

Metabolomic Data Analysis with MetaboAnalyst 3.0

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1 Background

MESA 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.

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)*);
- 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 Quantitative Enrichment Analysis (QEA) which requires a concentration table. This is the most common data format generated from quantitative metabolomics studies. The phenotype label can be discrete (binary or multi-class) or continuous.

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: Result from Compound Name Mapping

Query	Match
1 1,2-dilinoeoyl-GPC	NA
2 1,2-dioeoyl-GPC	NA
3 1,2-dioeoyl-GPE	NA
4 1,2-dipalmitoyl-GPC	NA
5 1,2-distearoyl-GPC	NA
6 1,5-anhydroglucitol	NA
7 1-(1-enyl-oleoyl)-GPE	NA
8 1-(1-enyl-palmitoyl)-2-arachidonoyl-GPC	NA
9 1-(1-enyl-palmitoyl)-2-arachidonoyl-GPE	NA
10 1-(1-enyl-palmitoyl)-2-linoleoyl-GPC	NA
11 1-(1-enyl-palmitoyl)-2-linoleoyl-GPE	NA
12 1-(1-enyl-palmitoyl)-2-oleoyl-GPC	NA
13 1-(1-enyl-palmitoyl)-2-oleoyl-GPE	NA
14 1-(1-enyl-palmitoyl)-2-palmitoleoyl-GPC	NA
15 1-(1-enyl-palmitoyl)-2-palmitoyl-GPC	NA
16 1-(1-enyl-palmitoyl)-GPC	NA
17 1-(1-enyl-palmitoyl)-GPE	NA
18 1-(1-enyl-stearoyl)-2-arachidonoyl-GPE	NA
19 1-(1-enyl-stearoyl)-2-linoleoyl-GPE	NA
20 1-(1-enyl-stearoyl)-2-oleoyl-GPE	NA
21 1-(1-enyl-stearoyl)-GPE	NA
22 1-(3-aminopropyl)-2-pyrrolidone	NA
23 1-arachidonoyl-GPC	NA
24 1-arachidonoyl-GPE	NA
25 1-arachidonoyl-GPI	NA
26 1-lignoceroyl-GPC	NA
27 1-linolenoyl-GPC	NA
28 1-linoleoyl-2-arachidonoyl-GPC	NA
29 1-linoleoyl-GPC	NA
30 1-linoleoyl-GPE	NA
31 1-linoleoyl-GPI	NA
32 1-linoleoylglycerol	NA
33 1-methylguanidine	Methylguanidine
34 1-methylhistidine	1-Methylhistidine
35 1-methylimidazoleacetate	NA
36 1-methylnicotinamide	1-Methylnicotinamide
37 1-oleoyl-2-linoleoyl-glycerol	NA
38 1-oleoyl-2-linoleoyl-GPC	NA
39 1-oleoyl-2-linoleoyl-GPE	NA
40 1-oleoyl-3-linoleoyl-glycerol	NA
41 1-oleoyl-GPC	NA
42 1-oleoyl-GPE	NA
43 1-oleoyl-GPI	NA
44 1-oleoyl-GPS	NA
45 1-oleoylglycerol	NA
46 1-palmitoleoyl-2-linoleoyl-GPC	NA
47 1-palmitoleoyl-2-oleoyl-glycerol	NA
48 1-palmitoleoyl-3-oleoyl-glycerol	NA
49 1-palmitoleoyl-GPC	NA
50 1-palmitoleoylglycerol	NA
51 1-palmitoyl-2-arachidonoyl-GPC	NA
52 1-palmitoyl-2-arachidonoyl-GPE	NA
53 1-palmitoyl-2-linoleoyl-glycerol	NA
54 1-palmitoyl-2-linoleoyl-GPC	NA
55 1-palmitoyl-2-linoleoyl-GPE	NA
56 1-palmitoyl-2-oleoyl-GPC	NA
57 1-palmitoyl-2-oleoyl-GPE	NA
58 1-palmitoyl-2-oleoyl-GPG	NA
59 1-palmitoyl-2-palmitoleoyl-GPC	NA
60 1-palmitoyl-2-stearoyl-GPC	NA
61 1-palmitoyl-3-linoleoyl-glycerol	NA
62 1-palmitoyl-GPC	NA

