

Analysis of L-arginine:glycine amidinotransferase-, creatine- and homoarginine-dependent gene regulation in the murine heart

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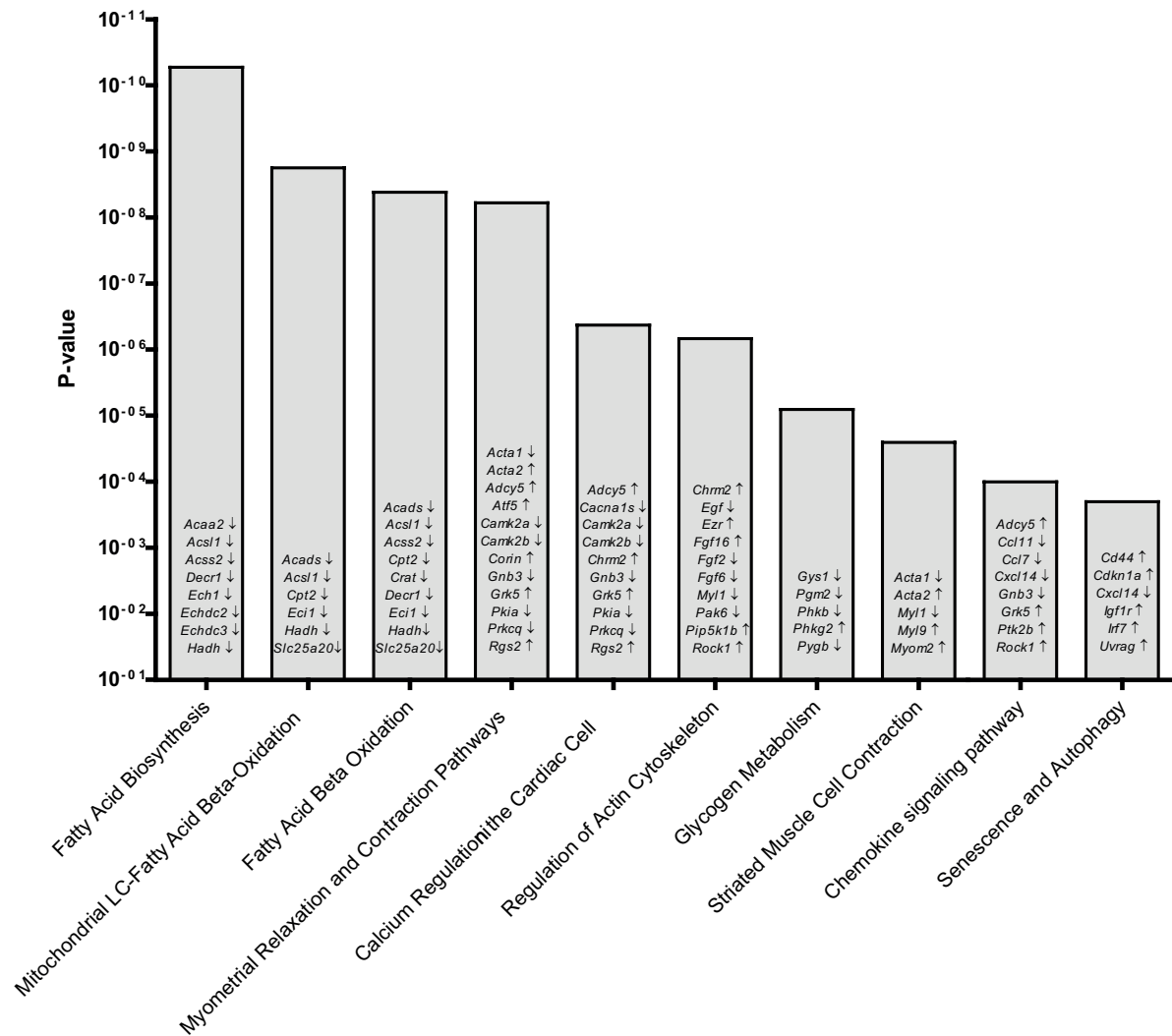
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Supplementary Figure S1. Pathway analysis (WebGestalt) within the 485 significantly regulated genes between WT and AGAT^{-/-} mice in heart tissue. The top ten pathways are shown, and the involved genes are listed in the bars. The direction of regulation is indicated by up and down arrows, respectively. P value ≤ 0.05 .

