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Supplementary Materials for

GADL1 is a multifunctional decarboxylase with tissue-specific roles in β-alanine and carnosine production

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The PDF file includes:

Other Supplementary Material for this manuscript includes the following:

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Table S1 A. Top 25 upregulated genes in OB tissue samples from *Gadl1*$^{-/-}$ compared to *Gadl1*$^{+/+}$ mice.

ENSEMBL ID	Abbreviation	Name	Log2Fold	P-value
ENSMUSG00000032226	*Gcnt3*	Glucosaminyl (N-acetyl) transferase 3, mucin type	6.05	0.00084
ENSMUSG00000020159	*Gabrp*	γ-aminobutyric acid (GABA) A receptor, pi	5.77	0.01167
ENSMUSG00000085224	*Gm13425*	Predicted gene 13425	5.40	0.00262
ENSMUSG00000038805	*Six3*	Sine oculis-related homeobox 3	5.23	0.00077
ENSMUSG00000093894	*Ighv1-53*	Immunoglobulin heavy variable 1-53	5.22	0.02869
ENSMUSG00000096225	*Lhx8*	LIM homeobox protein 8	5.17	0.00055
ENSMUSG00000045620	*Odf3l1*	Outer dense fiber of sperm tails 3-like 1	4.97	0.00314
ENSMUSG00000061959	*Ces1e*	Carboxylesterase 1E	4.91	0.00405
ENSMUSG00000004341	*Gpx6*	Glutathione peroxidase 6	4.86	0.00372
ENSMUSG00000029866	*Kel*	Kell blood group	4.67	0.00028
ENSMUSG00000046975	*Olfr1020*	Olfactory receptor 1020	4.57	0.01397
ENSMUSG00000027902	*Chil6*	Chitinase like 6	4.55	0.00405
ENSMUSG00000024681	*Ms4a3*	Membrane-spanning 4-domains A3	4.49	0.02221
ENSMUSG00000112343	*Sfta3-ps*	Surfactant associated 3, pseudogene	4.38	0.02155
ENSMUSG00000082308	*Gm15770*	Predicted gene 15770	4.36	0.03261
ENSMUSG00000083986	*Gm12213*	Predicted gene 12213	4.36	0.02563
ENSMUSG00000090475	*Gm6245*	Predicted gene 6245	4.36	0.02527
ENSMUSG00000074665	*Bpifb4*	BPI fold containing family B4	4.35	0.01778
ENSMUSG00000073920	*Olfr661*	Olfactory receptor 661	4.30	0.02962
ENSMUSG00000058884	*Olfr1025-ps1*	Olfactory receptor 1025, pseudogene 1	4.30	0.03356
ENSMUSG00000087340	*Gm15228*	Predicted gene 15228	4.25	0.02579
ENSMUSG00000094872	*Igkv9-120*	Immunoglobulin kappa chain variable 9-120	4.22	0.01533
ENSMUSG00000066108	*Muc5b*	Mucin 5, subtype B, tracheobronchial	4.21	0.00077
ENSMUSG00000105906	*Iglc1*	Immunoglobulin lambda constant 1	4.18	0.01064
ENSMUSG00000095765	*Olfr741*	Olfactory receptor 741	4.16	0.00863

Table S1 B. Top 25 downregulated genes in OB tissue samples from *Gadl1*$^{-/-}$ compared to *Gadl1*$^{+/+}$ mice.

