Metabolomic Data Analysis with MetaboAnalyst 6.0

Name: guest14586620120739914885

July 1, 2024

1 Background

MSEA or Metabolite Set Enrichment Analysis is a way to identify biologically meaningful patterns that are significantly enriched in quantitative metabolomic data. In conventional approaches, metabolites are evaluated individually for their significance under conditions of study. Those compounds that have passed certain significance level are then combined to see if any meaningful patterns can be discerned. In contrast, MSEA directly investigates if a set of functionally related metabolites without the need to preselect compounds based on some arbitrary cut-off threshold. It has the potential to identify subtle but consistent changes among a group of related compounds, which may go undetected with the conventional approaches.

Essentially, MSEA is a metabolomic version of the popular GSEA (Gene Set Enrichment Analysis) software with its own collection of metabolite set libraries as well as an implementation of user-friendly web-interfaces. GSEA is widely used in genomics data analysis and has proven to be a powerful alternative to conventional approaches. For more information, please refer to the original paper by Subramanian A, and a nice review paper by Nam D, Kim SY. [1]. [2]

2 MSEA Overview

Metabolite set enrichment analysis consists of four steps - data input, data processing, data analysis, and results download. Different analysis procedures are performed based on different input types. In addition, users can also browse and search the metabolite set libraries as well as upload their self-defined metabolite sets for enrichment analysis. Users can also perform metabolite name mapping between a variety of compound names, synonyms, and major database identifiers.

3 Data Input

There are three enrichment analysis algorithms offered by MSEA. Accordingly, three different types of data inputs are required by these three approaches:

- A list of important compound names - entered as a one column data (*Over Representation Analysis (ORA)*);
- A single measured biofluid (urine, blood, CSF) sample- entered as tab separated two-column data with the first column for compound name, and the second for concentration values (*Single Sample Profiling (SSP)*);

[1] Subramanian*Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles.*, Proc Natl Acad Sci USA. 2005 102(43): 15545-50

[2] Nam D, Kim SY. *Gene-set approach for expression pattern analysis*, Briefings in Bioinformatics. 2008 9(3): 189-197.

- A compound concentration table - entered as a comma separated (.csv) file with the each sample per row and each metabolite concentration per column. The first column is sample names and the second column for sample phenotype labels (*Quantitative Enrichment Analysis (QEA)*)

You selected Over Representation Analysis (ORA) which requires a list of compound names as input.

4 Data Process

The first step is to standardize the compound labels. It is an essential step since the compound labels will be subsequently compared with compounds contained in the metabolite set library. MSEA has a built-in tool to convert between compound common names, synonyms, identifiers used in HMDB ID, PubChem, ChEBI, BiGG, METLIN, KEGG, or Reactome. **Table 1** shows the conversion results. Note: *1* indicates exact match, *2* indicates approximate match, and *0* indicates no match. A text file contain the result can be found the downloaded file *name_map.csv*