63	1-palmitoyl-GPE	NA
64	1-palmitoyl-GPG	NA
65	1-palmitoyl-GPI	NA
66	1-stearoyl-2-arachidonoyl-GPC	NA
67	1-stearoyl-2-arachidonoyl-GPE	NA
68	1-stearoyl-2-arachidonoyl-GPI	NA
69	1-stearoyl-2-arachidonoyl-GPS	NA
70	1-stearoyl-2-linoleoyl-GPC	NA
71	1-stearoyl-2-linoleoyl-GPE	NA
72	1-stearoyl-2-oleoyl-GPC	NA
73	1-stearoyl-2-oleoyl-GPE	NA
74	1-stearoyl-2-oleoyl-GPS	NA
75	1-stearoyl-GPC	NA
76	1-stearoyl-GPE	NA
77	1-stearoyl-GPI	NA
78	1-stearoyl-GPS	NA
79	10-heptadecenoate	NA
80	10-nonadecenoate	NA
81	12,13-DiHOME	12,13-DHOME
82	12-HETE	12-HETE
83	15-HETE	15(S)-HETE
84	15-methylpalmitate	NA
85	16-hydroxypalmitate	NA
86	17-methylstearate	NA
87	2'-deoxycytidine	Deoxycytidine
88	2'-deoxyguanosine	Deoxyguanosine
89	2'-deoxyinosine	Deoxyinosine
90	2'-deoxyuridine	Deoxyuridine
91	2-aminoadipate	Amino adipic acid
92	2-aminoheptanoate	NA
93	2-aminooctanoate	DL-2-Amino octanoic acid
94	2-hydroxy-3-methylvalerate	2-Hydroxy-3-methylpentanoic acid
95	2-hydroxyadipate	2-Hydroxyadipic acid
96	2-hydroxybutyrate/2-hydroxyisobutyrate	NA
97	2-hydroxyglutarate	2-Hydroxyglutarate
98	2-hydroxystearate	NA
99	2-linoleoylglycerol	NA
100	2-methylbutyrylcarnitine	NA
101	2-methylbutyrylglycine	2-Methylbutyrylglycine
102	2-methylcitrate/homocitrate	NA
103	2-methylmalonyl carnitine	NA
104	2-oleoylglycerol	NA
105	2-palmitoleoyl-GPC	NA
106	2-palmitoyl-GPC	NA
107	2-stearoyl-GPE	NA
108	3-(4-hydroxyphenyl)lactate	3-(4-Hydroxyphenyl)lactate
109	3-aminoisobutyrate	3-Aminoisobutanoic acid
110	3-hydroxy-3-methylglutarate	3-Hydroxymethylglutaric acid
111	3-hydroxybutyrate	NA
112	3-hydroxybutyrylcarnitine	NA
113	3-hydroxyisobutyrate	(S)-3-Hydroxyisobutyric acid
114	3-indoxyl sulfate	Indoxyl sulfate
115	3-methylcytidine	NA
116	3-methylhistidine	3-Methylhistidine
117	3-phosphoglycerate	3-Phosphoglyceric acid
118	3-ureidopropionate	Ureidopropionic acid
119	4-cholesten-3-one	Cholestenone
120	4-ethylphenylsulfate	NA
121	4-guanidinobutanoate	4-Guanidinobutanoic acid
122	4-hydroxy-nonenal-glutathione	NA
123	4-hydroxybutyrate	NA
124	4-imidazoleacetate	Imidazoleacetic acid
125	4-vinylphenol sulfate	NA
126	5-aminovalerate	5-Aminopentanoic acid
127	5-dodecenoate	NA
128	5-hydroxylysine	5-Hydroxylysine
129	5-methylthioadenosine	NA
130	5-oxoproline	Pyroglutamic acid
131	6-oxopiperidine-2-carboxylic acid	NA
132	6-phosphogluconate	6-Phosphogluconic acid
133	7-hydroxycholesterol	NA
134	7-methylguanine	7-Methylguanine
135	9,10-DiHOME	9,10-DHOME
136	acetylcarnitine	L-Acetylcarnitine
137	acetylphosphate	Acetylphosphate
138	aconitate [cis or trans]	NA
139	adenine	Adenine
140	adenosine	Adenosine
141	adenosine 2'-monophosphate	NA
142	adenosine 3',5'-diphosphate	Adenosine 3',5'-diphosphate
143	adenosine 3'-monophosphate	NA
144	adenosine 5'-diphosphoribose	NA
145	adenosine 5'-monophosphate	NA
146	adrenate	NA
147	alanine	Alanine
148	allantoin	Allantoin
149	alpha-hydroxyisocaproate	Leucinic acid

