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Supplemental Information

Near-Complete Correction of Profound Metabolomic Impairments Corresponding to Functional Benefit in MPS IIIB Mice after IV rAAV9-hNAGLU Gene Delivery

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Supplementary Table S1 Metabolomic impairments in MPS IIIB mice and their responses to an IV injection of rAAV8-CMV-hNAGLU vector									
			Fold of Change						
Pathways	**Sub-pathways**	**Metabolites**	**IIIB-2m / WT-2m**	**IIIB-7m / WT-7m**	**AAV9-2m / WT-2m**	**AAV9-7m / WT-7m**	**WT-7m / WT-2m**	**IIIB-7m / IIIB-2m**	**AAV9-7m / AAV9-2m**
Amino Acid	Glycine, Serine and Threonine Metabolism	glycine	0.69	0.11	0.92	1.01	0.8	0.13	0.88
		N-acetylglycine	0.43	0.12	0.64	1.3	0.68	0.19	1.39
		sarcosine (N-Methylglycine)	1.22	2.44	0.77	0.86	0.9	1.81	1.01
		dimethylglycine	0.99	0.4	0.77	1.84	0.65	0.26	1.55
		betaine	0.99	0.84	1.13	0.85	0.9	0.77	0.67
		serine	0.83	0.09	1.09	0.85	0.95	0.11	0.74
		N-acetylserine	0.74	0.29	0.52	3.6	0.53	0.21	3.69
		beta-hydroxypyruvate	1.22	0.59	0.99	1.15	0.86	0.42	1
		threonine	1.45	1.11	0.6	1.47	0.76	0.58	1.85
	Alanine and Aspartate Metabolism	alanine	1.03	0.13	1.17	0.72	1.02	0.12	0.63
		N-acetylalanine	1.01	0.28	0.73	1.2	0.89	0.25	1.47
		aspartate	1.23	0.51	0.52	0.56	0.84	0.35	0.91
		asparagine	0.73	0.16	0.98	0.88	0.87	0.2	0.79
		N-acetylaspartate (NAA)	1.02	0.21	0.84	1.54	1.01	0.21	1.83
	Glutamate Metabolism	glutamate	0.95	0.37	0.77	0.96	0.96	0.37	1.19
		glutamine	1.15	0.53	1.01	0.92	0.97	0.45	0.89
		N-acetylglutamate	0.47	0.43	0.29	3.46	0.56	0.51	6.54
		N-acetylglutamine	0.45	0.3	0.44	2.47	0.66	0.45	3.69
	Histidine Metabolism	histidine	0.95	0.47	0.94	1.09	0.89	0.45	1.04
		N-acetylhistidine	0.49	0.18	0.5	1.68	0.68	0.25	2.28
		trans-urocanate	1.06	0.2	0.97	0.72	1.52	0.28	1.12
		cis-urocanate	0.81	0.33	0.76	1.2	1.17	0.47	1.85
		imidazole propionate	0.55	0.64	0.32	3.06	0.58	0.68	5.53
		1-methylimidazoleacetate	0.74	0.26	0.53	2.57	0.87	0.31	4.26
	Lysine Metabolism	lysine	0.77	0.18	0.68	0.61	0.67	0.16	0.6
		2-aminoadipate	1.08	0.99	0.61	1.27	0.66	0.61	1.4
		pipecolate	0.98	0.5	0.89	2.83	0.77	0.4	2.46
		5-aminovalerate	1.53	0.9	1.01	2.02	0.91	0.53	1.82
	Phenylalanine and Tyrosine Metabolism	phenylalanine	0.96	0.43	0.83	1.09	0.85	0.38	1.12
		N-acetylphenylalanine	0.9	0.33	0.87	0.99	0.86	0.32	0.97
		phenyllactate (PLA)	1.23	0.58	0.93	1.85	1.03	0.48	2.04

		phenylacetate	1	0.49	0.99	1.05	0.64	**0.31**	0.68
		phenylacetylglycine	0.34	**0.23**	0.25	**6.55**	0.42	**0.29**	**10.89**
		tyrosine	1.12	0.72	1.03	0.82	0.94	**0.6**	0.75
		N-acetyltyrosine	0.68	**0.26**	0.75	0.52	0.82	**0.31**	0.57
		4-hydroxycinnamate	**0.25**	**0.25**	**0.22**	0.38	**0.66**	*0.64*	1.12
		4-hydroxyphenylpyruvate	0.81	0.79	0.77	1.53	0.73	0.71	1.46
		3-(4-hydroxyphenyl)lactate	1.1	**0.41**	0.94	1.32	0.98	**0.36**	1.37
		phenol sulfate	0.46	**0.31**	0.46	**2.61**	0.52	**0.34**	**2.94**
		p-cresol sulfate	0.87	**0.26**	0.73	3.18	0.82	**0.24**	3.54
		2-amino-p-cresol sulfate	0.15	0.47	0.24	6.24	0.31	0.97	8.2
		homovanillate sulfate	0.28	0.46	0.22	6.65	0.41	0.67	**12.4**
		phenylpropionylglycine	0.44	0.23	0.59	2.71	0.95	0.49	4.39
		2-(4-hydroxyphenyl)propionate	0.7	0.53	0.39	**9.94**	0.62	0.46	**15.7**
		3-phenylpropionate (hydrocinnamate)	1.01	0.6	1.42	**0.36**	1.15	0.69	**0.29**
	Tryptophan Metabolism	tryptophan	0.73	**0.39**	0.72	0.97	**0.66**	**0.36**	0.89
		N-acetyltryptophan	**0.58**	**0.26**	0.64	1.18	**0.55**	**0.24**	1
		indolelactate	0.63	**0.18**	**0.45**	**4.26**	**0.56**	**0.16**	**5.37**
		indolepropionate	1.79	0.79	**1.8**	1.63	**0.59**	**0.26**	**0.53**
		3-indoxyl sulfate	0.92	0.64	0.69	**2.8**	0.65	**0.46**	**2.66**
		kynurenine	**0.61**	**0.26**	**0.6**	0.98	0.74	**0.32**	1.21
		kynurenate	**0.32**	0.62	**0.31**	3.25	0.54	1.06	**5.67**
		xanthurenate	0.15	0.36	0.14	3.93	0.47	1.15	**13.47**
		5-hydroxyindoleacetate	0.36	**0.12**	0.24	3.65	0.63	**0.21**	**9.49**
		serotonin (5HT)	0.75	**0.05**	0.74	0.57	0.97	**0.06**	0.75
		C-glycosyltryptophan	0.9	**0.24**	0.62	**3.11**	0.65	**0.17**	**3.26**
	Leucine, Isoleucine and Valine Metabolism	leucine	1	**0.39**	0.77	1	0.83	**0.33**	1.08
		N-acetylleucine	1.01	**0.46**	0.8	1.05	0.86	**0.39**	1.12
		4-methyl-2-oxopentanoate	**0.46**	**0.37**	0.63	0.65	0.64	0.51	0.67
		isovalerate	0.64	**0.28**	0.6	0.58	0.66	**0.29**	0.64
		isovalerylglycine	0.3	0.28	0.26	**6.33**	0.38	0.36	**9.34**
		isovalerylcarnitine	1.13	**0.49**	0.74	1.06	0.78	**0.34**	1.1
		3-methylcrotonylglycine	0.33	0.45	**0.24**	**4.2**	0.51	0.69	**8.78**
		beta-hydroxyisovalerate	0.74	**0.25**	0.7	**2.46**	0.66	**0.22**	**2.32**
		beta-hydroxyisovaleroylcarnitine	1.13	**0.51**	0.98	**1.42**	0.77	**0.35**	1.11