Table 1: Resu

	Query	Match	HMDB	PubChem	KEGG	SMILES
1	Montiporic Acid C	NA	NA	NA	NA	NA
2	Montiporic Acid B	NA	NA	NA	NA	NA
3	Montiporic Acid D	NA	NA	NA	NA	NA
4	Montiporic Acid A	NA	NA	NA	NA	NA
5	Cresol	p-Cresol	HMDB0001858	2879	C01468	CC1=CC=C(O)C=C1
6	Phenethylamine	Phenylethylamine	HMDB0012275	1001	C05332	NCCC1=CC=CC=C1
7	Uridine	Uridine	HMDB0000296	6029	C00299	OC[C@H]1O[C@H]([C@H
8	Glucose-6-phosphate	Glucose 6-phosphate	HMDB0001401	5958	C00092	OC1O[C@H](COP(O)(O)
9	Guanosine	Guanosine	HMDB0000133	6802	C00387	NC1=NC2=C(N=CN2[C
10	Indole	Indole	HMDB0000738	798	C00463	N1C=CC2=C1C=CC=C
11	Carbamoyl phosphate	Carbamoyl phosphate	HMDB0001096	278	C00169	NC(=O)OP(O)(O)=O
12	NADPH	NADPH	HMDB0000221	5884	C00005	NC(=O)C1=CN(C=CC1
13	UMP	Uridine 5'-monophosphate	HMDB0000288	6030	C00105	O[C@H]1[C@@H](O)[C@
14	ADP	ADP	HMDB0001341	6022	C00008	NC1=NC=NC2=C1N=C
15	O-Decanoyl-L-carnitine	Decanoylcarnitine	HMDB0000651	11953821	C03299	CCCCCCCCCC(=O)O[C
16	Glycyl-L-proline	Glycylproline	HMDB0000721	3013625		NCC(=O)N1CCC[C@H]1
17	Adenosine	Adenosine	HMDB0000050	60961	C00212	NC1=C2N=CN([C@@H]
18	Mannose-6-phosphate	Mannose 6-phosphate	HMDB0001078	439198	C00275	O[C@@H]1O[C@H](COP
19	Betaine	Betaine	HMDB0000043	247	C00719	C[N+](C)(C)CC(O)=O
20	Threonine	L-Threonine	HMDB0000167	6288	C00188	C[C@@H](O)[C@H](N)C
21	Serine	Serine	HMDB0000187	5951	C00065	N[C@@H](CO)C(O)=O
22	Lysine-Glutamine	Lysylglutamine	HMDB0028949	196305		NCCCC[C@H](N)C(=O)
23	Ribothymidine	Ribothymidine	HMDB0000884	445408		CC1=CN([C@@H]2O[C@
24	NG-dimethyl-L-arginine	Asymmetric dimethylarginine	HMDB0001539	123831	C03626	N[C@@H](CCC\N=C(/N
25	Tryptamine	Tryptamine	HMDB0000303	1150	C00398	NCCC1=CNC2=C1C=C
26	Glucose	D-Glucose	HMDB0000122	5793	C00031	OC[C@H]1O[C@@H](O)[
27	Cellobiose	Cellobiose	HMDB0000055	10712	C00185	OC[C@H]1O[C@@H](O[C
28	Arginine-Alanine	Arginylalanine	HMDB0028702	7020333		C[C@H](NC(=O)[C@@H
29	Arginine-Glutamine	Arginylglutamine	HMDB0028707	7019985		N[C@@H](CCCNC(N)=N
30	Pterin	Pterin	HMDB0000802	73000	C00715	NC1=NC2=NC=CN=C2
31	Adipic acid	Adipic acid	HMDB0000448	196	C06104	OC(=O)CCCCC(O)=O
32	Sorbitol	Sorbitol	HMDB0000247	5780	C00794	OC[C@H](O)[C@@H](O)
33	Isoleucine	Isoleucine	HMDB0000172	6306	C00407	CC[C@H](C)[C@H](N)C(
34	NAD	NAD	HMDB0000902	5892	C00003	NC(=O)C1=C[N+](=CC
35	N N N-Trimethyllysine	NA	NA	NA	NA	NA
36	Homoarginine	Homo-L-arginine	HMDB0000670	9085	C01924	N[C@@H](CCCCNC(N)=
37	Tyrosine	L-Tyrosine	HMDB0000158	6057	C00082	N[C@@H](CC1=CC=C(
38	Diethanolamine	Diethanolamine	HMDB0004437	8113	C06772	OCCNCCO
39	ATP	Adenosine triphosphate	HMDB0000538	5957	C00002	NC1=NC=NC2=C1N=C
40	CDP-Choline	Citicoline	HMDB0001413	13805	C00307	C[N+](C)(C)CCOP(O)(=
41	Sedoheptulose	Sedoheptulose	HMDB0003219	441483	C02076	OC[C@H]1O[C@](O)(CO
42	Lysine	Lysine	HMDB0000182	5962	C00047	NCCCC[C@H](N)C(O)=
43	Taurine	Taurine	HMDB0000251	1123	C00245	NCCS(O)(=O)=O
44	Sucrose	Sucrose	HMDB0000258	5988	C00089	OC[C@H]1O[C@@](CO)(
45	Riboflavin	Riboflavin	HMDB0000244	493570	C00255	CC1=C(C)C=C2N(C[C@
46	Acetyllysine	N-alpha-Acetyl-L-lysine	HMDB0000446	92907	C12989	CC(=O)N[C@@H](CCCC
47	Raffinose	Raffinose	HMDB0003213	439242	C00492	OC[C@H]1O[C@@](CO)(
48	Valine	L-Valine	HMDB0000883	6287	C00183	CC(C)[C@H](N)C(O)=O
49	Phenylalanine	Phenylalanine	HMDB0000159	6140	C00079	N[C@@H](CC1=CC=CC
50	CDP-ethanolamine	CDP-ethanolamine	HMDB0001564	123727	C00570	NCCOP(O)(=O)OP(O)(
51	N-Acetyl-Glucosamine	N-Acetyl-D-Glucosamine 6-Phosphate	HMDB0001062	440996	C00357	CC(=O)N[C@H]1C(O)O[
52	ADP-ribose	Adenosine diphosphate ribose	HMDB0001178	192	C00301	NC1=C2N=CN(C3OC(C
53	Glutamine	Glutamine	HMDB0000641	5961	C00064	N[C@@H](CCC(N)=O)C
54	Pyruvate	Pyruvic acid	HMDB0000243	1060	C00022	CC(=O)C(O)=O
55	FAD	FAD	HMDB0001248	643975	C00016	CC1=CC2=C(C=C1C)N
56	Trigonelline	Trigonelline	HMDB0000875	5570	C01004	C[N+]1=CC=CC(=C1)C
57	3-Phenylbutyric acid	3-Phenylbutyric acid	HMDB0001955	20724		CC(CC(O)=O)C1=CC=
58	Acetyl glycine	Phenylacetylglycine	HMDB0000821	68144	C05598	OC(=O)CNC(=O)CC1=