150	alpha-hydroxyisovalerate	2-Hydroxy-3-methylbutyric acid
151	alpha-ketoglutarate	NA
152	alpha-tocopherol	Alpha-Tocopherol
153	anserine	Anserine
154	arabitol/xylitol	NA
155	arabonate/xylonate	NA
156	arachidate	NA
157	arachidonate	NA
158	arachidonoyl ethanolamide	NA
159	arginine	L-Arginine
160	argininosuccinate	Argininosuccinic acid
161	ascorbate	NA
162	asparagine	L-Asparagine
163	aspartate	L-Aspartic acid
164	azelate	NA
165	behenoyl sphingomyelin	NA
166	beta-alanine	Beta-Alanine
167	beta-guanidinopropanoate	NA
168	beta-hydroxyisovaleroylcarnitine	NA
169	beta-muricholate	NA
170	betaine	Betaine
171	betaine aldehyde	Betaine aldehyde
172	butyrylcarnitine	Butyrylcarnitine
173	C-glycosyltryptophan	NA
174	campesterol	Campesterol
175	carboxyethyl-GABA	N-Carboxyethyl-g-aminobutyric acid
176	carnitine	Carnitine
177	carnosine	Carnosine
178	catechol sulfate	NA
179	cholesterol	Cholesterol
180	choline	Choline
181	choline phosphate	Phosphorylcholine
182	citrate	Citric acid
183	citrulline	Citrulline
184	corticosterone	Corticosterone
185	creatine	Creatine
186	creatine phosphate	Phosphocreatine
187	creatinine	Creatinine
188	cystathionine	L-Cystathionine
189	cysteine	Cysteine
190	cysteine s-sulfate	NA
191	cysteine sulfinic acid	3-Sulfinioalanine
192	cystine	L-Cystine
193	cytidine	Cytidine
194	cytidine 3'-monophosphate	NA
195	cytidine 5'-diphosphocholine	Citicoline
196	cytidine 5'-monophosphate	NA
197	cytidine 5'-monophospho-N-acetylneuraminic acid	NA
198	cytidine-5'-diphosphoethanolamine	NA
199	cytosine	Cytosine
200	decanoylcarnitine	Decanoylcarnitine
201	dehydroascorbate	Dehydroascorbate
202	deoxycarnitine	4-Trimethylammoniobutanoic acid
203	dihomo-linoleate	NA
204	dihomo-linolenate	NA
205	dihydroxyphenylalanine	NA
206	dihydroxyacetone phosphate	NA
207	dimethyl sulfone	Dimethyl sulfone
208	dimethylarginine	NA
209	dimethylglycine	Dimethylglycine
210	docosadienoate	NA
211	docosahexaenoate	NA
212	docosapentaenoate	NA
213	dopamine sulfate	NA
214	eicosapentaenoate	NA
215	eicosenoate	NA
216	equol sulfate	NA
217	ergothioneine	Ergothioneine
218	erucate	NA
219	erythronate	Erythronic acid
220	ethylmalonate	Ethylmalonic acid
221	flavin adenine dinucleotide	NA
222	fructose	D-Fructose
223	fumarate	Fumaric acid
224	galactitol	NA
225	galactonate	Galactonic acid
226	gamma-aminobutyrate	NA
227	gamma-carboxyglutamate	NA
228	gamma-glutamyl-epsilon-lysine	NA
229	gamma-glutamylalanine	5-L-Glutamyl-L-alanine
230	gamma-glutamylglutamate	Gamma Glutamylglutamic acid
231	gamma-glutamylglutamine	Gamma-Glutamyl Glutamine
232	gamma-glutamylglycine	NA
233	gamma-glutamylhistidine	NA
234	gamma-glutamylisoleucine	L-gamma-glutamyl-L-isoleucine
235	gamma-glutamylleucine	L-gamma-glutamyl-L-leucine
236	gamma-glutamylphenylalanine	Glutamylphenylalanine

