

**Supplementary Table 2. Levels of 99 metabolites in urine from 20w and 40w from the WT and FD groups**

Number	Metabolite	Concentration (pg/ng creatinine, mean $\pm$ SD)		Normalized value <sup>a</sup>		p-value <sup>b</sup>		VIP score <sup>c</sup>	
		20w (WT)	20w (FD)	40w (WT)	40w (FD)	20w (WT vs. FD)	40w (WT vs. FD)	20w (WT vs. FD)	40w (WT vs. FD)
<b>Organic acid</b>									
1	Pyruvic acid	92.6 $\pm$ 12.5	171.4 $\pm$ 55.0	69.3 $\pm$ 25.2	66.5 $\pm$ 23.9	1.85	0.96	0.002	2.58
2	3-Hydroxyisovaleric acid	4.9 $\pm$ 2.3	5.3 $\pm$ 2.6	2.3 $\pm$ 1.3	2.7 $\pm$ 0.78	1.09	1.18	0.82	0.28
3	Acetoacetic acid	230.9 $\pm$ 86.6	424.0 $\pm$ 239.4	65.8 $\pm$ 39.1	106.8 $\pm$ 42.3	1.84	1.62	0.09	1.75
4	Lactic acid	207.6 $\pm$ 63.5	295.4 $\pm$ 116.8	102.2 $\pm$ 26.8	128.4 $\pm$ 24.7	1.42	1.26	0.09	1.50
5	Glycolic acid	400.2 $\pm$ 46.3	512.7 $\pm$ 59.2	258.4 $\pm$ 66.3	294.1 $\pm$ 39.8	1.28	1.14	0.004	0.82
6	Phenylacetic acid	27.6 $\pm$ 15.6	27.7 $\pm$ 10.2	8.3 $\pm$ 1.6	12.8 $\pm$ 3.3	1.00	1.54	0.82	0.27
7	Oxalic acid	938.0 $\pm$ 260.1	913.9 $\pm$ 551.1	341.8 $\pm$ 145.3	299.8 $\pm$ 71.7	0.97	0.88	0.49	0.46
8	2-Hydroxybutyric acid	7.9 $\pm$ 0.9	10.4 $\pm$ 1.3	4.2 $\pm$ 0.8	6.8 $\pm$ 1.8	1.33	1.62	0.004	2.51
9	3-Hydroxypropionic acid	86.1 $\pm$ 12.1	135.8 $\pm$ 46.6	54.7 $\pm$ 11.2	71.7 $\pm$ 12.8	1.58	1.31	0.04	2.02
10	2-Hydroxyisovaleric acid	9.7 $\pm$ 6.4	10.3 $\pm$ 3.4	2.0 $\pm$ 0.4	3.1 $\pm$ 1.0	1.06	1.52	0.59	0.63
11	Malonic acid	80.4 $\pm$ 9.3	79.6 $\pm$ 14.7	41.6 $\pm$ 12.6	70.8 $\pm$ 8.3	0.99	1.70	0.94	0.21
12	Methylmalonic acid	3.6 $\pm$ 0.8	3.9 $\pm$ 0.7	2.1 $\pm$ 0.5	2.7 $\pm$ 1.0	1.08	1.27	0.70	0.71
13	2-Hydroxy-3-methylvaleric acid	23.0 $\pm$ 9.0	23.4 $\pm$ 6.4	5.8 $\pm$ 1.3	8.6 $\pm$ 2.5	1.02	1.48	0.94	0.24
14	Ethylmalonic acid	25.0 $\pm$ 4.6	23.7 $\pm$ 2.9	10.4 $\pm$ 2.5	21.1 $\pm$ 7.3	0.95	2.04	0.59	0.43
15	Isovalerylglycine	1,206.3 $\pm$ 176.1	1,198.5 $\pm$ 211.9	612.8 $\pm$ 178.5	913.1 $\pm$ 406.4	0.99	1.49	0.94	0.12
16	Succinic acid	1,381.5 $\pm$ 381.7	1,671.2 $\pm$ 410.0	735.8 $\pm$ 178.3	619.6 $\pm$ 224.1	1.21	0.84	0.39	1.05
17	Methylsuccinic acid	41.7 $\pm$ 5.5	40.6 $\pm$ 3.0	22.5 $\pm$ 4.1	29.2 $\pm$ 2.3	0.97	1.30	0.82	0.30
18	Fumaric acid	61.5 $\pm$ 27.0	131.6 $\pm$ 116.9	50.5 $\pm$ 16.4	42.2 $\pm$ 26.5	2.14	0.84	0.39	1.11