59	CMP	Cytidine monophosphate	HMDB0000095	6131	C00055	NC1=NC(=O)N(C=C1)[
60	O-Phosphorylethanolamine	O-Phosphoethanolamine	HMDB0000224	1015	C00346	NCCOP(O)(O)=O
61	GDP-Mannose	Guanosine diphosphate mannose	HMDB0001163	18396	C00096	NC1=NC2=C(N=CN2[C
62	Malonic acid	Malonic acid	HMDB0000691	867	C00383	OC(=O)CC(O)=O
63	4-Guanidinobutanoic acid	4-Guanidinobutanoic acid	HMDB0003464	500	C01035	NC(=N)NCCCC(O)=O
64	GDP	Guanosine diphosphate	HMDB0001201	8977	C00035	NC1=NC2=C(N=CN2[C
65	Fructose	D-Fructose	HMDB0000660	439709	C00095	OC[C@H]1O[C@](O)(CO
66	Glutamate	Glutamic acid	HMDB0000148	33032	C00025	N[C@@H](CCC(O)=O)C
67	L-Octanoylcarnitine	Octanoylcarnitine	HMDB0000791	11953814	C02838	CCCCCCCC(=O)O[C@H
68	Nicotinamide riboside	Nicotinamide riboside	HMDB0000855	439924	C03150	NC(=O)C1=C[N+](=CC
69	1-Methylhistidine	1-Methylhistidine	HMDB0000001	92105	C01152	CN1C=NC(C[C@H](N)C
70	Proline	Proline	HMDB0000162	145742	C00148	OC(=O)[C@@H]1CCCN1
71	Glutaric acid	Glutaric acid	HMDB0000661	743	C00489	OC(=O)CCCC(O)=O
72	5-Hydroxytryptophan	5-Hydroxy-L-tryptophan	HMDB0000472	439280	C00643	N[C@@H](CC1=CNC2=
73	UDP-N-acetyl-glucosamine	Uridine diphosphate-N-acetylglucosamine	HMDB0000290	445675	C00043	CC(=O)N[C@@H]1[C@@
74	UDP-D-Glucose	Uridine diphosphate glucose	HMDB0000286	8629	C00029	OC[C@H]1O[C@H](OP(O
75	Pantothenate	Pantothenic acid	HMDB0000210	6613	C00864	CC(C)(CO)[C@@H](O)C
76	NADP	NADP	HMDB0000217	5885	C00006	NC(=O)C1=C[N+](=CC
77	Homocitrulline	Homocitrulline	HMDB0000679	65072	C02427	N[C@@H](CCCCNC(N)=
78	Acetyl CoA	Acetoacetyl-CoA	HMDB0001484	92153	C00332	CC(=O)CC(=O)SCCNC
79	Glutathione	Glutathione	HMDB0000125	124886	C00051	N[C@@H](CCC(=O)N[C
80	S-Adenosyl-homocysteine	S-Adenosylhomocysteine	HMDB0000939	439155	C00021	N[C@@H](CCSC[C@H]1O
81	Pirbuterol	Pirbuterol	HMDB0015407	4845	C07807	CC(C)(C)NCC(O)C1=N
82	Orotate	Orotic acid	HMDB0000226	967	C00295	OC(=O)C1=CC(=O)NC