Supplementary Table S2. Network analysis (Network 1) within differentially expressed genes between WT and AGAT^{-/-} mice. The influence of creatine and HA is indicated by the comparison of WT and AGAT^{-/-}HA/Cr. False-Discovery-Rate ≤ 0.05 . Abbreviations: FC, fold change; NS, not significant.

Gene	Gene name	WT vs AGAT ^{-/-}		WT vs AGAT ^{-/-} Cr		WT vs AGAT ^{-/-} HA	
		P Value	FC	P Value	FC	P Value	FC
<i>Scn4a</i>	sodium channel, type IV, alpha	3.02×10^{-13}	-3.22	NS	-1.13	6.63×10^{-11}	-2.81
<i>Scn4b</i>	sodium channel, type IV, beta	1.47×10^{-12}	-3.74	NS	1.12	6.13×10^{-8}	-3.34

<i>Tmod4</i>	tropomodulin 4	8.93×10 ⁻¹¹	-1.76	NS	2.17	6.27×10 ⁻⁸	-1.74
<i>Tmem150c</i>	transmembrane protein 150C	9.97×10 ⁻¹¹	-2.96	NS	-1.12	8.76×10 ⁻¹⁰	-2.94
<i>Fah</i>	fumarylacetoacetate hydrolase	1.08×10 ⁻¹⁰	-2.36	NS	-1.09	3.36×10 ⁻⁹	-2.33
<i>Lgi1</i>	leucine-rich repeat LGI family, member 1	2.07×10 ⁻¹⁰	-3.1	NS	1.06	9.99×10 ⁻¹⁰	-4.27
<i>Lad1</i>	ladinin	2.63×10 ⁻¹⁰	2.17	NS	1.01	2.23×10 ⁻⁹	2.42
<i>Stom</i>	stomatin	1.12×10 ⁻⁹	-1.41	NS	-1.05	7.04×10 ⁻⁹	-1.46
<i>Zfp106</i>	zinc finger protein 106	1.31×10 ⁻⁹	1.49	3.68×10 ⁻⁵	1.33	2×10 ⁻⁷	1.41
<i>Egf</i>	epidermal growth factor	6.62×10 ⁻⁹	-1.55	NS	-1.15	2.86×10 ⁻⁷	-1.46
<i>Vwa8</i>	von Willebrand factor A domain containing 8	1.2×10 ⁻⁸	-1.35	2.65×10 ⁻²	-1.1	6.77×10 ⁻⁶	-1.27
<i>Ano5</i>	anoctamin 5	1.78×10 ⁻⁸	-2.27	1.51×10 ⁻²	-1.42	2.22×10 ⁻⁷	-2.27
<i>Ivd</i>	isovaleryl coenzyme A dehydrogenase	2.54×10 ⁻⁸	-1.41	NS	-1.06	1.11×10 ⁻⁷	-1.53
<i>AcsM5</i>	acyl-CoA synthetase medium-chain family member 5	4.32×10 ⁻⁸	-1.88	NS	-1.2	1.63×10 ⁻⁶	-1.69
<i>Ehd4</i>	EH-domain containing 4	6.03×10 ⁻⁸	1.36	NS	-1.04	3.15×10 ⁻⁶	1.34
<i>Myot</i>	myotilin	7.62×10 ⁻⁸	-2.36	NS	1.18	7.11×10 ⁻¹⁰	-2.88
<i>Sema4d</i>	sema domain, immunoglobulin domain, transmembrane domain and short cytoplasmic domain, 4D	8.91×10 ⁻⁸	-1.36	2.76×10 ⁻²	-1.13	2.4×10 ⁻⁷	-1.43