19	Phenylpyruvic acid	30.8 $\pm$ 12.9	41.6 $\pm$ 21.1	19.1 $\pm$ 8.8	27.4 $\pm$ 12.9	1.35	1.43	0.59	0.61
20	2-Methylfumaric acid	13.1 $\pm$ 2.4	11.9 $\pm$ 3.4	9.6 $\pm$ 1.7	12.3 $\pm$ 3.2	0.91	1.28	0.82	0.71
21	Oxaloacetic acid	401.1 $\pm$ 61.4	423.9 $\pm$ 54.6	295.3 $\pm$ 64.3	276.8 $\pm$ 37.3	1.06	0.94	0.59	0.66
22	Glutaric acid	172.9 $\pm$ 51.5	171.5 $\pm$ 53.8	116.8 $\pm$ 19.0	182.5 $\pm$ 114.1	0.99	1.56	0.94	0.12
23	Hexanoylglycine	840.1 $\pm$ 162.8	928.0 $\pm$ 261.9	329.4 $\pm$ 190.9	741.3 $\pm$ 488.5	1.10	2.25	0.59	0.42
24	Mandelic acid	3.2 $\pm$ 1.5	3.2 $\pm$ 1.2	1.1 $\pm$ 0.3	1.7 $\pm$ 0.7	0.98	1.46	0.94	0.05
25	3-Hydroxy-3-methylglutaric acid	185.3 $\pm$ 27.7	177.1 $\pm$ 28.7	107.1 $\pm$ 11.8	121.3 $\pm$ 19.4	0.96	1.13	0.94	0.93
26	Adipic acid	259.9 $\pm$ 36.1	229.0 $\pm$ 44.5	101.5 $\pm$ 45.5	191.7 $\pm$ 72.4	0.88	1.89	0.31	1.54
27	3-Methyladipic acid	7.4 $\pm$ 0.7	7.0 $\pm$ 1.5	3.5 $\pm$ 0.5	7.4 $\pm$ 2.5	0.95	2.09	0.94	1.89
28	$\alpha$ -Ketoglutaric acid	3,483.1 $\pm$ 1,327.8	6,723.5 $\pm$ 3,410.5	3,331.2 $\pm$ 861.8	2,876.8 $\pm$ 1,536.7	1.93	0.86	0.04	0.66
29	2-Hydroxyphenylacetic acid	9.2 $\pm$ 2.1	9.9 $\pm$ 2.3	7.2 $\pm$ 2.1	7.3 $\pm$ 1.8	1.07	1.02	0.70	0.04
30	Phenylacetic acid	3.7 $\pm$ 2.8	3.5 $\pm$ 3.5	1.2 $\pm$ 0.6	1.0 $\pm$ 0.5	0.95	0.81	0.94	0.06
31	3-Hydroxyphenylacetic acid	10.7 $\pm$ 4.3	10.3 $\pm$ 3.0	6.1 $\pm$ 1.3	6.3 $\pm$ 1.7	0.96	1.03	0.70	0.13
32	4-Hydroxyphenylacetic acid	11.2 $\pm$ 4.4	10.8 $\pm$ 3.2	6.3 $\pm$ 1.4	6.5 $\pm$ 1.8	0.97	1.04	0.70	0.16
33	Pimelic acid	24.5 $\pm$ 3.9	23.5 $\pm$ 2.4	11.0 $\pm$ 2.5	17.0 $\pm$ 5.2	0.96	1.54	0.59	0.41
34	Hippuric acid	1,018.1 $\pm$ 296.2	1,235.8 $\pm$ 312.5	979.3 $\pm$ 434.5	801.3 $\pm$ 552.4	1.21	0.82	0.31	0.63
35	Malic acid	251.8 $\pm$ 75.1	472.3 $\pm$ 340.0	211.7 $\pm$ 59.2	180.3 $\pm$ 83.3	1.88	0.85	0.24	0.57
36	Suberic acid	5.9 $\pm$ 3.3	7.2 $\pm$ 1.5	3.8 $\pm$ 0.9	5.8 $\pm$ 2.4	1.21	1.51	0.94	1.15
37	3-Indoleacetic acid	8.9 $\pm$ 2.9	7.7 $\pm$ 1.4	5.7 $\pm$ 1.6	6.7 $\pm$ 2.0	0.86	1.17	0.59	0.66
38	2-Hydroxyglutaric acid	878.8 $\pm$ 551.3	920.1 $\pm$ 472.0	479.8 $\pm$ 114.8	412.5 $\pm$ 166.2	1.05	0.86	0.94	0.69
39	Homovanillic acid	2.3 $\pm$ 0.2	2.0 $\pm$ 0.2	1.3 $\pm$ 0.5	1.4 $\pm$ 0.2	0.87	1.07	0.09	0.53