ENSEMBL ID	Abbreviation	Name	Log2Fold	P-value
ENSMUSG00000022485	*Hoxc5*	Homeobox Protein Hox C5	-8.25	0.00033
ENSMUSG00000038700	*Hoxb5*	Homeobox Protein Hox B5	-7.65	0.00325
ENSMUSG00000087658	*Hotairm1*	Hoxa transcript antisense RNA, myeloid-specific 1	-6.90	0.00079
ENSMUSG00000038253	*Hoxa5*	Homeobox Protein Hox A5	-6.46	0.00381
ENSMUSG00000056423	*Uts2b*	Urotensin-2B	-6.04	0.00188
ENSMUSG00000048763	*Hoxb3*	Homeobox Protein Hox B3	-5.99	0.00081
ENSMUSG00000001661	*Hoxc6*	Homeobox Protein Hox C6	-5.97	0.01110
ENSMUSG00000056468	*5730596B20Rik*	RIKEN cDNA 5730596B20 gene	-5.84	0.03447
ENSMUSG00000084844	*Hoxb3os*	Homeobox B3 and homeobox B2, opposite strand	-5.76	0.03083
ENSMUSG00000075394	*Hoxc4*	Homeobox Protein Hox C4	-5.67	0.00327
ENSMUSG00000085696	*Hoxaas3*	Hoxa cluster antisense RNA 3	-5.02	0.00906
ENSMUSG00000060738	*Prl7c1*	Prolactin 7c1	-4.85	0.00353
ENSMUSG00000005503	*Evx1*	Even-skipped homeobox 1	-4.65	0.03972
ENSMUSG00000067684	*Obp1a*	Odorant binding protein IA	-4.55	0.02233
ENSMUSG00000001670	*Tat*	Tyrosine aminotransferase	-4.48	0.02410
ENSMUSG00000103430	*Gm36996*	Predicted gene 36996	-4.45	0.01718
ENSMUSG00000108282	*Gm44317*	Predicted gene 44317	-4.41	0.01906
ENSMUSG00000026976	*Pax8*	Paired box 8	-4.29	0.00069
ENSMUSG00000038155	*Gstp2*	Glutathione S-transferase, pi 2	-4.28	0.03740
ENSMUSG00000042279	*H1foo*	H1.8 linker histone	-4.27	0.02103
ENSMUSG00000109753	*Gm45633*	Predicted gene 45633	-4.26	0.02596
ENSMUSG00000041333	*Mup4*	Major urinary protein 4	-4.26	0.02462
ENSMUSG00000073242	*Dnmt3aos*	DNA methyltransferase 3A, opposite strand	-4.18	0.02929
ENSMUSG00000074385	*Gm10684*	Predicted gene 10684	-4.14	0.00057
ENSMUSG00000029844	*Hoxa1*	Homeobox Protein Hox A1	-4.11	0.03148

Table S1 C. Transcript levels of 30 predicted genes close to the *Gadl1* locus (yellow: downregulated in knockout, green: upregulated in knockout, blank: not detected).

Gene name	ENSEBML ID	Log2FoldChange	P-value
Loc102633324 (Gm16142)	ENSMUSG00000087469	-1.145644169	0.331003828
Loc102633106 (Gm31014)			
Loc102633399 (Gm31234)			
Loc102633476 (Gm31292)			
Tgfbr2	ENSMUSG00000032440	0.153321074	0.11705412
Gm9385	ENSMUSG00000080848	-0.131387484	0.400319186
Gm5921	ENSMUSG00000074034	-0.062966245	0.955064616
Gm9385	ENSMUSG00000080848	-0.131387484	0.400319186
Rbms3	ENSMUSG00000039607	-0.041538879	0.816216697
Cmc1	ENSMUSG00000039163	0.043065942	0.678703046
Azi2	ENSMUSG00000039285	0.113416692	0.251718473
Stt3b	ENSMUSG00000032437	0.143339379	0.156764486
Gm18328			
Gm40582			
d73003k21rik			
Gm39447			
Gm40587			
Mir467h			
Gm9487			
4930428G15rik			
Gm30762			
Stmn1-rs1			
Gm31599			
Gm39449			
Gm18489			
Gm39452			
Loc102635502			
Gm36451			
Gm39450			
Loc108167721			
Gm4668			
Gm48038			
Gm31410			

Table S1 D. Transcript levels of ABAT or AGXT2 in the OB extracts of *Gadl1*$^{+/+}$ and *Gadl1*$^{-/-}$ mice. (yellow: downregulated in knockout, green: upregulated in knockout, blank: not detected).