		alpha-hydroxyisovalerate	1.01	0.54	1.22	1.05	0.83	**0.45**	0.71
		isoleucine	0.83	**0.38**	0.78	0.94	0.8	**0.37**	0.97
		3-methyl-2-oxovalerate	**0.33**	**0.39**	0.65	0.69	0.61	0.72	0.64
		2-methylbutyrylcarnitine (C5)	1.31	**0.55**	0.67	**1.61**	**0.63**	**0.27**	1.52
		2-methylbutyrylglycine	0.44	0.45	0.38	3.41	0.65	0.66	5.8
		tigloylglycine	0.48	0.5	**0.37**	**2.44**	0.53	0.55	**3.49**
		2-hydroxy-3-methylvalerate	0.82	0.53	0.79	1.46	0.68	**0.44**	1.27
		valine	0.81	**0.41**	0.77	0.93	0.85	**0.43**	1.03
		3-methyl-2-oxobutyrate	**0.43**	**0.41**	0.71	0.81	0.76	0.71	0.86
		isobutyrylcarnitine	2.25	0.63	1.16	1.93	0.8	**0.23**	1.34
		3-hydroxyisobutyrate	0.75	**0.47**	0.72	0.83	**0.63**	**0.4**	0.74
		alpha-hydroxyisocaproate	0.81	0.54	0.8	0.97	0.84	0.55	1.02
	Methionine, Cysteine, SAM and Taurine Metabolism	methionine	1.21	**0.64**	1	0.97	0.84	**0.45**	0.81
		N-acetylmethionine	1.28	0.65	0.96	1.34	**0.6**	**0.31**	0.84
		N-formylmethionine	0.73	**0.29**	0.47	**2.41**	0.6	**0.24**	**3.1**
		2-aminobutyrate	0.93	**0.42**	0.9	1.09	0.88	**0.4**	1.06
		2-hydroxybutyrate (AHB)	0.57	**0.2**	0.62	0.89	0.81	**0.29**	1.17
		cysteine	1.11	0.59	0.6	**2.91**	0.73	**0.39**	**3.56**
		cystine	1	1.56	1	**1.88**	1	1.56	**1.88**
		taurine	1.12	0.44	0.39	1.91	0.99	0.39	4.88
	Urea cycle; Arginine and Proline Metabolism	arginine	1.27	0.98	1.61	1.04	1.22	0.94	0.79
		urea	0.93	**0.56**	0.68	**2.38**	**0.65**	**0.39**	**2.29**
		ornithine	0.99	**0.16**	0.53	**0.35**	0.75	**0.12**	0.49
		proline	1.27	**0.51**	0.9	0.92	0.81	**0.32**	0.82
		citrulline	1.03	0.87	0.87	**1.52**	**0.73**	**0.61**	1.27
		N-alpha-acetylornithine	1.23	**0.46**	0.97	**1.41**	**0.59**	**0.22**	0.85
		trans-4-hydroxyproline	1.1	**0.2**	1.17	0.78	0.61	**0.11**	**0.41**
		pro-hydroxy-pro	0.64	**0.25**	0.61	**2.93**	**0.35**	**0.14**	1.71
	Creatine Metabolism	creatine	1.04	**0.23**	0.71	0.74	1.08	**0.24**	1.12
		creatinine	0.55	0.73	0.5	2.43	0.66	0.89	**3.23**
	Polyamine Metabolism	spermidine	1.63	0.9	0.8	**2.34**	0.98	**0.54**	**2.88**
		5-methylthioadenosine (MTA)	0.67	0.5	0.58	**2.84**	0.6	**0.45**	**2.93**
	Guanidino and Acetamido Metabolism	4-guanidinobutanoate	0.67	0.59	0.28	**5.96**	0.44	**0.39**	**9.3**

	Glutathione Metabolism	glutathione, oxidized (GSSG)	1.39	0.56	0.61	1.48	0.71	0.28	1.71
		cysteine-glutathione disulfide	1.32	0.6	0.81	2.2	0.69	0.31	1.86
		S-methylglutathione	0.65	0.62	0.21	2.61	0.29	0.28	3.66
		5-oxoproline	1.02	0.39	0.76	0.96	0.94	0.36	1.19
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylalanine	1.13	0.84	1.26	1.59	0.55	0.41	0.7
		gamma-glutamylglutamate	1.19	0.45	0.89	1.01	1.15	0.43	1.3
		gamma-glutamylisoleucine*	0.84	0.78	0.85	1.24	0.79	0.73	1.15
		gamma-glutamylleucine	1	0.49	0.7	1.24	0.61	0.3	1.08
		gamma-glutamylphenylalanine	0.98	0.62	0.77	1.52	0.55	0.34	1.09
		gamma-glutamylthreonine*	0.93	0.59	0.73	1.42	0.71	0.46	1.38
		gamma-glutamyltryptophan	1.01	0.47	0.74	1.45	0.72	0.34	1.43
		gamma-glutamyltyrosine	1.23	0.81	0.97	1.01	0.65	0.42	0.67
		gamma-glutamylvaline	0.74	0.4	0.73	1.57	0.63	0.34	1.35
	Dipeptide Derivative	anserine	0.87	0.4	0.59	0.64	1.65	0.76	1.77
	Dipeptide	alanylalanine	0.56	0.27	0.8	1.38	0.69	0.33	1.19
		alpha-glutamylalanine	1.08	1.18	0.97	0.97	1.16	1.26	1.16
	Polypeptide	bradykinin	1	1.17	1	1	1	1.17	1
	Fibrinogen Cleavage Peptide	TDTEDKGEFLSEGGGV*	0.86	0	0.96	0.83	0.91	0	0.79
		TDTEDKGEFLSEGGGVR*	2.22	0.45	1.16	5.09	0.82	0.17	3.61
Carbohydrate	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism	1,5-anhydroglucitol (1,5-AG)	0.8	0.28	0.7	1.26	0.82	0.29	1.49
		glucose	0.92	0.47	0.94	1.29	0.77	0.39	1.05
		fructose-6-phosphate	1.02	0.18	0.43	1.1	1.19	0.21	3.05
		2,3-diphosphoglycerate	0.79	5.57	0.75	1.07	1.01	7.12	1.45
		3-phosphoglycerate	1.1	0.66	0.48	0.77	1.32	0.79	2.1
		phosphoenolpyruvate (PEP)	1.14	0.45	0.54	0.91	1.15	0.45	1.95
		pyruvate	0.78	1.3	1.38	0.97	0.95	1.59	0.67
		lactate	1.37	0.74	1.12	0.97	0.9	0.49	0.77
		glycerate	0.76	0.22	0.77	1.1	0.77	0.23	1.1
	Pentose Phosphate Pathway	sedoheptulose-7-phosphate	1.81	0.24	0.49	1.11	1.84	0.25	4.14
		ribulose/xylulose 5-phosphate	1.1	0.13	0.5	0.91	0.88	0.1	1.6
	Pentose Metabolism	ribulose	0.93	0.2	0.9	1.06	0.72	0.15	0.84
		ribose	0.56	0.19	0.92	0.64	0.63	0.21	0.44
		ribitol	0.57	0.35	0.67	1.54	0.8	0.49	1.83
		xylonate	0.41	0.33	0.31	6.97	0.44	0.36	10.04