40	Vanillic acid	11.2 $\pm$ 3.9	7.8 $\pm$ 3.4	9.6 $\pm$ 3.0	5.3 $\pm$ 3.1	0.70	0.55	0.24	1.39
41	Azelatic acid	5.5 $\pm$ 2.8	4.3 $\pm$ 0.8	2.9 $\pm$ 1.3	2.9 $\pm$ 1.0	0.78	1.00	0.39	0.44

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Supplementary Table 2. Continued

Number	Metabolite	Concentration (pg/ng creatinine, mean ± SD)			Normalized value <sup>a</sup>		p-value <sup>b</sup>		VIP score <sup>c</sup>	
		20w (WT)	40w (WT)	40w (FD)	20w (WT vs. FD)	40w (WT vs. FD)	20w (WT vs. FD)	40w (WT vs. FD)	20w (WT vs. FD)	40w (WT vs. FD)
42	4-Hydroxyphenylpyruvic acid	387.6 ± 148.6	606.9 ± 323.3	648.5 ± 322.7	2.03	1.07	0.04	0.62	1.72	0.18
43	cis-Aconitic acid	514.2 ± 123.0	379.1 ± 79.0	447.4 ± 95.2	1.12	1.18	0.59	0.17	0.63	0.82
44	4-Hydroxymandelic acid	41.0 ± 7.6	20.3 ± 5.4	20.7 ± 2.9	0.84	1.02	0.07	0.90	1.58	0.25
45	3-Indolecarboxylic acid	18.3 ± 2.6	9.0 ± 1.2	11.1 ± 1.2	0.90	1.24	0.49	0.004	1.09	1.55
46	Vanillylmandelic acid	1.3 ± 0.2	0.61 ± 0.13	0.82 ± 0.18	0.94	1.35	0.59	0.02	0.76	1.34
47	2-Hydroxyhippuric acid	2.5 ± 0.6	2.8 ± 0.7	2.2 ± 1.0	1.07	0.79	0.49	0.26	0.56	0.88
48	4-Hydroxyphenyllactic acid	27.8 ± 12.9	13.1 ± 4.3	11.3 ± 2.0	0.76	0.87	0.49	0.46	0.90	0.45
49	3-Indolelactic acid	17.0 ± 9.1	7.5 ± 2.3	9.0 ± 3.1	0.83	1.21	0.94	0.32	0.52	0.51
50	Citric acid	5,009.4 ± 2,695.6	4,355.3 ± 821.3	3,444.1 ± 2,466.2	1.51	0.79	0.49	0.13	0.77	0.91
51	Isoctic acid	689.8 ± 169.7	472.0 ± 100.7	535.7 ± 100.8	1.26	1.13	0.24	0.38	0.85	0.75
52	3-Indoleglyoxalic acid	8.7 ± 1.3	5.6 ± 1.0	5.2 ± 1.0	1.01	0.95	0.82	0.71	0.11	0.35
Amino acid										
53	Tryptophan	2.1 ± 0.9	2.9 ± 0.6	4.5 ± 5.1	0.95	1.57	0.39	0.71	0.49	0.27
54	Phenylalanine	17.7 ± 5.1	16.9 ± 2.9	32.8 ± 37.9	0.99	1.94	0.94	0.38	0.13	0.62
55	Tyrosine	11.8 ± 4.3	17.5 ± 4.9	28.7 ± 26.0	0.90	1.64	0.70	0.54	0.20	0.63
56	Leucine	26.7 ± 10.2	46.6 ± 13.0	100.3 ± 107.8	1.17	2.15	0.70	0.13	0.55	0.91
57	Isoleucine	8.7 ± 3.7	23.0 ± 2.8	23.5 ± 25.9	1.15	1.83	0.82	0.90	0.89	0.57
58	Methionine	13.1 ± 11.9	12.8 ± 5.8	22.8 ± 16.0	0.74	0.99	0.70	0.62	0.55	0.45
59	Valine	7.3 ± 3.2	12.6 ± 2.7	24.0 ± 22.5	1.28	1.90	0.39	0.21	1.02	0.92
60	Pipecolic acid	125.6 ± 79.5	112.9 ± 11.6	194.9 ± 161.9	0.78	1.73	>0.99	0.46	0.54	0.83
61	Glutamic acid	2.8 ± 1.1	3.6 ± 1.6	3.9 ± 2.4	0.69	1.09	0.39	>0.99	1.14	0.04