The second step is to check concentration values. For SSP analysis, the concentration must be measured in *umol* for blood and CSF samples. The urinary concentrations must be first converted to *umol/mmol_creatinine* in order to compare with reported concentrations in literature. No missing or negative values are allowed in SSP analysis. The concentration data for QEA analysis is more flexible. Users can upload either the original concentration data or normalized data. Missing or negative values are allowed (coded as *NA*) for QEA.

5 Selection of Metabolite Set Library

Before proceeding to enrichment analysis, a metabolite set library has to be chosen. There are seven built-in libraries offered by MSEA:

- Metabolic pathway associated metabolite sets (*currently contains 99 entries*);
- Disease associated metabolite sets (reported in blood) (*currently contains 344 entries*);
- Disease associated metabolite sets (reported in urine) (*currently contains 384 entries*)
- Disease associated metabolite sets (reported in CSF) (*currently contains 166 entries*)
- Metabolite sets associated with SNPs (*currently contains 4598 entries*)
- Predicted metabolite sets based on computational enzyme knockout model (*currently contains 912 entries*)
- Metabolite sets based on locations (*currently contains 73 entries*)
- Drug pathway associated metabolite sets (*currently contains 461 entries*)

In addition, MSEA also allows user-defined metabolite sets to be uploaded to perform enrichment analysis on arbitrary groups of compounds which researchers want to test. The metabolite set library is simply a two-column comma separated text file with the first column for metabolite set names and the second column for its compound names (**must use HMDB compound name**) separated by "; ". Please note, the built-in libraries are mainly from human studies. The functional grouping of metabolites may not be valid. Therefore, for data from subjects other than human being, users are suggested to upload their self-defined metabolite set libraries for enrichment analysis.

6 Enrichment Analysis

Over Representation Analysis (ORA) is performed when a list of compound names is provided. The list of compound list can be obtained through conventional feature selection methods, or from a clustering algorithm, or from the compounds with abnormal concentrations detected in SSP, to investigate if some biologically meaningful patterns can be identified.

ORA was implemented using the *hypergeometric test* to evaluate whether a particular metabolite set is represented more than expected by chance within the given compound list. One-tailed p values are provided after adjusting for multiple testing. **Figure 2** below summarizes the result.