		xylose	0.77	1.33	**0.32**	**9.55**	0.38	0.66	**11.46**
		xylitol	0.81	**0.29**	**0.53**	1.56	**0.58**	**0.21**	1.73
		threitol	0.88	0.79	**0.39**	**6.94**	**0.4**	**0.36**	**7.12**
		arabitol	0.67	**0.24**	0.35	**7.66**	**0.41**	**0.14**	8.78
		fucose	0.4	**0.21**	0.41	**6.12**	0.47	**0.25**	**7.01**
	Fructose, Mannose and Galactose Metabolism	fructose	0.69	**0.12**	0.86	1.82	0.65	**0.11**	1.37
		sorbitol	0.81	**0.27**	0.71	**1.92**	0.65	**0.22**	1.76
		mannose	0.75	**0.29**	0.83	**1.5**	**0.63**	**0.24**	1.14
		mannitol	0.93	0.57	0.49	15.4	1.04	0.64	**32.57**
	Aminosugar Metabolism	N-acetylglucosamine	1.15	0.43	**0.45**	**3.33**	**0.5**	**0.18**	**3.69**
		N-acetylneuraminate	0.78	**0.3**	0.53	**2.87**	0.66	**0.25**	**3.54**
		erythronate*	0.39	**0.17**	**0.35**	**4.1**	0.49	**0.21**	**5.71**
	Advanced Glycation End-product	erythrulose	0.94	**0.49**	0.74	1.8	0.67	**0.34**	1.62
Energy	TCA Cycle	citrate	0.82	0.48	0.72	**4.18**	0.79	**0.47**	**4.58**
		cis-aconitate	0.89	0.79	0.85	**1.74**	0.88	0.78	**1.8**
		alpha-ketoglutarate	0.51	0.29	1.11	1.15	3.21	1.85	3.34
		succinylcarnitine	0.93	**0.29**	0.7	1.22	1.18	**0.36**	**2.04**
		succinate	6.65	0.44	1.23	0.84	2.34	0.15	1.59
		fumarate	1.2	**0.42**	0.83	1.33	0.97	**0.34**	1.56
		malate	1.5	**0.33**	0.9	0.9	1.23	**0.27**	1.23
	Oxidative Phosphorylation	pyrophosphate (PPi)	0.83	0.62	0.85	**0.42**	1.24	0.93	0.61
		phosphate	1.22	**1.76**	0.74	**0.62**	1.36	**1.96**	1.14
Lipid	Medium Chain Fatty Acid	caproate (6:0)	**0.5**	**0.54**	**0.58**	1.01	0.62	**0.67**	1.09
		heptanoate (7:0)	**0.57**	**0.52**	0.84	1.08	0.87	0.8	1.12
		caprylate (8:0)	0.67	**0.46**	0.76	0.94	0.85	**0.58**	1.06
		pelargonate (9:0)	0.78	**0.46**	0.93	1.06	1.14	0.67	1.29
		caprate (10:0)	0.8	**0.6**	0.92	0.97	1.04	0.77	1.1
		undecanoate (11:0)	0.91	1.07	0.86	1.01	1	1.17	1.18
		laurate (12:0)	0.75	**0.52**	0.89	0.85	0.98	0.69	0.94
	Long Chain Fatty Acid	myristate (14:0)	**0.62**	**0.28**	0.88	0.67	1.01	**0.46**	0.77
		myristoleate (14:1n5)	**0.51**	**0.1**	0.82	0.54	1.17	**0.22**	0.77
		pentadecanoate (15:0)	0.87	**0.33**	0.79	0.97	1.09	**0.41**	1.33
		palmitate (16:0)	0.82	**0.28**	0.93	1.08	0.9	**0.31**	1.06
		palmitoleate (16:1n7)	**0.5**	**0.15**	0.67	0.63	1.06	**0.33**	1

		margarate (17:0)	0.89	0.3	0.94	1.13	0.95	0.32	1.14
		10-heptadecenoate (17:1n7)	0.64	0.16	0.84	0.71	1.17	0.29	0.98
		stearate (18:0)	0.93	0.37	1.01	1.32	0.83	0.33	1.09
		oleate (18:1n9)	0.65	0.14	0.74	0.91	0.97	0.22	1.18
		cis-vaccenate (18:1n7)	0.62	0.23	0.94	0.94	1.07	0.4	1.07
		nonadecanoate (19:0)	1.05	0.42	1.3	1.32	0.97	0.38	0.98
		10-nonadecenoate (19:1n9)	0.64	0.14	0.92	0.7	1.07	0.23	0.8
		arachidate (20:0)	1.19	0.61	1.1	1.53	0.75	0.38	1.04
		eicosenoate (20:1n9 or 11)	0.94	0.19	1.22	1.06	0.99	0.2	0.86
	Polyunsaturated Fatty Acid (n3 and n6)	stearidonate (18:4n3)	0.7	0.16	0.68	0.86	0.73	0.17	0.93
		eicosapentaenoate (EPA; 20:5n3)	0.65	0.27	1.04	1.09	0.94	0.38	0.99
		docosapentaenoate (n3 DPA; 22:5n3)	0.8	0.22	0.96	1.12	0.82	0.22	0.96
		docosahexaenoate (DHA; 22:6n3)	0.82	0.21	1.12	1.49	0.92	0.23	1.22
		linoleate (18:2n6)	0.84	0.19	0.85	0.9	0.97	0.22	1.04
		linolenate [alpha or gamma; (18:3n3 or 6)]	0.79	0.12	0.83	0.85	0.91	0.14	0.94
		dihomo-linolenate (20:3n3 or n6)	0.96	0.33	1.07	1.45	0.79	0.27	1.07
		arachidonate (20:4n6)	0.87	0.21	1.03	1.66	0.9	0.22	1.46
		adrenate (22:4n6)	1.25	0.38	0.96	1.23	0.94	0.29	1.2
		docosapentaenoate (n6 DPA; 22:5n6)	0.94	0.19	1.2	1.81	0.84	0.17	1.25
		docosadienoate (22:2n6)	1.58	0.48	1.55	1.45	0.87	0.27	0.82
		dihomo-linoleate (20:2n6)	0.85	0.21	1.04	1.18	0.8	0.2	0.91
		mead acid (20:3n9)	0.81	0.26	0.88	1.35	0.84	0.26	1.29
	Fatty Acid, Branched	15-methylpalmitate (isobar with 2-methylpalmitate)	0.73	0.48	0.96	0.89	1.09	0.72	1
		17-methylstearate	0.7	0.24	1.25	0.9	0.98	0.34	0.71
	Fatty Acid, Dicarboxylate	2-hydroxyglutarate	0.8	0.19	0.53	5.36	1.11	0.27	11.29
		azelate (nonanedioate)	0.86	0.69	0.68	1.29	0.83	0.66	1.57
		tetradecanedioate	0.76	0.28	0.87	0.83	1.26	0.46	1.2
		hexadecanedioate	0.81	0.16	0.99	0.82	1.15	0.22	0.95
		octadecanedioate	0.78	0.24	1.12	0.73	1.14	0.34	0.74
	Fatty Acid, Amide	stearamide	0.73	0.58	0.58	1.41	0.66	0.52	1.61
	Fatty Acid Metabolism (also BCAA Metabolism)	butyrylcarnitine	1.46	0.61	1.03	1.27	0.87	0.37	1.06
		butyrylglycine	0.2	0.19	0.23	4.43	0.39	0.37	7.68
		propionylcarnitine	1.72	1.07	0.97	0.88	1.09	0.68	0.99
	Fatty Acid Metabolism	valerylglycine	0.39	0.37	0.38	3.4	0.55	0.52	4.97