<i>Abcc8</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	1.03×10 ⁻⁷	1.33	NS	1.03	8.64×10 ⁻⁷	1.39
<i>Igsf1</i>	immunoglobulin superfamily, member 1	1.03×10 ⁻⁷	-1.48	NS	-1.1	1.63×10 ⁻⁷	-1.58
<i>Cpt2</i>	carnitine palmitoyltransferase 2	1.13×10 ⁻⁷	-1.27	NS	1.02	4.52×10 ⁻⁶	-1.28
<i>Smim4</i>	small integral membrane protein 4	1.5×10 ⁻⁷	1.32	NS	1.02	1.26×10 ⁻⁵	1.27
<i>Pex11a</i>	peroxisomal biogenesis factor 11 alpha	3.05×10 ⁻⁷	-1.41	NS	-1.02	4.1×10 ⁻⁶	-1.41
<i>Acaa2</i>	acetyl-Coenzyme A acyltransferase 2	5.5×10 ⁻⁷	-1.22	NS	-1.04	1.2×10 ⁻⁴	-1.18
<i>Corin</i>	corin	7.77×10 ⁻⁷	1.36	NS	-1.07	4.64×10 ⁻⁶	1.37
<i>Mme</i>	membrane metallo endopeptidase	7.88×10 ⁻⁷	-1.72	3.86×10 ⁻²	1.18	1.25×10 ⁻⁶	-1.56
<i>Ldhd</i>	lactate dehydrogenase D	8.15×10 ⁻⁷	-1.29	NS	-1.02	8.15×10 ⁻⁷	-1.37
<i>Prune2</i>	prune homolog 2 (Drosophila)	8.62×10 ⁻⁷	-1.56	NS	1.04	1.5×10 ⁻⁶	-1.46
<i>Slc25a20</i>	solute carrier family 25, member 20	9.42×10 ⁻⁷	-1.31	NS	-1.03	1.53×10 ⁻⁶	-1.38
<i>Spta1</i>	spectrin alpha, erythrocytic 1	1.79×10 ⁻⁶	1.43	NS	1.01	1.31×10 ⁻⁵	1.42
<i>Gys1</i>	glycogen synthase 1, muscle	2.21×10 ⁻⁶	-1.29	NS	1.01	6.01×10 ⁻⁷	-1.41
<i>Cenpf</i>	centromere protein F	4.76×10 ⁻⁶	1.9	NS	-1.15	3.11×10 ⁻⁵	1.98
<i>Bckdha</i>	branched chain ketoacid dehydrogenase E1, alpha polypeptide	6.49×10 ⁻⁶	-1.23	NS	1.02	5.34×10 ⁻⁴	-1.18
<i>Ncam1</i>	neural cell adhesion molecule 1	7.68×10 ⁻⁶	1.42	NS	-1.13	9.55×10 ⁻⁵	1.4
<i>Adig</i>	adipogenin	1.15×10 ⁻⁵	-1.32	NS	1.02	1.39×10 ⁻⁵	-1.39
<i>Lmf1</i>	lipase maturation factor 1	3.63×10 ⁻⁵	-1.17	NS	1.01	3.51×10 ⁻⁴	-1.17
<i>Adam9</i>	a disintegrin and metallopeptidase domain 9 (meltrin gamma)	9.79×10 ⁻⁵	-1.16	NS	-1.02	2.86×10 ⁻⁴	-1.17
<i>Slc25a35</i>	solute carrier family 25, member 35	1.05×10 ⁻⁴	-1.15	NS	1.12	1.06×10 ⁻⁴	-1.25