237	gamma-glutamylvaline	L-gamma-glutamyl-L-valine
238	gamma-tocopherol/beta-tocopherol	NA
239	gluconate	Gluconic acid
240	glucose	D-Glucose
241	glucuronate	D-Glucuronic acid
242	glutamate	D-Glutamic acid
243	glutamate, gamma-methyl ester	NA
244	glutamine	L-Glutamine
245	glutarate	NA
246	glutarylcarntine	NA
247	glutathione, oxidized	NA
248	glutathione, reduced	NA
249	glycerate	Glyceric acid
250	glycerol	Glycerol
251	glycerol 3-phosphate	Glycerol 3-phosphate
252	glycerophosphoethanolamine	Glycerylphosphorylethanolamine
253	glycerophosphoglycerol	NA
254	glycerophosphoinositol	NA
255	glycerophosphorylcholine	NA
256	glycine	Glycine
257	glycosyl-N-palmitoyl-sphingosine	NA
258	glycosyl-N-stearoyl-sphingosine	NA
259	glycylleucine	Glycyl-L-leucine
260	glycylvaline	NA
261	guanidinoacetate	Guanidoacetic acid
262	guanidiniosuccinate	Guanidiniosuccinic acid
263	guanine	Guanine
264	guanosine	Guanosine
265	guanosine 5'- monophosphate	NA
266	gulonic acid	Gulonic acid
267	heme	Heme
268	hexadecanedioate	Hexadecanedioic acid
269	hexanoylcarnitine	Hexanoylcarnitine
270	hexanoylglycine	Hexanoylglycine
271	hippurate	Hippuric acid
272	histamine	Histamine
273	histidine	L-Histidine
274	homoarginine	Homo-L-arginine
275	homocitrulline	Homocitrulline
276	homostachydrine	Proline betaine
277	hypotaurine	Hypotaurine
278	hypoxanthine	Hypoxanthine
279	imidazole lactate	Imidazole lactate
280	imidazole propionate	NA
281	indolelactate	Indolelactic acid
282	inosine	Inosine
283	inosine 5'-monophosphate	NA
284	Isobar: fructose 1,6-diphosphate, glucose 1,6-diphosphate, myo-inositol 1,4 or 1,3-diphosphate	NA
285	isobutyrylcarnitine	NA
286	isocitrate	Isocitric acid
287	isoleucine	(+/-)-erythro-Isoleucine
288	isoleucylglycine	NA
289	isovalerylcarnitine	Isovalerylcarnitine
290	isovalerylglycine	Isovalerylglycine
291	kynurenate	Kynurenic acid
292	kynurenine	L-Kynurenine
293	lactate	L-Lactic acid
294	laurylcarnitine	NA
295	leucine	L-Leucine
296	leucylglycine	NA
297	linoleate	NA
298	linolenate [alpha or gamma; (18:3n3 or 6)]	NA
299	linoleoylcarnitine	NA
300	lysine	L-Lysine
301	malate	NA
302	malonylcarnitine	Malonylcarnitine
303	maltose	D-Maltose
304	maltotriose	Maltotriose
305	mannitol/sorbitol	NA
306	mannose	D-Mannose
307	margarate	NA
308	mead acid	NA
309	methionine	NA
310	methionine sulfoxide	Methionine sulfoxide
311	methyl glucopyranoside	NA
312	methylmalonate	NA
313	methylphosphate	NA
314	methylsuccinate	Methylsuccinic acid
315	myo-inositol	Myoinositol
316	myristate	NA
317	myristoleate	NA
318	myristoylcarnitine	Tetradecanoylcarnitine
319	N-acetyl-aspartyl-glutamate	NA
320	N-acetyl-beta-alanine	N-Acetyl-beta-alanine
321	N-acetyl-glucosamine 1-phosphate	N-Acetyl-glucosamine 1-phosphate
322	N-acetylalanine	N-Acetyl-L-alanine
323	N-acetylarginine	NA