	(Acyl Glycine)	hexanoylglycine	0.12	0.05	0.22	1.29	0.53	0.24	3.06
	Fatty Acid Metabolism(Acyl Carnitine)	acetylcarnitine	0.9	0.37	0.88	0.9	0.91	0.38	0.94
		hexanoylcarnitine	1.05	0.26	0.9	0.93	0.84	0.21	0.86
		octanoylcarnitine	0.9	0.42	0.71	1.02	0.88	0.41	1.26
		decanoylcarnitine	0.9	0.54	0.81	0.78	0.78	0.47	0.76
		laurylcarnitine	0.38	0.58	0.69	1.18	0.5	0.76	0.85
		myristoylcarnitine	0.42	0.23	0.52	0.94	0.47	0.25	0.85
		palmitoylcarnitine	0.44	0.13	0.53	0.92	0.56	0.16	0.96
		stearoylcarnitine	0.46	0.24	0.81	1.14	0.62	0.32	0.87
		oleoylcarnitine	0.44	0.09	0.57	0.87	0.72	0.15	1.08
	Carnitine Metabolism	deoxycarnitine	1.18	0.67	0.98	1.02	0.95	0.54	0.98
		carnitine	1.13	0.85	1.05	0.9	1.03	0.78	0.88
		3-dehydrocarnitine	0.84	0.32	0.81	1.2	0.87	0.33	1.29
	Ketone Bodies	3-hydroxybutyrate (BHBA)	0.37	0.07	0.79	0.62	0.75	0.15	0.59
	Fatty Acid, Monohydroxy	4-hydroxybutyrate (GHB)	0.83	0.46	0.78	0.93	0.55	0.31	0.66
		2-hydroxypalmitate	1.08	0.19	0.8	0.81	0.94	0.16	0.95
		2-hydroxystearate	0.81	0.22	0.77	0.77	0.91	0.25	0.91
		3-hydroxypropanoate	1.3	0.84	0.94	0.87	0.88	0.57	0.81
		3-hydroxydecanoate	0.82	0.28	1.17	0.54	0.92	0.32	0.43
		3-hydroxylaurate	0.61	0.22	1.34	0.61	1.01	0.36	0.46
		16-hydroxypalmitate	0.67	0.17	0.89	0.73	0.95	0.25	0.78
		13-HODE + 9-HODE	1.17	0.14	0.69	0.68	1.19	0.14	1.18
	Fatty Acid, Dihydroxy	12,13-DiHOME	1.35	0.24	0.89	0.68	1.06	0.19	0.81
	Eicosanoid	12-HETE	1.35	0.15	1.29	1.18	1.52	0.17	1.39
	Endocannabinoid	palmitoyl ethanolamide	0.97	0.33	0.86	0.88	1.04	0.35	1.06
	Inositol Metabolism	myo-inositol	0.82	0.24	0.62	1.46	0.65	0.19	1.52
		pinitol	1.11	0.94	0.23	20.97	0.37	0.31	33.8
		scyllo-inositol	0.74	0.22	0.57	1.52	0.64	0.19	1.73
		inositol 1-phosphate (I1P)	0.81	0.4	0.95	1.02	0.94	0.47	1.01
	Phospholipid Metabolism	choline	0.89	0.4	0.88	1.04	0.89	0.4	1.04
		ethanolamine	1.11	0.59	0.69	1.83	1.12	0.6	2.97
		phosphoethanolamine	1.39	0.74	0.48	1	0.79	0.42	1.64
	Lysolipid	2-myristoylglycerophosphocholine*	0.29	0.17	0.81	0.79	0.75	0.45	0.73
		1-pentadecanoylglycerophosphocholine (15:0)*	0.63	0.37	0.9	0.84	0.96	0.57	0.9

		1-palmitoylglycerophosphocholine (16:0)	0.69	**0.36**	0.94	0.97	0.84	**0.44**	0.86
		2-palmitoylglycerophosphocholine*	0.57	**0.22**	1.01	0.89	0.91	**0.34**	0.8
		1-palmitoleoylglycerophosphocholine (16:1)*	**0.24**	**0.26**	0.9	0.79	0.82	0.91	0.72
		2-palmitoleoylglycerophosphocholine*	**0.35**	**0.34**	0.91	0.93	0.94	0.9	0.96
		1-margaroylglycerophosphocholine (17:0)	0.52	**0.13**	1	0.81	1.03	**0.26**	0.83
		1-stearoylglycerophosphocholine (18:0)	0.61	**0.2**	0.87	1.01	0.82	**0.27**	0.95
		2-stearoylglycerophosphocholine*	0.67	**0.19**	1.03	1.25	0.89	**0.26**	1.08
		1-oleoylglycerophosphocholine (18:1)	0.6	**0.24**	1.04	1.11	0.86	**0.35**	0.92
		2-oleoylglycerophosphocholine*	0.55	**0.44**	1.07	1.11	0.79	0.64	0.83
		1-linoleoylglycerophosphocholine (18:2n6)	0.78	**0.38**	1.12	1.02	0.88	**0.43**	0.8
		2-linoleoylglycerophosphocholine*	**0.53**	**0.51**	1.1	1.13	0.73	0.7	0.75
		1-dihomo-linoleoylglycerophosphocholine (20:2n6)*	0.6	**0.21**	1.41	1.13	0.96	**0.33**	0.77
		2-arachidoylglycerophosphocholine*	0.48	0.23	0.91	0.61	0.94	0.44	0.63
		1-eicosatrienoylglycerophosphocholine (20:3)*	0.61	**0.41**	1.34	1.4	0.75	**0.5**	0.79
		1-arachidonoylglycerophosphocholine (20:4n6)*	**0.51**	**0.23**	1.01	1.26	0.79	**0.35**	0.98
		2-arachidonoylglycerophosphocholine*	**0.35**	**0.27**	0.83	**1.81**	**0.58**	**0.45**	1.27
		1-docosapentaenoylglycerophospho-choline (22:5n3)*	0.93	**0.34**	1.6	**2.7**	0.65	**0.24**	1.09
		1-docosahexaenoylglycerophosphocholine (22:6n3)*	0.52	**0.25**	1.12	1.56	0.71	**0.34**	0.99
		2-docosahexaenoylglycerophosphocholine*	0.54	**0.3**	1	**2.11**	**0.66**	**0.36**	1.39
		1-palmitoylglycerophosphoethanolamine	0.71	**0.16**	0.95	1.02	0.86	**0.19**	0.92
		2-palmitoylglycerophosphoethanolamine*	0.77	**0.47**	0.93	1.15	0.78	**0.47**	0.96
		1-stearoylglycerophosphoethanolamine	0.69	**0.25**	1.2	1.2	0.73	**0.27**	0.73
		1-oleoylglycerophosphoethanolamine	0.81	**0.17**	0.93	0.85	0.98	**0.2**	0.9
		2-oleoylglycerophosphoethanolamine*	1.09	**0.19**	1.33	0.85	1.17	**0.21**	0.75
		1-linoleoylglycerophosphoethanolamine*	1.05	**0.3**	1.01	1.1	0.75	**0.21**	0.82
		2-linoleoylglycerophosphoethanolamine*	0.96	**0.36**	1	0.96	0.92	**0.34**	0.88
		1-arachidonoylglycerophosphoetha-nolamine*	0.78	**0.23**	1.04	1.43	0.75	**0.23**	1.03
		2-arachidonoylglycerophosphoetha-nolamine*	0.75	**0.3**	1.29	1.52	0.71	**0.28**	0.84