62	Proline	15.3 ± 8.9	7.0 ± 1.4	14.0 ± 10.1	0.87	1.99	0.70	0.05	0.54	1.22
63	Threonine	4.5 ± 2.1	17.2 ± 5.3	31.1 ± 22.5	1.37	1.81	0.24	0.21	0.40	1.00
64	4-Hydroxyproline	3.7 ± 2.4	2.9 ± 1.1	5.6 ± 3.2	1.02	1.93	0.70	0.13	0.65	1.10
65	Alanine	14.3 ± 7.5	24.3 ± 6.3	36.8 ± 23.8	0.67	1.51	0.82	0.62	1.09	0.60
66	Homoserine	1.2 ± 0.6	2.0 ± 1.0	2.7 ± 2.1	1.03	1.30	0.82	>0.99	0.34	0.23
67	Glutamine	101.8 ± 78.0	87.5 ± 26.8	136.1 ± 102.4	2.28	1.56	0.13	0.81	1.22	0.48
68	Creatine	506.6 ± 244.6	483.4 ± 202.0	717.7 ± 631.7	0.97	1.48	>0.99	0.54	0.20	0.53
69	Asparagine	3.1 ± 1.2	7.2 ± 2.4	8.5 ± 7.3	0.85	1.18	0.31	0.54	0.70	0.18
70	β-Aminoisobutyric acid	16.3 ± 4.8	10.8 ± 3.5	21.2 ± 16.2	0.83	1.96	0.39	0.07	0.90	1.14
71	γ-Aminobutyric acid	3.9 ± 1.2	7.5 ± 2.9	12.1 ± 9.7	1.16	1.61	0.31	0.32	0.67	0.75
72	GSSG	ND	14.7 ± 10.7	6.9 ± 5.5	-	0.47	-	0.13	-	1.06
73	1-Methylhistidine	14.7 ± 5.6	14.1 ± 7.2	11.5 ± 7.2	0.83	0.81	0.39	0.46	0.78	0.56
74	Histidine	4.3 ± 1.0	3.2 ± 1.3	2.8 ± 3.1	0.96	0.86	0.59	0.10	0.90	0.80
75	3-Methylhistidine	66.9 ± 41.2	63.5 ± 27.8	34.1 ± 22.2	0.76	0.54	0.24	0.10	1.04	1.22
76	Arginine	1.0 ± 0.7	1.6 ± 0.5	2.4 ± 2.1	0.86	1.50	0.82	0.90	0.07	0.26
Kynurenine pathway metabolite										
53	Tryptophan	2.1 ± 0.9	2.9 ± 0.6	4.5 ± 5.1	0.95	1.57	0.39	0.71	0.49	0.27
77	Picolinic acid	5.0 ± 4.5	0.52 ± 0.21	2.6 ± 2.8	1.01	5.06	0.59	0.03	0.56	1.43
78	3-Hydroxykynurenine	0.42 ± 0.10	0.34 ± 0.08	0.52 ± 0.25	1.16	1.54	0.39	0.13	0.79	1.07
79	3-Hydroxyanthranilic acid	2.0 ± 0.7	1.2 ± 0.2	1.5 ± 0.2	0.97	1.21	>0.99	0.07	0.01	1.32
80	5-Hydroxyindoleacetic acid	34.9 ± 7.8	12.9 ± 2.3	16.3 ± 1.6	0.93	1.27	0.59	0.01	0.57	1.49

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Supplementary Table 2. Continued

Number	Metabolite	Concentration (pg/ng creatinine, mean $\pm$ SD)			Normalized value <sup>a</sup>		p-value <sup>b</sup>		VIP score <sup>c</sup>		
		20w (WT)	20w (FD)	40w (WT)	40w (FD)	20w (WT vs. FD)	40w (WT vs. FD)	20w (WT vs. FD)	40w (WT vs. FD)	20w (WT vs. FD)	40w (WT vs. FD)
81	Kynurenic acid	30.3 $\pm$ 4.0	25.9 $\pm$ 3.0	7.4 $\pm$ 2.0	9.8 $\pm$ 1.9	0.85	1.33	0.04	0.04	1.77	1.35
82	Anthranilic acid	1.9 $\pm$ 0.5	1.3 $\pm$ 0.3	0.44 $\pm$ 0.16	0.64 $\pm$ 0.17	0.71	1.46	0.13	0.05	1.72	1.26
83	Serotonin	1.6 $\pm$ 0.2	1.5 $\pm$ 0.2	0.51 $\pm$ 0.12	0.40 $\pm$ 0.07	0.92	0.79	0.82	0.13	0.86	1.10