Gene name	ENSEMBL ID	Log2FoldChange	P-value
Abat	ENSMUSG00000057880	0.063686739	0.554421048
Agxt2	ENSMUSG00000089678	-1.638874888	0.686109037

Table S3. Overview of the data used for genetic analysis using MAGMA software.

phenotype	Sample size*	Reference and data source
Neuropsychiatric		
ADHD**	53,293	Demontis et al. (64)
Alzheimer's disease	452,010	Jansen et al. (67)
ALS***	80,610	Nicolas et al.(70, 75)
Anorexia	72,517	Watson et al.(75)
Anxiety	18,186	Otowa et al. (71)
Autism	46,351	Grove et al. (66)
Bipolar disorder	51,710	Stahl et al. (72)
Depression	173,005	Wray et al. (76)
Educational attainment	766,345	Lee et al. (68)
Epilepsy	34,852	International League Against Epilepsy Consortium on Complex Epilepsies (79)
Parkinson's disease	482,730	Nalls et al. (69)
Schizophrenia	77,096	Ripke et al. (81)
SWB****	298,420	Okbay et al. (82)
Acetyl carnosine (in blood serum)	6279	Shin et al. (27)
AMD	33,976	Fritsche et al (65)
Body mass index	795,640	Yengo et al. (78)
Coronary heart disease	547,261	van der Harst & Verweij (74)
Muscular strength******	335,842	UKBIOBANK http://www.nealelab.is/uk-biobank http://ldsc.broadinstitute.org/
Type 2 diabetes	605,056	Xue et al. (77)
Kidney function*	567,460	Wuttke et al. (39)
UACR in diabetes**	5826	Teumer et al.(73)

*Maximum total sample size
** Attention-deficit/hyperactivity disorder
*** Amyotrophic lateral sclerosis
****Subjective well-being
***** Age-related macular degeneration
****** Right hand grip strength
* glomerular filtration rate estimated from serum creatinine (eGFR)
** urinary albumin-to-creatinine ratio among individuals with diabetes