		2-docosahexaenoylglycerophosphoe-thanolamine*	0.36	0.35	0.85	1.11	0.68	0.66	0.89
		1-palmitoylglycerophosphoinositol*	1.28	0.27	1.26	0.96	1.15	0.24	0.87
		1-stearoylglycerophosphoinositol	1.08	0.24	1.09	1.37	0.95	0.21	1.2
		1-linoleoylglycerophosphoinositol*	1.2	0.2	1.54	1.72	1.04	0.17	1.16
		1-arachidonoylglycerophosphoinositol*	1	0.11	1.35	2.43	0.96	0.11	1.73
		2-arachidonoylglycerophosphoinositol*	0.84	0.1	1.34	1.95	1.15	0.14	1.68
	Glycerolipid Metabolism	glycerol	0.93	0.62	0.82	0.78	1	0.67	0.95
		glycerol 3-phosphate (G3P)	0.89	0.21	0.74	1.15	0.94	0.22	1.46
	Monoacylglycerol	1-palmitoylglycerol (1-monopalmitin)	0.91	0.22	0.64	1.5	0.74	0.18	1.75
		1-stearoylglycerol (1-monostearin)	1.21	0.36	1.42	1.21	0.81	0.24	0.69
		1-oleoylglycerol (1-monoolein)	1.58	0.37	0.67	1.38	0.63	0.15	1.29
		1-linoleoylglycerol (1-monolinolein)	1.81	0.26	0.73	1.18	0.8	0.11	1.31
	Sphingolipid Metabolism	sphinganine	0.4	0.27	0.72	0.79	0.56	0.37	0.61
		palmitoyl sphingomyelin	0.65	0.19	0.75	1.24	0.73	0.21	1.2
		stearoyl sphingomyelin	0.78	0.12	0.69	1.08	0.66	0.1	1.03
		sphingosine	0.9	0.23	0.74	0.49	1.66	0.42	1.1
	Sterol	cholesterol	0.84	0.37	0.87	1.43	0.74	0.33	1.21
		7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	0.84	0.23	0.84	1.21	0.89	0.25	1.29
		cholestanol	0.66	0.47	0.72	1.5	0.66	0.47	1.38
		beta-sitosterol	0.82	0.66	1.14	1.7	0.63	0.51	0.95
		campesterol	0.75	0.41	0.86	1.24	0.7	0.39	1.02
	Steroid	corticosterone	0.7	0.14	0.75	1.03	0.88	0.17	1.21
	Primary Bile Acid Metabolism	cholate	1.02	0.5	0.32	5.22	0.2	0.1	3.28
		glycocholate	0.64	0.85	0.13	4.25	0.14	0.19	4.8
		taurocholate	0.43	0.07	0.01	12.19	0.05	0.01	40.9
		beta-muricholate	2.18	0.27	1.26	1.18	0.92	0.11	0.86
		alpha-muricholate	0.14	0.34	0.01	25.44	0.03	0.08	62.35
	Secondary Bile Acid Metabolism	deoxycholate	0.9	0.2	1.09	0.97	1.44	0.33	1.29
		taurodeoxycholate	0.3	0.17	0.03	14.26	0.04	0.02	23.63
		taurolithocholate	0.47	1	0.05	26.96	0.05	0.11	26.96
		tauroursodeoxycholate	0.51	0.08	0.01	32.09	0.04	0.01	94.96
Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosi	inosine	0.93	0.13	1.35	0.48	0.5	0.07	0.18
		hypoxanthine	1.58	0.04	0.96	2.22	1.59	0.04	3.66

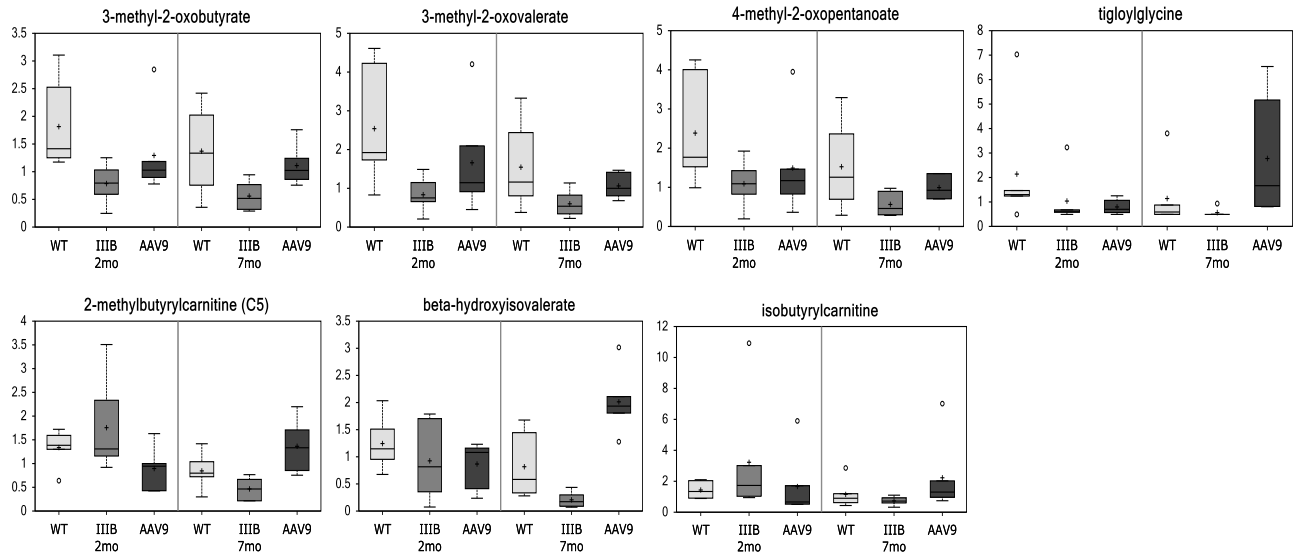
	ne containing	xanthine	1.74	0.05	0.93	1.3	2.03	0.06	2.84
		xanthosine	2.24	0.4	0.68	1.63	1.09	0.19	2.63
		urate	1.35	0.12	0.7	0.93	1	0.09	1.32
		allantoin	0.47	0.18	0.38	4.25	0.46	0.18	5.16
	Purine Metabolism, Adenine containing	adenosine 5'-monophosphate (AMP)	0.94	34.51	0.72	1.36	0.72	26.41	1.36
		adenine	0.67	0.58	0.67	4.69	0.54	0.47	3.77
		N1-methyladenosine	0.6	0.31	0.46	3.55	0.56	0.28	4.28
		N6-carbamoylthreonyladenosine	0.56	0.33	0.5	4.66	0.55	0.33	5.07
	Purine Metabolism, Guanine containing	7-methylguanine	0.77	1.11	0.35	3.81	0.57	0.82	6.21
		N1-methylguanosine	0.62	0.73	0.37	4.56	0.5	0.59	6.19
	Pyrimidine Metabolism, Orotate containing	orotate	0.56	0.58	0.56	4.55	0.48	0.5	3.93
	Pyrimidine Metabolism, Uracil containing	uridine	1.34	0.56	1.06	0.75	0.96	0.41	0.69
		uracil	2	0.53	0.78	0.89	1.07	0.28	1.23
		pseudouridine	0.92	0.68	0.84	2.45	0.68	0.5	2.01
		5,6-dihydrouracil	0.79	0.38	1.08	1.23	1.18	0.56	1.33
		2'-deoxyuridine	1.04	0.53	0.97	1.18	0.72	0.37	0.88
		3-ureidopropionate	0.7	0.17	0.38	2.37	0.55	0.14	3.43
		N-acetyl-beta-alanine	1.17	0.51	0.86	1.71	0.8	0.35	1.6
	Pyrimidine Metabolism, Cytidine containing	cytidine	1.12	0.38	0.85	0.73	0.95	0.32	0.82
		N4-acetylcytidine	0.79	0.76	0.75	1.97	0.85	0.82	2.23
		2'-deoxycytidine	0.85	0.58	0.88	1.08	0.75	0.52	0.92
	Pyrimidine Metabolism, Thymine containing	thymidine	0.8	0.47	0.93	0.79	0.76	0.45	0.64
Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	nicotinamide	0.94	0.2	0.68	1.02	0.95	0.2	1.42
	Riboflavin Metabolism	riboflavin (Vitamin B2)	0.75	0.4	0.42	5.04	0.45	0.24	5.39
		flavin adenine dinucleotide (FAD)	1.05	0.65	0.99	1	0.9	0.56	0.91
	Pantothenate and CoA Metabolism	pantothenate	1.08	0.25	0.81	2.24	0.75	0.17	2.06
	Ascorbate and Aldarate Metabolism	gulono-1,4-lactone	0.44	0.19	0.32	6.03	0.3	0.13	5.73
		ascorbate (Vitamin C)	0.98	0.27	0.48	4.39	0.32	0.09	2.9
		threonate	0.79	0.08	0.66	1.69	0.76	0.08	1.94
		arabonate	0.47	0.17	0.32	3.89	0.51	0.18	6.21