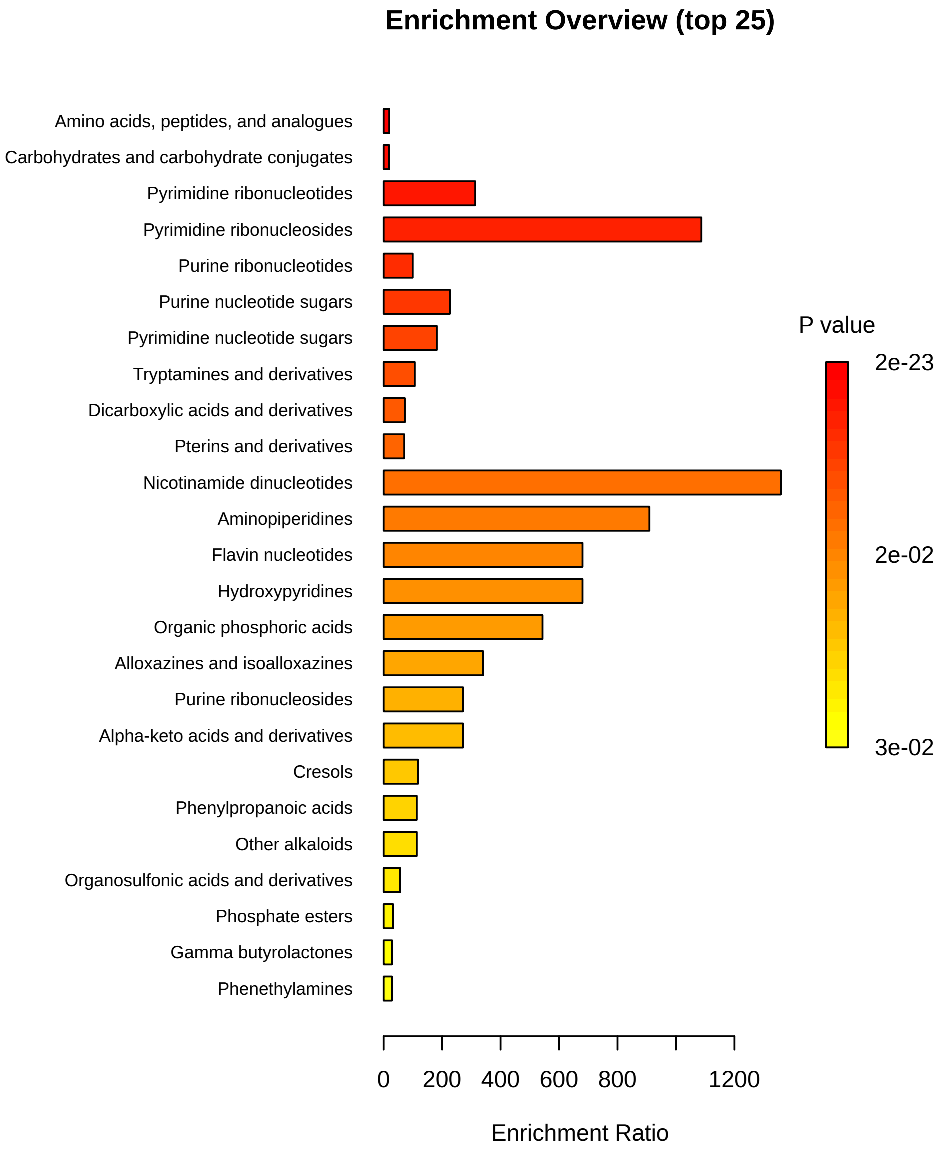

Figure 1: Summary Plot for Over Representation Analysis (ORA)