324	N-acetylasparagine	N-Acetylasparagine
325	N-acetylaspartate	NA
326	N-acetylglucosamine 6-phosphate	N-Acetylglucosamine 6-phosphate
327	N-acetylglutamate	N-Acetylglutamic acid
328	N-acetylglutamine	N-Acetylglutamine
329	N-acetylglycine	Acetylglycine
330	N-acetylhistidine	N-Acetylhistidine
331	N-acetylleucine	N-Acetylleucine
332	N-acetylmethionine	N-Acetyl-L-methionine
333	N-acetylneuraminate	NA
334	N-acetylphenylalanine	N-Acetyl-L-phenylalanine
335	N-acetylputrescine	N-Acetylputrescine
336	N-acetylserine	N-Acetylserine
337	N-acetyltaurine	NA
338	N-acetylthreonine	NA
339	N-alpha-acetylornithine	NA
340	N-carbamoylaspartate	Ureidosuccinic acid
341	N-delta-acetylornithine	NA
342	N-formylmethionine	NA
343	N-formylphenylalanine	NA
344	N-glycolylneuraminate	N-Glycolylneuraminic acid
345	N-methyl-4-aminobutyric acid	NA
346	N-monomethylarginine	NA
347	N-palmitoyl-sphinganine	NA
348	N-palmitoyl-sphingosine	NA
349	N-palmitoyltaurine	NA
350	N-stearoyltaurine	NA
351	N1-Methyl-2-pyridone-5-carboxamide	N1-Methyl-2-pyridone-5-carboxamide
352	N1-methyladenosine	1-Methyladenosine
353	N2-acetyllysine/N6-acetyllysine	NA
354	N6,N6,N6-trimethyllysine	NA
355	N6-carboxymethyllysine	NA
356	N6-succinyladenosine	NA
357	nicotinamide	Niacinamide
358	nicotinamide adenine dinucleotide	NA
359	nicotinamide riboside	Nicotinamide riboside
360	nonadecanoate	NA
361	O-sulfo-L-tyrosine	NA
362	octanoylcarnitine	L-Octanoylcarnitine
363	oleamide	Oleamide
364	oleate/vaccenate	NA
365	oleoyl ethanolamide	NA
366	oleoylcarnitine	Oleoylcarnitine
367	ornithine	Ornithine
368	orotate	Orotic acid
369	orotidine	Orotidine
370	oxalate	NA
371	p-cresol sulfate	p-Cresol sulfate
372	p-cresol-glucuronide	NA
373	palmitate	NA
374	palmitoleate	NA
375	palmitoyl dihydrosphingomyelin	NA
376	palmitoyl ethanolamide	Palmitoylethanolamide
377	palmitoyl sphingomyelin	NA
378	palmitoylcarnitine	NA
379	pantothenate	Pantothenic acid
380	phenol sulfate	NA
381	phenylacetyl glycine	Phenylacetyl glycine
382	phenylalanine	L-Phenylalanine
383	phenylalanyl glycine	NA
384	phenyllactate	NA
385	phosphate	Phosphate
386	phosphoenolpyruvate	NA
387	phosphoethanolamine	O-Phosphoethanolamine
388	phosphopantetheine	Pantetheine 4'-phosphate
389	pipecolate	Pipecolic acid
390	pro-hydroxy-pro	NA
391	proline	L-Proline
392	prolylglycine	L-prolyl-L-glycine
393	propionylcarnitine	Propionylcarnitine
394	pseudouridine	Pseudouridine
395	putrescine	Putrescine
396	pyridoxal	Pyridoxal
397	pyridoxamine	Pyridoxamine
398	pyridoxamine phosphate	NA
399	pyridoxate	NA
400	pyroglutamine	NA
401	quinolinate	Quinolinic acid
402	retinol	NA
403	ribitol	Ribitol
404	riboflavin	NA
405	ribonate	Ribonic acid
406	ribose	D-Ribose
407	ribulose 5-phosphate	D-Ribulose 5-phosphate
408	S-adenosylhomocysteine	NA
409	S-adenosylmethionine	NA
410	saccharopine	Saccharopine

411	salicylate	Salicylic acid
412	sarcosine	NA
413	sebacate	NA
414	sedoheptulose-7-phosphate	D-Sedoheptulose 7-phosphate
415	serine	L-Serine
416	spermidine	Spermidine
417	sphinganine	Sphinganine
418	sphingomyelin	NA
419	sphingosine	Sphingosine
420	stachydrine	Proline betaine
421	stearate	NA
422	stearidonate	NA
423	stearoyl ethanolamide	Stearoylethanolamide
424	stearoyl sphingomyelin	NA
425	stearoylcarnitine	Stearoylcarnitine
426	succinate	Succinic acid
427	succinylcarnitine	NA
428	sucrose	Sucrose
429	sulfate	Sulfate
430	tartronate	NA
431	taurine	Taurine
432	tauro-beta-muricholate	Tauro-b-muricholic acid
433	taurochenodeoxycholate	Taurochenodesoxycholic acid
434	taurocholate	Taurocholic acid
435	taurocyamine	Taurocyamine
436	taurodeoxycholate	NA
437	tauroursodeoxycholate	Tauroursodeoxycholic acid
438	tetradecanedioate	Tetradecanedioic acid
439	thiamin	NA
440	thiamin monophosphate	Thiamine monophosphate
441	threonate	Threonic acid
442	threonine	L-Threonine
443	thymidine	Thymidine
444	tiglylcarnitine	Tiglylcarnitine
445	trans-4-hydroxyproline	4-Hydroxyproline
446	trans-uocanate	NA
447	tricosanoyl sphingomyelin	NA
448	trigonelline	NA
449	trimethylamine N-oxide	Trimethylamine N-oxide
450	tryptophan	D-Tryptophan
451	tyrosine	L-Tyrosine
452	tyrosylglycine	NA
453	UDP-galactose	Uridine diphosphategalactose
454	UDP-glucose	Uridine diphosphate glucose
455	UDP-glucuronate	Uridine diphosphate glucuronic acid
456	UDP-N-acetylgalactosamine	Uridine diphosphate-N-acetylgalactosamine
457	UDP-N-acetylglucosamine	Uridine diphosphate-N-acetylglucosamine
458	uracil	Uracil
459	urate	Uric acid
460	urea	Urea
461	uridine	Uridine
462	uridine 5'-diphosphate	NA
463	uridine 5'-monophosphate	NA
464	valine	L-Valine
465	valylglycine	NA
466	xanthine	Xanthine
467	xanthosine	Xanthosine