		oxalate (ethanedioate)	0.7	0.43	0.79	1.48	0.68	0.42	1.28
	Tocopherol Metabolism	alpha-tocopherol	0.85	0.18	1.05	1.29	0.84	0.18	1.03
	Tetrahydrobiopterin Metabolism	dihydrobiopterin	0.53	0.23	0.35	4.13	0.43	0.19	5.07
	Hemoglobin and Porphyrin Metabolism	heme	0.95	1.09	1.31	0.67	1.04	1.2	0.53
		bilirubin (E,E)*	0.38	0.5	0.67	0.65	1.12	1.49	1.09
		biliverdin	0.81	0.31	1.03	0.88	0.95	0.36	0.81
		L-urobilin	1	1	1	1	1	1	1
	Vitamin B6 Metabolism	pyridoxate	0.63	0.24	0.38	6.33	0.45	0.17	7.57
Xenobiotics	Benzoate Metabolism	hippurate	0.36	0.4	0.28	9.78	0.48	0.53	16.34
		4-hydroxyhippurate	0.28	0.26	0.15	3.39	0.56	0.52	12.9
		benzoate	0.8	0.84	1.24	1.33	1.13	1.17	1.21
		catechol sulfate	0.72	0.46	0.43	5.15	0.73	0.47	8.72
		4-ethylphenylsulfate	0.8	0.61	0.49	7.1	0.49	0.37	7.08
		4-vinylphenol sulfate	0.49	0.06	0.61	1.15	0.72	0.09	1.35
	Food Component/Plant	2-oxindole-3-acetate	0.64	0.6	0.43	13.25	0.41	0.38	12.72
		5-hydroxymethylfurfural	0.9	0.36	0.94	0.97	0.77	0.31	0.8
		cinnamoylglycine	0.22	0.22	0.26	5.1	0.59	0.6	11.51
		daidzein	0.9	1	0.9	4.56	0.9	1	4.56
		equol glucuronide	0.82	0.61	0.36	33.73	0.22	0.16	20.59
		equol sulfate	1.17	0.82	0.95	4.59	0.68	0.48	3.3
		ergothioneine	0.67	0.36	0.7	1.37	1.26	0.67	2.46
		erythritol	0.61	0.34	0.39	4.33	0.55	0.31	6.13
		galacturonate	0.65	0.4	0.67	3.94	0.71	0.43	4.18
		indoleacrylate	1.57	0.93	1.33	1.63	0.7	0.42	0.87
		N-(2-furoyl)glycine	0.21	0.42	0.22	4.5	0.5	1	10.38
		N-glycolylneuraminate	0.64	0.07	0.15	0.81	0.59	0.06	3.1
		stachydrine	1.53	0.73	1.09	2.31	0.79	0.38	1.68
	Drug	4-acetylphenol sulfate	0.26	0.55	0.24	15.54	0.37	0.8	24.54
	Chemical	1-(3-aminopropyl)-2-pyrrolidone	0.42	0.54	0.39	3.84	0.42	0.54	4.09
		2-ethylhexanoate	0.67	0.34	0.91	1.39	1.09	0.54	1.67
		2-hydroxyisobutyrate	0.76	0.51	1.08	1.31	0.89	0.6	1.07
		diisopropanolamine	0.56	0.38	0.85	0.77	1.1	0.74	0.99
		EDTA	1	1.13	1	1	1	1.13	1

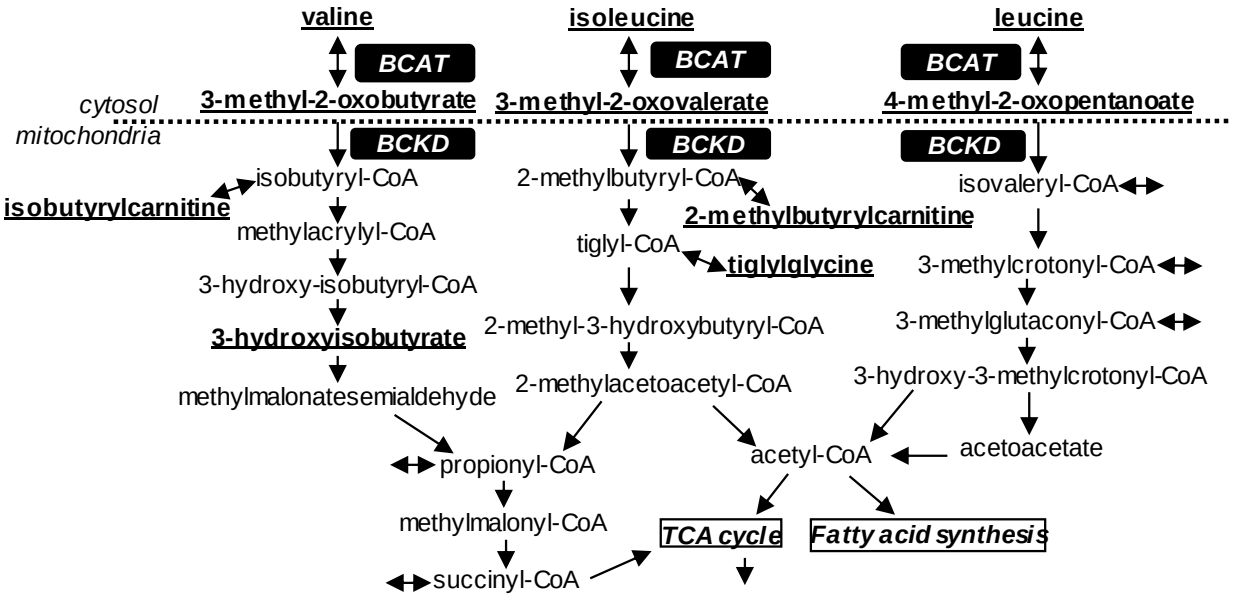
		glycolate (hydroxyacetate)	0.83	**0.36**	0.73	**1.39**	**0.71**	**0.31**	1.35
		iminodiacetate (IDA)	1	**1.49**	1	1	1	**1.49**	1
		trizma acetate	0.76	84.69	0.61	3.98	1.05	117.21	6.82

Serum samples were assayed for 361 metabolites at 2mo and 7mo of age, using mass spectrometry (n=6/group).
Green highlight: decrease, $p \leq 0.05$; Light green highlight: decrease, $0.05 < p > 0.10$; Red highlight: increase, $p \leq 0.05$; Pink highlight: increase, $0.05 < p \geq 0.10$; No highlight: $p > 0.10$.