Table 2: Result from Over Representation Analysis

	total	expected	hits	Raw p	Holm p	FDR
Amino acids, peptides, and analogues	3220	1.19	23	1.89E-23	1.68E-20	1.68E-20
Carbohydrates and carbohydrate conjugates	1600	0.59	11	2.03E-11	1.80E-08	9.02E-09
Pyrimidine ribonucleotides	26	0.01	3	1.24E-07	1.10E-04	3.67E-05
Pyrimidine ribonucleosides	5	0.00	2	1.34E-06	1.18E-03	2.97E-04
Purine ribonucleotides	82	0.03	3	4.15E-06	3.68E-03	7.39E-04
Purine nucleotide sugars	24	0.01	2	3.67E-05	3.25E-02	5.44E-03
Pyrimidine nucleotide sugars	30	0.01	2	5.78E-05	5.11E-02	7.34E-03
Tryptamines and derivatives	51	0.02	2	1.68E-04	1.49E-01	1.87E-02
Dicarboxylic acids and derivatives	75	0.03	2	3.65E-04	3.22E-01	3.42E-02
Pterins and derivatives	77	0.03	2	3.84E-04	3.38E-01	3.42E-02
Nicotinamide dinucleotides	2	0.00	1	7.36E-04	6.48E-01	5.96E-02
Aminopiperidines	3	0.00	1	1.10E-03	9.70E-01	8.19E-02
Flavin nucleotides	4	0.00	1	1.47E-03	1.00E+00	9.35E-02
Hydroxypyridines	4	0.00	1	1.47E-03	1.00E+00	9.35E-02
Organic phosphoric acids	5	0.00	1	1.84E-03	1.00E+00	1.09E-01
Alloxazines and isoalloxazines	8	0.00	1	2.94E-03	1.00E+00	1.64E-01
Purine ribonucleosides	10	0.00	1	3.67E-03	1.00E+00	1.82E-01
Alpha-keto acids and derivatives	10	0.00	1	3.67E-03	1.00E+00	1.82E-01
Cresols	23	0.01	1	8.43E-03	1.00E+00	3.73E-01
Phenylpropanoic acids	24	0.01	1	8.80E-03	1.00E+00	3.73E-01
Other alkaloids	24	0.01	1	8.80E-03	1.00E+00	3.73E-01
Organosulfonic acids and derivatives	48	0.02	1	1.75E-02	1.00E+00	7.09E-01
Phosphate esters	84	0.03	1	3.05E-02	1.00E+00	1.00E+00
Gamma butyrolactones	94	0.03	1	3.40E-02	1.00E+00	1.00E+00
Phenethylamines	95	0.04	1	3.44E-02	1.00E+00	1.00E+00
Benzenediols	105	0.04	1	3.79E-02	1.00E+00	1.00E+00
Indoles	133	0.05	1	4.78E-02	1.00E+00	1.00E+00
Pyrimidines and pyrimidine derivatives	210	0.08	1	7.44E-02	1.00E+00	1.00E+00
Alcohols and polyols	309	0.11	1	1.08E-01	1.00E+00	1.00E+00
Amines	350	0.13	1	1.21E-01	1.00E+00	1.00E+00
Fatty acid esters	1650	0.61	2	1.24E-01	1.00E+00	1.00E+00
Fatty acids and conjugates	941	0.35	1	2.93E-01	1.00E+00	1.00E+00