Supplementary Table S3. Network analysis (Network 2) within differentially expressed genes between WT and AGAT^{-/-} mice. The influence of creatine and HA is indicated by the comparison of WT and AGAT^{-/-}HA/Cr. False-Discovery-Rate ≤ 0.05 . Abbreviations: FC, fold change; NS, not significant.

Gene	Gene name	WT vs. AGAT ^{-/-}		WT vs AGAT ^{-/-} Cr		WT vs AGAT ^{-/-} HA	
		P Value	FC	P Value	FC	P Value	FC
<i>Rpp25</i>	ribonuclease P/MRP 25 subunit	8.71×10^{-8}	1.69	NS	1	2×10^{-5}	1.57
<i>Fbp2</i>	fructose biphosphatase 2	1.06×10^{-7}	-1.57	1.64×10^{-2}	-1.12	4.66×10^{-7}	-1.46
<i>Naa35</i>	N(alpha)-acetyltransferase 35, NatC auxiliary subunit	1.32×10^{-7}	1.33	NS	1.04	2.64×10^{-4}	1.2
<i>Clcn1</i>	chloride channel 1	2.22×10^{-7}	-1.57	NS	1.01	3.03×10^{-4}	-1.37
<i>2210407C18Rik</i>	RIKEN cDNA 2210407C18 gene	2.31×10^{-7}	-2.39	1.41×10^{-2}	1.44	9.46×10^{-5}	-2.25
<i>Fgl2</i>	fibrinogen-like protein 2	3.1×10^{-7}	1.44	2.69×10^{-3}	-1.2	3.65×10^{-2}	1.15
<i>Ucp2</i>	uncoupling protein 2	3.49×10^{-7}	1.85	NS	-1.13	8.67×10^{-6}	1.53
<i>Ctgf</i>	connective tissue growth factor	5.21×10^{-7}	1.78	3.1×10^{-3}	-1.33	1.36×10^{-7}	1.83
<i>Stk39</i>	serine/threonine kinase 39	7.93×10^{-7}	1.4	NS	-1.01	3.91×10^{-4}	1.29
<i>Trim7</i>	tripartite motif-containing 7	1.51×10^{-6}	-1.37	NS	1.02	1.16×10^{-3}	-1.28
<i>Gpam</i>	glycerol-3-phosphate acyltransferase, mitochondrial	1.92×10^{-6}	-1.6	NS	-1.09	1×10^{-6}	-1.5
<i>Hk1</i>	hexokinase 1	3.64×10^{-6}	1.28	NS	1.03	2.73×10^{-4}	1.21
<i>Lrrc51</i>	leucine rich repeat containing 51	9.01×10^{-6}	1.23	NS	1.04	1.32×10^{-3}	1.19
<i>Nppa</i>	natriuretic peptide type A	1.17×10^{-5}	1.93	NS	1.02	1.16×10^{-2}	1.55
<i>Klhl13</i>	kelch-like 13	1.26×10^{-5}	1.31	1.03×10^{-2}	-1.15	2.75×10^{-2}	1.17
<i>Hcn2</i>	hyperpolarization-activated, cyclic nucleotide-gated K ⁺ 2	1.48×10^{-5}	1.33	9.67×10^{-3}	-1.17	2.57×10^{-3}	1.2
<i>Pla2g5</i>	phospholipase A2, group V	1.97×10^{-5}	1.26	4.64×10^{-2}	-1.12	2.27×10^{-2}	1.13
<i>Tmem100</i>	transmembrane protein 100	2×10^{-5}	1.56	NS	1	1.12×10^{-4}	1.47
<i>Perp</i>	PERP, TP53 apoptosis effector	3.08×10^{-5}	1.2	NS	1	8.06×10^{-4}	1.18
<i>Ezr</i>	ezrin	3.69×10^{-5}	1.25	NS	-1.09	1.74×10^{-5}	1.26
<i>Dsc2</i>	desmocollin 2	4.33×10^{-5}	1.35	NS	-1.07	NS	1.10
<i>Rock1</i>	Rho-associated coiled-coil containing protein kinase 1	5.68×10^{-5}	1.23	NS	1.03	8.07×10^{-4}	1.22
<i>Camk2n1</i>	calcium/calmodulin-dependent protein kinase II inhibitor 1	5.92×10^{-5}	1.27	NS	1.06	6.36×10^{-4}	1.24
<i>Polq</i>	polymerase (DNA directed), theta	7.66×10^{-5}	-1.31	NS	1.01	1.24×10^{-3}	-1.27
<i>Ppm1e</i>	protein phosphatase 1E	8.5×10^{-5}	1.34	NS	1.02	1.89×10^{-3}	1.27
<i>Slc4a4</i>	solute carrier family 4, member 4	9.44×10^{-5}	1.19	3.14×10^{-2}	-1.09	4.62×10^{-3}	1.15
<i>Slc25a42</i>	solute carrier family 25, member 42	1.33×10^{-4}	-1.29	NS	-1.07	4.75×10^{-3}	-1.15
<i>F3</i>	coagulation factor III	1.8×10^{-4}	1.24	NS	-1.03	1.01×10^{-3}	1.21