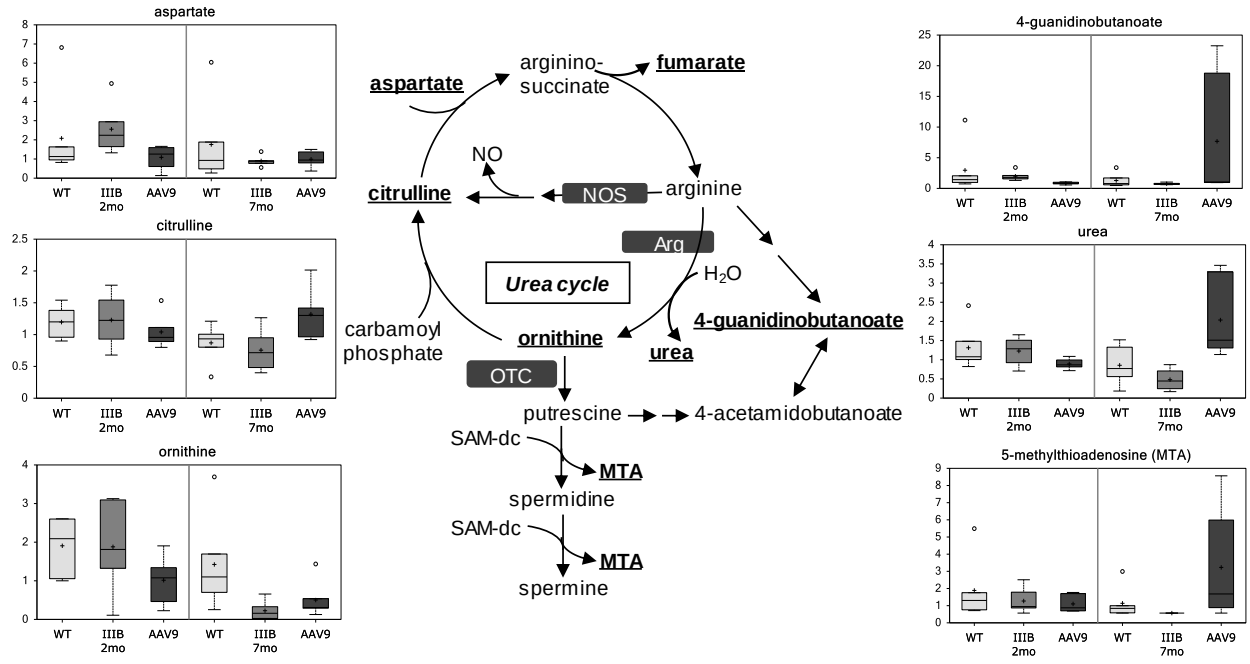
a.



b.

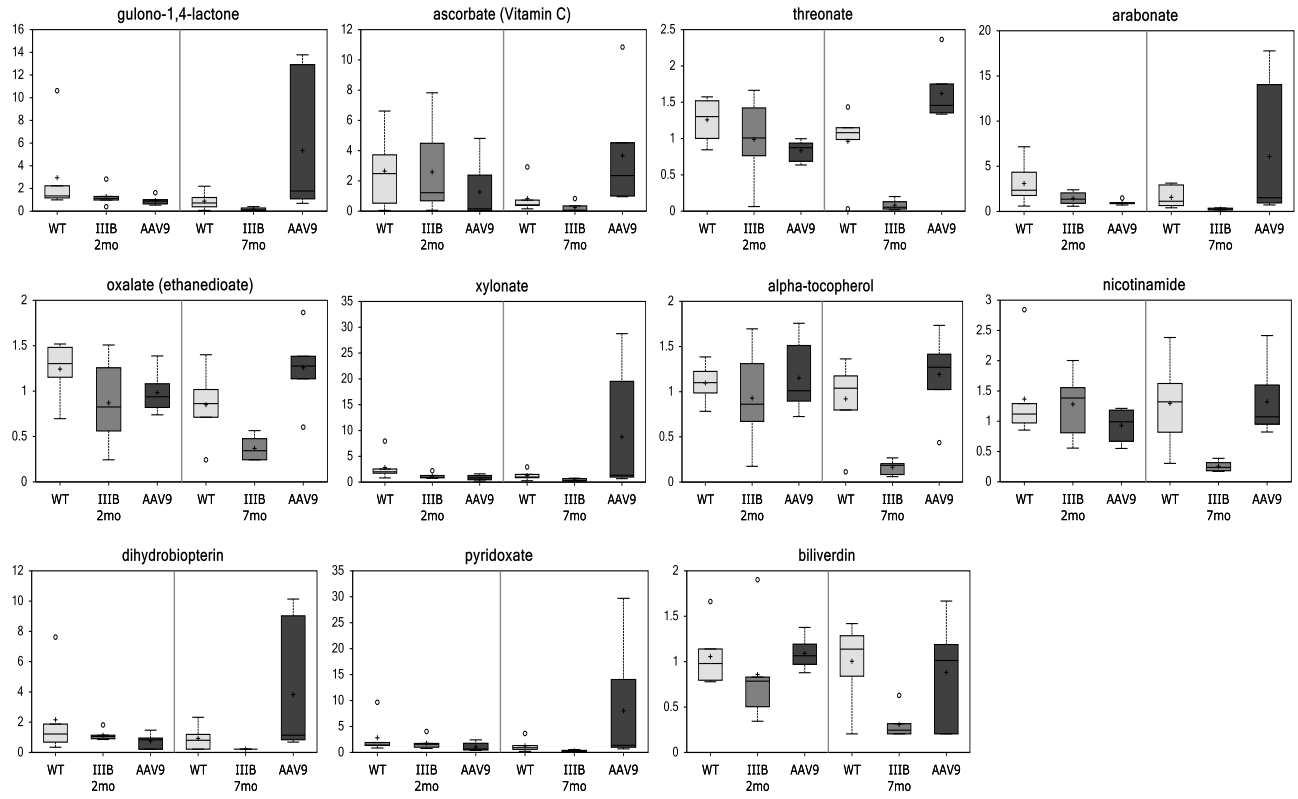


Supplementary Fig. S1 Impairments of branched-chain amino acid metabolism during disease progression in MPS IIIB mice Mouse serum samples were analyzed by global metabolomic profiling using mass spectrometry at age 2m or 7mo (n=6/group). **a.** Metabolomic comparison: data are presented as Scaled Intensity (y-axis), $p \leq 0.05$ IIIB-7m vs. WT-7m; **WT:** wildtype mice; **IIIB:** MPS IIIB mice; **AAV9:** MPS IIIB mice treated at age 1m with an IV injection of $5x10^{12}$vg/kg rAAV9-CMV-hNAGLU. **b.** Branched-chain amino acid metabolism pathway: **BCAT:** branched chain aminotransferase; **BCKD:** branched-chain alpha-keto acid dehydrogenase complex; Bold and underlined metabolites: $p \leq 0.05$ IIIB-7m vs. WT-7m.