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. Please note, MSEA does not perform data normalization. If normalization is important, you should first normalize your data before upload. You can use our companion website **MetaboAnalyst** www.metaboanalyst.ca for a variety of data processing and normalization methods.

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 88 entries*);
- Disease associated metabolite sets (reported in blood) (*currently contains 416 entries*);
- Disease associated metabolite sets (reported in urine) (*currently contains 346 entries*);
- Disease associated metabolite sets (reported in CSF) (*currently contains 124 entries*);
- Metabolite sets associated with SNPs (*currently contains 4500 entries*);
- Predicted metabolite sets based on computational enzyme knockout model (*currently contains 912 entries*);
- Metabolite sets based on locations (*currently contains 57 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

Quantitative enrichment analysis (QEA) will be performed when the user uploads a concentration table. The enrichment analysis is performed using package **globaltest**¹. It uses a generalized linear model to estimate a *Q-statistic* for each metabolite set, which describes the correlation between compound concentration profiles, X, and clinical outcomes, Y. The *Q statistic* for a metabolite set is the average of the *Q* statistics for each metabolite in the set. **Figure 2** below summarizes the result.

¹Jelle J. Goeman, Sara A. van de Geer, Floor de Kort and Hans C. van Houwelingen. *A global test for groups of genes: testing association with a clinical outcome*, Bioinformatics Vol. 20 no. 1 2004, pages 93-99

Enrichment Overview (top 50)