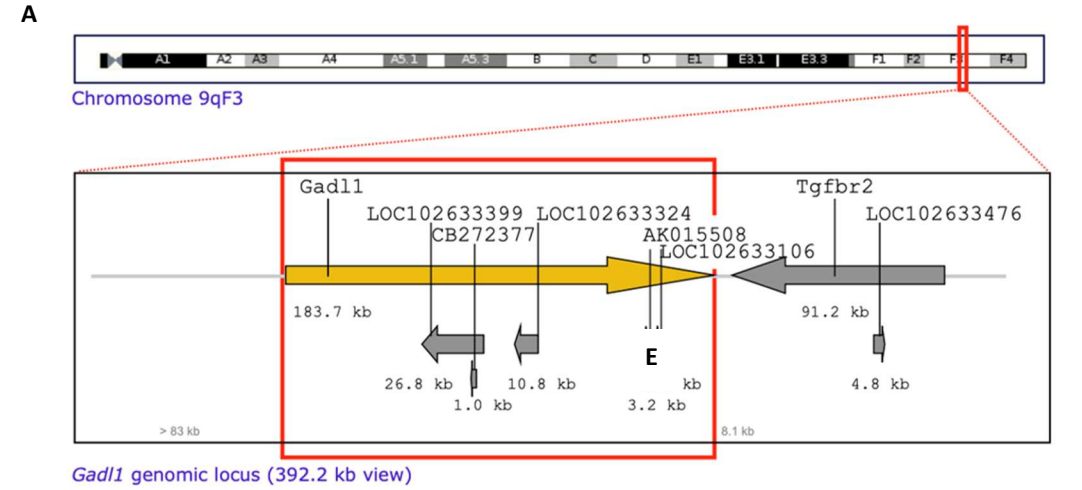
Table S4. Analysis of mouse diet

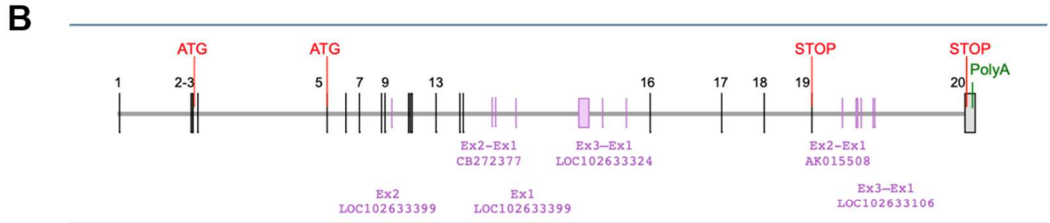
Parameter analyzed	Result (g/kg)
1-Methylhistidine (Free)	<0.5
3-Methylhistidine (Free)	<0.5
Alanine (Free)	<0.5
Alpha-Aminoadipic acid (Free)	<0.5
Alpha-Amino-n-butyric acid (Free)	<0.5
Anserine (Free)	<0.5
Arginine (Free)	<0.5
Asparagine (Free)	0.535
Aspartic Acid (Free)	<0.5
β-Alanine (Free)	<0.5
β-Aminoisobutyric acid (Free)	<0.5
Carnosine	<0.5
Citrulline	<0.5
Cystathionine (Free)	<0.5
Cystin (Free)	<0.5
Delta-Hydroxylysine (Free)	<0.5
Ethanolamine	<0.5
γ-Amino-butyric acid (Free)	<0.5
Glutamic acid (Free)	<0.5
Glutamine (Free)	<0.5
Glycine (Free)	<0.5
Histidine (Free)	<0.5
Homocysteine (Free)	<0.5
Hydroxyproline (Free)	<0.5
Isoleucine (Free)	<0.5
Leucine (Free)	<0.5
Lysine (Free)	0.843
Methionine (Free)	<0.5
Ornithine (Free)	<0.5
Phenylalanine (Free)	<0.5
Phosphothanolamine (Free)	<0.5
Phosphoserine (Free)	<0.5
Proline (Free)	<0.5
Sarcosine (Free)	<0.5
Serine (Free)	<0.5
Taurine (Free)	<0.5
Threonine (Free)	<0.5
Tryptophan (Free)	<0.5
Tyrosine (Free)	<0.5
Urea	<0.5

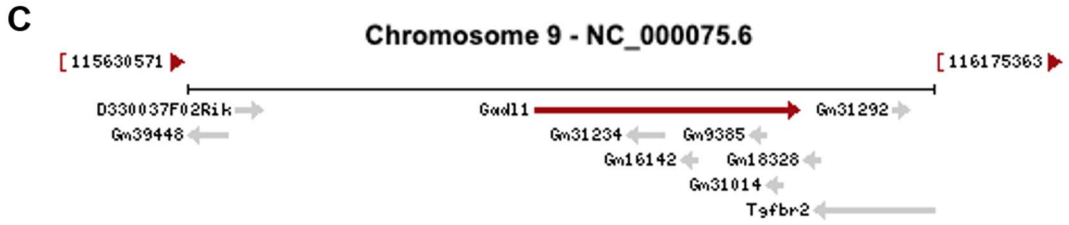
Table S5. Sequences of PCR primers and sizes of PCR products.

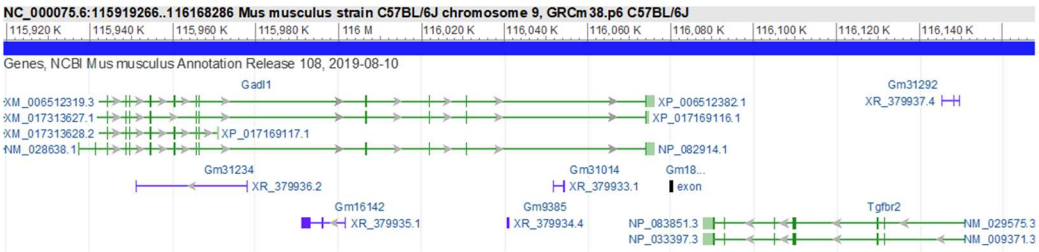
Primer	Primer Sequence 5'-3'	PCR Product Size	
		WT	**KO**
136258Cre-HAA2	TCAGTTGAGAAGCCCTTCCTTGGTGTA	330 and 750 bp	166 bp
136249Cre-HAA2	CCTTGAACGTGGTTCTCTAGTAGCCACC		
136248Cre-HAA2	AGACCTGGTTAAGCAACTCTCCACTAACTCC		