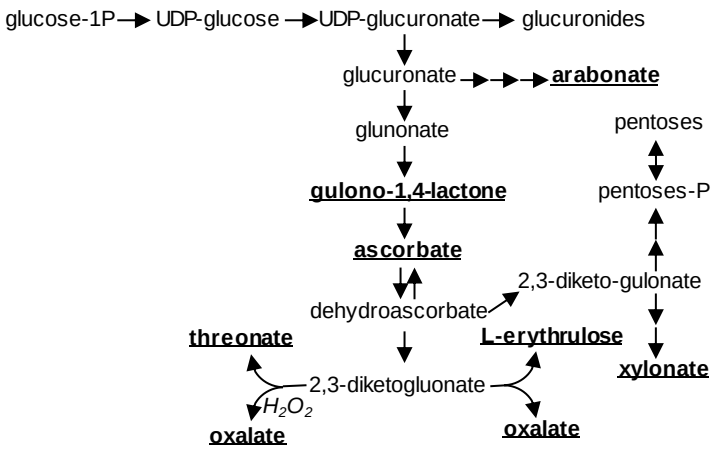


Supplementary Fig. S2. Impairments of urea cycle during disease progression in MPS IIIB mice Mouse serum samples were analyzed by global metabolomic profiling using mass spectrometry at age 2m or 7mo (n=6/group). **a.** Metabolomic comparison: data are presented as Scaled Intensity (y-axis), $p \leq 0.05$ IIIB-7m vs. WT-7m; **WT:** wildtype mice; **IIIB:** MPS IIIB mice; **AAV9:** MPS IIIB mice treated at age 1m with an IV injection of $5x10^{12}$vg/kg rAAV9-CMV-hNAGLU. Bold and underlined metabolites in urea cycle pathway: $p \leq 0.05$ IIIB-7m vs. WT-7m.

a.

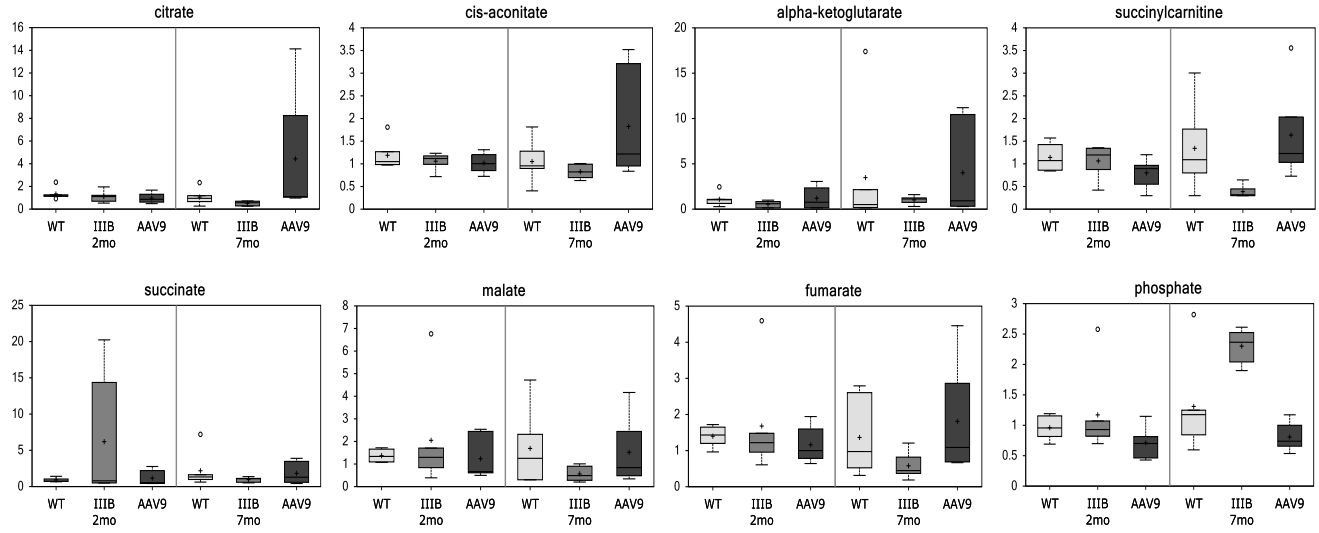


b. Ascorbate (Vitamin C) metabolism pathway

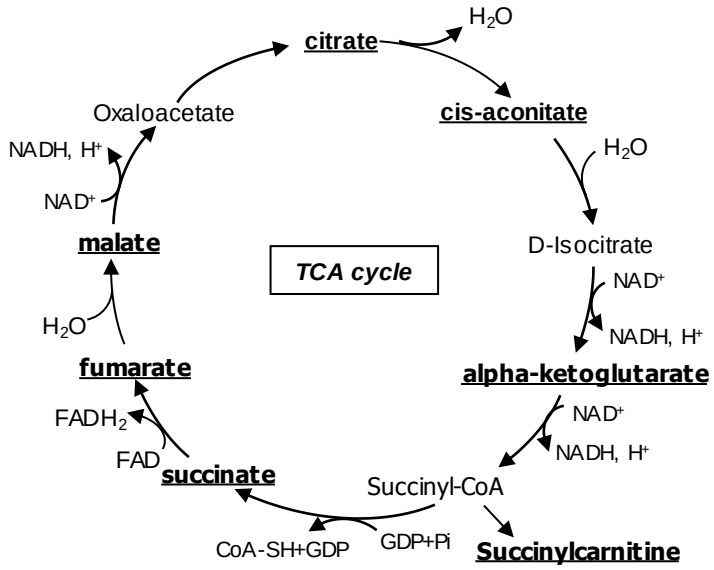


Supplementary Fig. S3. Depressed Vitamin metabolism in MPS IIIB during disease progress Mouse serum samples were analyzed by global metabolomic profiling using mass spectrometry at age 2m or 7mo (n=6/group). **a.** Metabolomic comparison: data are presented as Scaled Intensity (y-axis), $p \leq 0.05$ IIIB-7m vs. WT-7m; **WT:** wildtype mice; **IIIB:** MPS IIIB mice; **AAV9:** MPS IIIB mice treated at age 1m with an IV injection of $5x10^{12}$vg/kg rAAV9-CMV-hNAGLU. **b.** Disturbance of Vitamin C metabolism pathway: Bold and underlined metabolites: $p \leq 0.05$ IIIB-7m vs. WT-7m.

a.



b. TCA pathway



Supplementary Fig. S4. Depressed energy metabolism in MPS IIIB during disease progress Mouse serum samples were analyzed by global metabolomic profiling using mass spectrometry at age 2m or 7mo (n=6/group). **a.** Metabolomic comparison: data are presented as Scaled Intensity (y-axis), $p \leq 0.05$ IIIB-7m vs. WT-7m; **WT:** wildtype mice; **IIIB:** MPS IIIB mice; **AAV9:** MPS IIIB mice treated at age 1m with an IV injection of $5x10^{12}$vg/kg rAAV9-CMV-hNAGLU. **b.** Disturbance of energy metabolism pathway: Bold and underlined metabolites: $p \leq 0.05$ IIIB-7m vs. WT-7m.