7 Appendix: R Command History

```
 [1] "mSet<-InitDataObjects(\"conc\", \"msetora\", FALSE)"
 [2] "cmpd.vec<-c(\"Montiporic Acid C\",\"Montiporic Acid B\",\"Montiporic Acid D\",\"Montiporic Aci
 [3] "mSet<-Setup.MapData(mSet, cmpd.vec);"
 [4] "mSet<-CrossReferencing(mSet, \"name\");"
 [5] "mSet<-CreateMappingResultTable(mSet)"
 [6] "mSet<-PerformDetailMatch(mSet, \"Cresol\");"
 [7] "mSet<-GetCandidateList(mSet);"
 [8] "mSet<-SetCandidate(mSet, \"Cresol\", \"p-Cresol\");"
 [9] "mSet<-PerformDetailMatch(mSet, \"O-Decanoyl-L-carnitine\");"
[10] "mSet<-GetCandidateList(mSet);"
[11] "mSet<-SetCandidate(mSet, \"O-Decanoyl-L-carnitine\", \"Decanoylcarnitine\");"
[12] "mSet<-PerformDetailMatch(mSet, \"Lysine-Glutamine\");"
[13] "mSet<-GetCandidateList(mSet);"
[14] "mSet<-SetCandidate(mSet, \"Lysine-Glutamine\", \"Lysylglutamine\");"
[15] "mSet<-PerformDetailMatch(mSet, \"NG-dimethyl-L-arginine\");"
[16] "mSet<-GetCandidateList(mSet);"
[17] "mSet<-SetCandidate(mSet, \"NG-dimethyl-L-arginine\", \"Asymmetric dimethylarginine\");"
[18] "mSet<-PerformDetailMatch(mSet, \"Arginine-Alanine\");"
[19] "mSet<-GetCandidateList(mSet);"
[20] "mSet<-SetCandidate(mSet, \"Arginine-Alanine\", \"Arginylalanine\");"
[21] "mSet<-PerformDetailMatch(mSet, \"Arginine-Glutamine\");"
[22] "mSet<-GetCandidateList(mSet);"
[23] "mSet<-SetCandidate(mSet, \"Arginine-Glutamine\", \"Arginylglutamine\");"
[24] "mSet<-PerformDetailMatch(mSet, \"N N N-Trimethyllysine\");"
[25] "mSet<-GetCandidateList(mSet);"
[26] "mSet<-PerformDetailMatch(mSet, \"N-Acetyl-Glucosamine\");"
[27] "mSet<-GetCandidateList(mSet);"
[28] "mSet<-SetCandidate(mSet, \"N-Acetyl-Glucosamine\", \"N-Acetyl-D-Glucosamine 6-Phosphate\");"
[29] "mSet<-PerformDetailMatch(mSet, \"Acetyl glycine\");"
[30] "mSet<-GetCandidateList(mSet);"
[31] "mSet<-SetCandidate(mSet, \"Acetyl glycine\", \"Phenylacetylglycine\");"
[32] "mSet<-PerformDetailMatch(mSet, \"Acetyl CoA\");"
[33] "mSet<-GetCandidateList(mSet);"
[34] "mSet<-SetCandidate(mSet, \"Acetyl CoA\", \"Acetoacetyl-CoA\");"
[35] "mSet<-SetMetabolomeFilter(mSet, F);"
[36] "mSet<-SetCurrentMsetLib(mSet, \"main_class\", 2);"
[37] "mSet<-CalculateHyperScore(mSet)"
[38] "mSet<-PlotORA(mSet, \"ora_0_\", \"net\", \"png\", 72, width=NA)"
[39] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_0_\", \"png\", 72, width=NA)"
[40] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_0_\", \"png\", 72)"
[41] "mSet<-CalculateHyperScore(mSet)"
[42] "mSet<-PlotORA(mSet, \"ora_1_\", \"net\", \"png\", 72, width=NA)"
[43] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_1_\", \"png\", 72, width=NA)"
[44] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_1_\", \"png\", 72)"
[45] "mSet<-CalculateHyperScore(mSet)"
[46] "mSet<-PlotORA(mSet, \"ora_2_\", \"net\", \"png\", 72, width=NA)"
[47] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_2_\", \"png\", 72, width=NA)"
[48] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_2_\", \"png\", 72)"
[49] "mSet<-CalculateHyperScore(mSet)"
[50] "mSet<-PlotORA(mSet, \"ora_3_\", \"net\", \"png\", 72, width=NA)"
[51] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_3_\", \"png\", 72, width=NA)"
[52] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_3_\", \"png\", 72)"
[53] "mSet<-SaveTransformedData(mSet)"
[54] "mSet<-PreparePDFReport(mSet, \"guest14586620120739914885\")\n"
[55] "mSet<-SetMetabolomeFilter(mSet, F);"
[56] "mSet<-SetCurrentMsetLib(mSet, \"sub_class\", 2);"
```

```
[57] "mSet<-CalculateHyperScore(mSet)"
[58] "mSet<-PlotORA(mSet, \"ora_4_\", \"net\", \"png\", 72, width=NA)"
[59] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_4_\", \"png\", 72, width=NA)"
[60] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_4_\", \"png\", 72)"
[61] "mSet<-CalculateHyperScore(mSet)"
[62] "mSet<-PlotORA(mSet, \"ora_5_\", \"net\", \"png\", 72, width=NA)"
[63] "mSet<-PlotEnrichDotPlot(mSet, \"ora\", \"ora_dot_5_\", \"png\", 72, width=NA)"
[64] "mSet<-PlotEnrichPieChart(mSet, \"ora\", \"ora_pie_5_\", \"png\", 72)"
[65] "mSet<-SaveTransformedData(mSet)"
[66] "mSet<-PreparePDFReport(mSet, \"guest14586620120739914885\")\n"
```

The report was generated on Mon Jul 1 16:04:59 2024 with R version 4.3.2 (2023-10-31), OS system: Linux, version: -Ubuntu SMP Tue Mar 5 20:16:58 UTC 2024 .