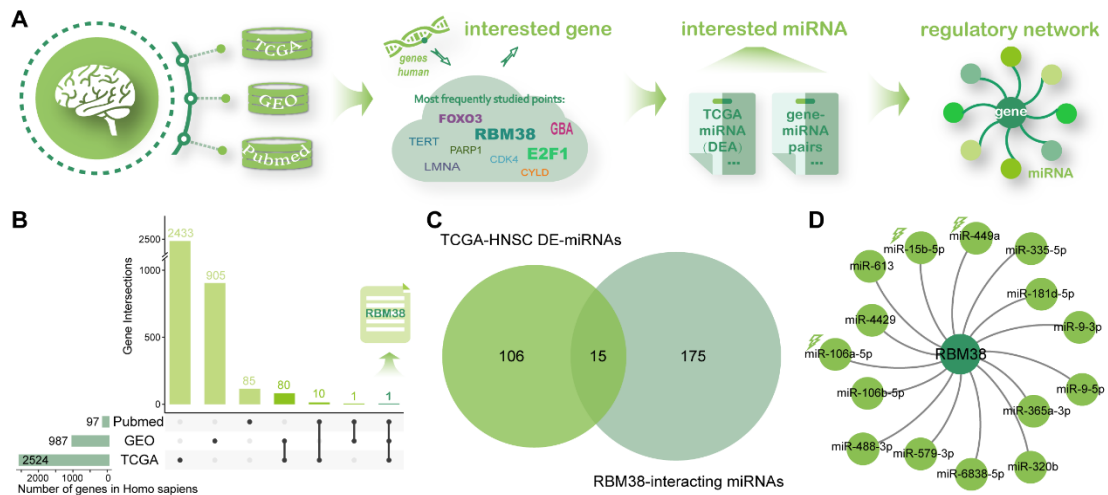
**Figure 9**

## 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*<sup>1</sup>. 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 (imprinting[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 (imprinting[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).