Nucleoside											
84	5,6-Dihydrouridine	430.6 $\pm$ 68.0	381.5 $\pm$ 51.3	134.1 $\pm$ 22.7	146.8 $\pm$ 10.4	0.89	1.09	0.31	0.32	1.17	0.80
85	Pseudouridine	494.6 $\pm$ 104.8	494.4 $\pm$ 117.3	296.5 $\pm$ 64.2	375.8 $\pm$ 69.1	1.00	1.27	0.82	0.10	0.08	1.20
86	Uridine	52.7 $\pm$ 24.2	67.4 $\pm$ 34.7	39.3 $\pm$ 12.6	55.6 $\pm$ 12.4	1.28	1.41	0.39	0.07	0.45	1.29
87	Inosine	15.9 $\pm$ 9.5	23.1 $\pm$ 12.6	10.3 $\pm$ 4.5	15.5 $\pm$ 6.2	1.45	1.51	0.49	0.05	0.22	1.13
88	Guanosine	7.9 $\pm$ 2.8	7.4 $\pm$ 2.0	4.9 $\pm$ 2.1	6.9 $\pm$ 3.8	0.94	1.41	0.94	0.17	0.22	0.84
89	Xanthosine	6.3 $\pm$ 3.1	8.4 $\pm$ 3.4	6.1 $\pm$ 1.5	10.7 $\pm$ 2.5	1.33	1.75	0.31	0.004	0.95	1.77
90	3-Methyluridine	6.2 $\pm$ 1.3	5.2 $\pm$ 1.1	4.3 $\pm$ 0.7	5.0 $\pm$ 0.4	0.84	1.15	0.39	0.07	1.31	1.16
91	1-Methylguanosine	36.8 $\pm$ 7.8	33.8 $\pm$ 8.4	21.0 $\pm$ 4.9	24.5 $\pm$ 3.2	0.92	1.17	0.59	0.17	0.60	0.92
92	Cytidine	1.8 $\pm$ 0.9	1.5 $\pm$ 0.8	0.47 $\pm$ 0.16	0.71 $\pm$ 0.27	0.81	1.50	0.70	0.13	0.73	1.14
93	N2-Methylguanosine	4.6 $\pm$ 1.4	4.3 $\pm$ 1.7	2.2 $\pm$ 0.4	2.9 $\pm$ 0.6	0.93	1.32	0.94	0.07	0.50	1.33
94	Adenosine	19.7 $\pm$ 17.0	26.2 $\pm$ 16.1	26.5 $\pm$ 4.6	27.4 $\pm$ 7.7	1.33	1.04	0.39	0.81	0.14	0.02
95	N <sup>2</sup> ,N <sup>2</sup> -Dimethylguanosine	13.4 $\pm$ 2.8	11.4 $\pm$ 1.5	9.4 $\pm$ 2.4	10.3 $\pm$ 1.2	0.85	1.09	0.24	0.71	1.21	0.62
96	1-Methyladenosine	1.2 $\pm$ 1.1	0.22 $\pm$ 0.14	0.33 $\pm$ 0.21	0.14 $\pm$ 0.02	0.18	0.43	0.02	0.007	2.27	1.52
97	N6-Methyladenosine	1.2 $\pm$ 1.1	0.23 $\pm$ 0.15	0.31 $\pm$ 0.20	0.14 $\pm$ 0.03	0.18	0.45	0.02	0.02	2.27	1.43
98	MTA	3.5 $\pm$ 2.1	3.7 $\pm$ 1.7	5.6 $\pm$ 1.4	4.0 $\pm$ 1.2	1.04	0.71	0.94	0.13	0.11	1.10
99	N <sup>6</sup> -Acetylcytidine	362.0 $\pm$ 95.3	386.0 $\pm$ 84.6	748.9 $\pm$ 136.1	883.7 $\pm$ 97.7	1.07	1.18	0.70	0.05	0.42	1.13

FD, Fabry disease; GSSG, glutathione disulfide; MTA, 5'-deoxy-5'-methylthioadenosine; ND, not determined; SD, standard deviation; VIP, variable importance in projection; WT, wild-type; 20w, 20-week-old; 40w, 40-week-old.

<sup>a</sup>Values normalized to the corresponding mean value of the WT concentration. <sup>b</sup>p-value calculated by Wilcoxon rank-sum test. <sup>c</sup>VIP score of partial least squares discriminant analysis.