<i>Ehbp1</i>	EH domain binding protein 1	2×10 ⁻⁴	1.16	NS	1	4.98×10 ⁻³	1.13
<i>Zdhhc2</i>	zinc finger, DHHC domain containing 2	2.05×10 ⁻⁴	1.39	NS	-1.02	9.46×10 ⁻⁴	-1.17
<i>Ldb3</i>	LIM domain binding 3	2.65×10 ⁻⁴	-1.15	NS	-1.02	1.48×10 ⁻²	-1.13
<i>Capn6</i>	calpain 6	2.81×10 ⁻⁴	1.19	NS	1.02	NS	1.08
<i>Hcn4</i>	hyperpolarization-activated, cyclic nucleotide-gated K ⁺ 4	2.93×10 ⁻⁴	-1.42	NS	-1.07	8.8×10 ⁻³	-1.28
<i>Ghitm</i>	growth hormone inducible transmembrane protein	3.23×10 ⁻⁴	1.14	NS	1.02	3.07×10 ⁻⁴	1.18
<i>Gcnt1</i>	glucosaminyl (N-acetyl) transferase 1, core 2	3.42×10 ⁻⁴	1.21	NS	1.11	NS	1.07
<i>Uvrag</i>	UV radiation resistance associated gene	3.45×10 ⁻⁴	1.14	NS	-1.03	NS	1.05
<i>2310007L24Rik</i>	RIKEN cDNA 2310007L24 gene	4.28×10 ⁻⁴	-1.2	NS	-1.01	NS	-1.07
<i>Trpm7</i>	transient receptor potential cation channel, subfamily M, member 7	4.66×10 ⁻⁴	1.24	NS	1.01	4.64×10 ⁻⁴	1.25
<i>Nt5c2</i>	5'-nucleotidase, cytosolic II	5.03×10 ⁻⁴	1.2	NS	-1.1	NS	1.09
<i>Pgm5</i>	phosphoglucomutase 5	5.07×10 ⁻⁴	1.16	NS	1	3.45×10 ⁻²	1.11
<i>Slc38a1</i>	solute carrier family 38, member 1	5.54×10 ⁻⁴	1.23	NS	-1.01	2.06×10 ⁻¹	1.09
<i>Nomo1</i>	nodal modulator 1	6.03×10 ⁻⁴	1.13	NS	-1.02	NS	1.07
<i>Nt5dc2</i>	5'-nucleotidase domain containing 2	6.1×10 ⁻⁴	1.15	NS	-1.14	NS	1.1
<i>Peli1</i>	pellino 1	6.1×10 ⁻⁴	1.22	NS	1.09	NS	1.12
<i>Nebl</i>	nebulin	6.4×10 ⁻⁴	1.14	NS	1	7.7×10 ⁻³	1.13
<i>Ubxn6</i>	UBX domain protein 6	6.49×10 ⁻⁴	1.13	NS	-1.01	1.8×10 ⁻³	1.16
<i>R3hcc1</i>	R3H domain and coiled-coil containing 1	6.56×10 ⁻⁴	1.16	NS	-1.04	NS	1.08
<i>Hipk1</i>	homeodomain interacting protein kinase 1	1.04×10 ⁻³	1.16	NS	-1.01	2.65×10 ⁻³	1.17
<i>Sh3bp4</i>	SH3-domain binding protein 4	1.06×10 ⁻³	1.2	NS	1.05	NS	1.12

Supplementary Table S4. Gene expression assays used for qPCR.

Gene	Assay ID
<i>18S rRNA</i>	Hs99999901_s1
<i>Ctgf</i>	Mm00515790_g1
<i>Dsc2</i>	Mm00516355_m1
<i>Ehd4</i>	Mm00505588_m1
<i>Fbp2</i>	Mm00484280_m1
<i>Fgl2</i>	Mm00433327_m1
<i>Gatm (Agat)</i>	Mm01268678_m1
<i>Hcn2</i>	Mm00468538_m1
<i>Hcn4</i>	Mm01176086_m1
<i>Nppa</i>	Mm01255748_g1
<i>Rpp25</i>	Mm00547632_s1
<i>Scn4a</i>	Mm00500103_m1
<i>Scn4b</i>	Mm01175562_m1
<i>Sema4d</i>	Mm00443147_m1
<i>Ucp2</i>	Mm00627599_m1
<i>Uvrags</i>	Mm00724370_m1