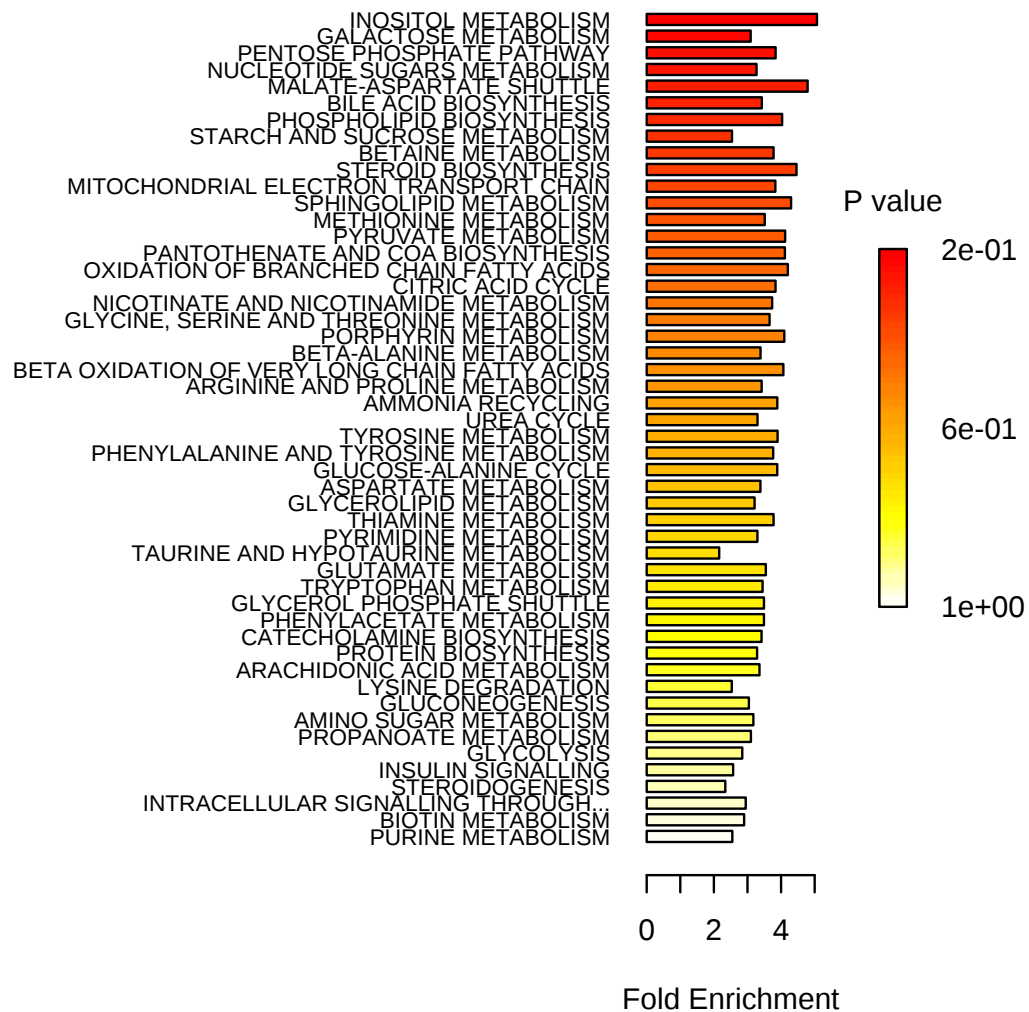


Figure 1: Summary Plot for Quantitative Enrichment Analysis (QEA)

Table 2: Result from Quantitative Enrichment Analysis

	Total Cmpd	Hits	Statistic Q	Expected Q	Raw p	Holm p	FDR
INOSITOL METABOLISM	19	2	72.41	14.29	4.04E-03	2.34E-01	6.92E-02
GALACTOSE METABOLISM	25	9	44.22	14.29	4.36E-03	2.49E-01	6.92E-02
PENTOSE PHOSPHATE PATHWAY	18	4	54.81	14.29	7.40E-03	4.15E-01	6.92E-02
NUCLEOTIDE SUGARS METABOLISM	9	3	46.72	14.29	1.06E-02	5.82E-01	6.92E-02
MALATE-ASPARTATE SHUTTLE	8	1	68.43	14.29	1.13E-02	6.09E-01	6.92E-02
BILE ACID BIOSYNTHESIS	49	4	48.96	14.29	1.18E-02	6.28E-01	6.92E-02
PHOSPHOLIPID BIOSYNTHESIS	19	4	57.59	14.29	1.19E-02	6.28E-01	6.92E-02
STARCH AND SUCROSE METABOLISM	14	6	36.27	14.29	1.28E-02	6.53E-01	6.92E-02
BETAINE METABOLISM	10	4	53.96	14.29	1.33E-02	6.67E-01	6.92E-02
STEROID BIOSYNTHESIS	31	1	63.71	14.29	1.76E-02	8.60E-01	6.92E-02
MITOCHONDRIAL ELECTRON TRANSPORT CHAIN	15	3	54.71	14.29	1.83E-02	8.77E-01	6.92E-02
SPHINGOLIPID METABOLISM	15	4	61.41	14.29	1.84E-02	8.77E-01	6.92E-02
METHIONINE METABOLISM	24	8	50.20	14.29	2.06E-02	9.49E-01	6.92E-02
PYRUVATE METABOLISM	20	2	58.88	14.29	2.10E-02	9.49E-01	6.92E-02
PANTOTHENATE AND COA BIOSYNTHESIS	10	2	58.77	14.29	2.13E-02	9.49E-01	6.92E-02
OXIDATION OF BRANCHED CHAIN FATTY ACIDS	14	2	60.02	14.29	2.16E-02	9.49E-01	6.92E-02
CITRIC ACID CYCLE	23	4	54.78	14.29	2.49E-02	1.00E+00	6.92E-02
NICOTINATE AND NICOTINAMIDE METABOLISM	13	5	53.35	14.29	2.52E-02	1.00E+00	6.92E-02
GLYCINE, SERINE AND THREONINE METABOLISM	26	9	52.25	14.29	2.62E-02	1.00E+00	6.92E-02
PORPHYRIN METABOLISM	22	2	58.52	14.29	2.64E-02	1.00E+00	6.92E-02
BETA-ALANINE METABOLISM	13	7	48.41	14.29	2.65E-02	1.00E+00	6.92E-02
BETA OXIDATION OF VERY LONG CHAIN FATTY ACIDS	14	1	58.12	14.29	2.79E-02	1.00E+00	6.92E-02
ARGININE AND PROLINE METABOLISM	26	11	48.89	14.29	3.05E-02	1.00E+00	6.92E-02
AMMONIA RECYCLING	18	6	55.55	14.29	3.08E-02	1.00E+00	6.92E-02
UREA CYCLE	20	8	47.13	14.29	3.10E-02	1.00E+00	6.92E-02
TYROSINE METABOLISM	38	2	55.66	14.29	3.29E-02	1.00E+00	6.92E-02
PHENYLALANINE AND TYROSINE METABOLISM	13	3	53.79	14.29	3.37E-02	1.00E+00	6.92E-02
GLUCOSE-ALANINE CYCLE	12	1	55.52	14.29	3.39E-02	1.00E+00	6.92E-02
ASPARTATE METABOLISM	12	6	48.36	14.29	3.64E-02	1.00E+00	6.92E-02
GLYCEROLIPID METABOLISM	13	4	45.88	14.29	3.68E-02	1.00E+00	6.92E-02
THIAMINE METABOLISM	4	1	53.95	14.29	3.80E-02	1.00E+00	6.92E-02
PYRIMIDINE METABOLISM	36	11	47.08	14.29	3.82E-02	1.00E+00	6.92E-02
TAURINE AND HYPOTAURINE METABOLISM	7	3	30.83	14.29	4.41E-02	1.00E+00	7.66E-02
GLUTAMATE METABOLISM	18	2	50.67	14.29	4.49E-02	1.00E+00	7.66E-02
TRYPTOPHAN METABOLISM	34	3	49.28	14.29	4.97E-02	1.00E+00	7.88E-02
GLYCEROL PHOSPHATE SHUTTLE	8	1	49.87	14.29	5.03E-02	1.00E+00	7.88E-02
PHENYLACETATE METABOLISM	4	1	49.87	14.29	5.03E-02	1.00E+00	7.88E-02
CATECHOLAMINE BIOSYNTHESIS	5	1	48.85	14.29	5.38E-02	1.00E+00	8.10E-02
PROTEIN BIOSYNTHESIS	19	12	46.95	14.29	5.44E-02	1.00E+00	8.10E-02
ARACHIDONIC ACID METABOLISM	37	1	47.96	14.29	5.69E-02	1.00E+00	8.20E-02
LYSINE DEGRADATION	13	3	36.18	14.29	5.80E-02	1.00E+00	8.20E-02
GLUCONEOGENESIS	27	3	43.46	14.29	6.48E-02	1.00E+00	8.91E-02
AMINO SUGAR METABOLISM	15	1	45.37	14.29	6.71E-02	1.00E+00	8.91E-02
PROPANOATE METABOLISM	18	2	44.32	14.29	6.76E-02	1.00E+00	8.91E-02
GLYCOLYSIS	21	2	40.64	14.29	7.43E-02	1.00E+00	9.57E-02
INSULIN SIGNALLING	19	2	36.76	14.29	7.63E-02	1.00E+00	9.58E-02
STEROIDOGENESIS	32	2	33.43	14.29	7.76E-02	1.00E+00	9.58E-02
INTRACELLULAR SIGNALLING THROUGH ADENOSINE RECEPTOR A2A AND ADENOSINE INTRACELLULAR SIGNALLING THROUGH ADENOSINE RECEPTOR A2B AND ADENOSINE	7	1	42.12	14.29	8.17E-02	1.00E+00	9.87E-02
BIOTIN METABOLISM	4	1	41.44	14.29	8.50E-02	1.00E+00	9.95E-02
PURINE METABOLISM	45	10	36.42	14.29	8.58E-02	1.00E+00	9.95E-02
HISTIDINE METABOLISM	11	4	31.03	14.29	1.03E-01	1.00E+00	1.17E-01
GLUTATHIONE METABOLISM	10	2	36.27	14.29	1.05E-01	1.00E+00	1.17E-01
VALINE, LEUCINE AND ISOLEUCINE DEGRADATION	36	3	27.56	14.29	1.34E-01	1.00E+00	1.47E-01

SULFATE/SULFITE METABOLISM	7	2	24.58	14.29	1.92E-01	1.00E+00	2.06E-01
CYSTEINE METABOLISM	8	1	16.60	14.29	3.16E-01	1.00E+00	3.34E-01
INTRACELLULAR SIGNALING THROUGH HISTAMINE H2 RECEPTOR AND HISTAMINE	5	1	13.94	14.29	3.62E-01	1.00E+00	3.75E-01
VITAMIN B6 METABOLISM	10	2	9.33	14.29	4.71E-01	1.00E+00	4.79E-01
FRUCTOSE AND MANNOSE DEGRADATION	18	2	2.63	14.29	8.57E-01	1.00E+00	8.57E-01

The report was generated on Sat Oct 17 16:24:58 2015 with R version 3.2.0 (2015-04-16). Thank you for using MetaboAnalyst! For suggestions and feedback please contact Jeff Xia (jeff.xia@mcgill.ca).