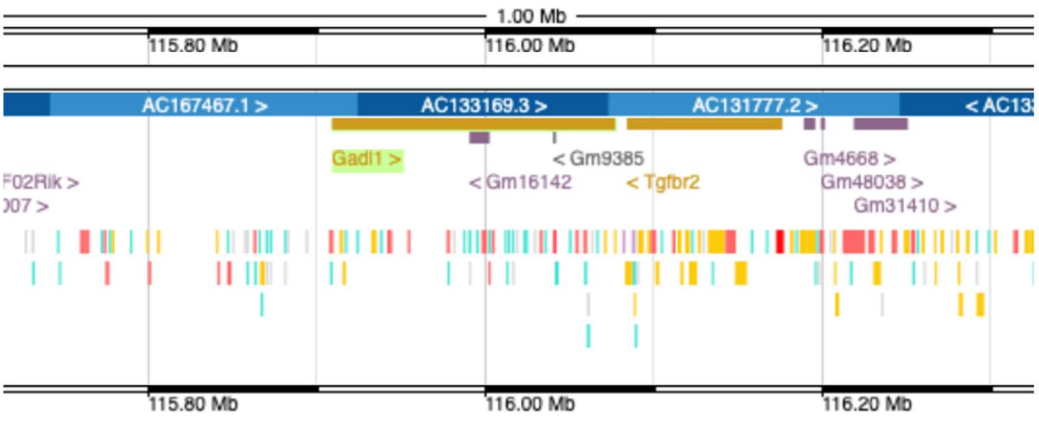
Supplementary Figures











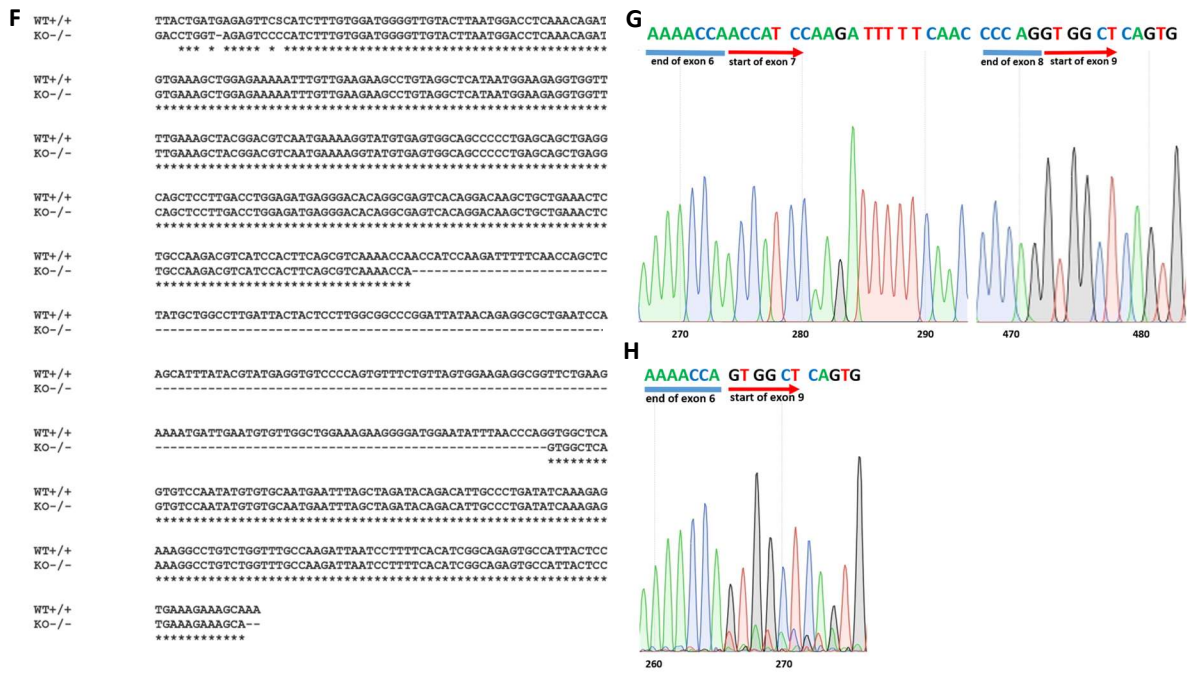


Fig. S1. Overview of the mouse *Gadl1* locus (A, B, C, D and E) and sequencing alignment of *Gadl1*$^{+/+}$ and *Gadl1*$^{-/-}$mRNA confirming that exon 7 and 8 are missing from the *Gadl1*$^{-/-}$ muscle transcript (F, G and H). (A) *Gadl1* genomic locus in mouse chromosome as analyzed at Genoway, **(B)** overview of exon organization using Genoway software, **(C)** overview of *Gadl1* locus from NCBI gene database, **(D)** *Gadl1* and closest neighboring genes (NCBI), **(E)** *Gadl1* and closest neighboring genes (EMBL-EBI). **(F)** Alignment of mRNA sequences of the *Gadl1*$^{+/+}$ and *Gadl1*$^{-/-}$ mice. Cluster omega was used for alignment (https://www.ebi.ac.uk/Tools/msa/muscle/). **(G-H)** Sequencing chromatogram of **(G)** *Gadl1*$^{+/+}$ and **(H)** *Gadl1*$^{-/-}$ mice. Exon 7 and 8 are missing in the *Gadl1*$^{-/-}$ mice mRNA. Created in SnapGene (v4.2, GSL Biotech LLC, San Diego, CA 92108, USA).

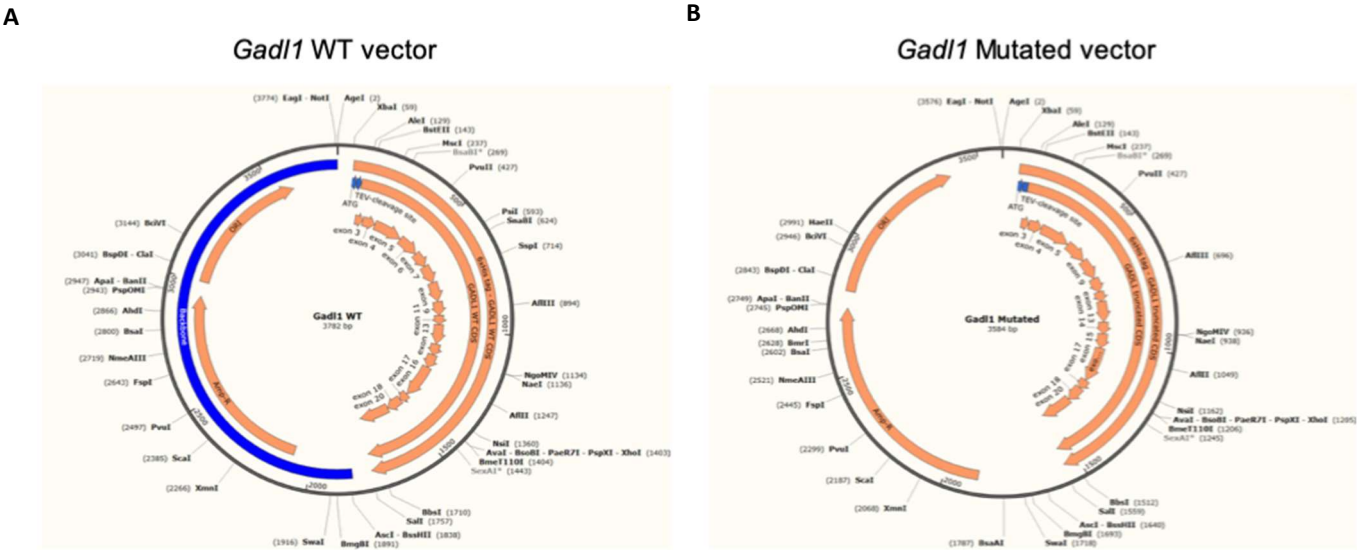


Fig. S2. Vectors designed for *Gadl1* wild type (WT) (A) and mutated (B). The vectors were made in BL21 E-coli. The proteins were expressed and purified using Histidine-tag. Created using SnapGene (v4.2, GSL Biotech).

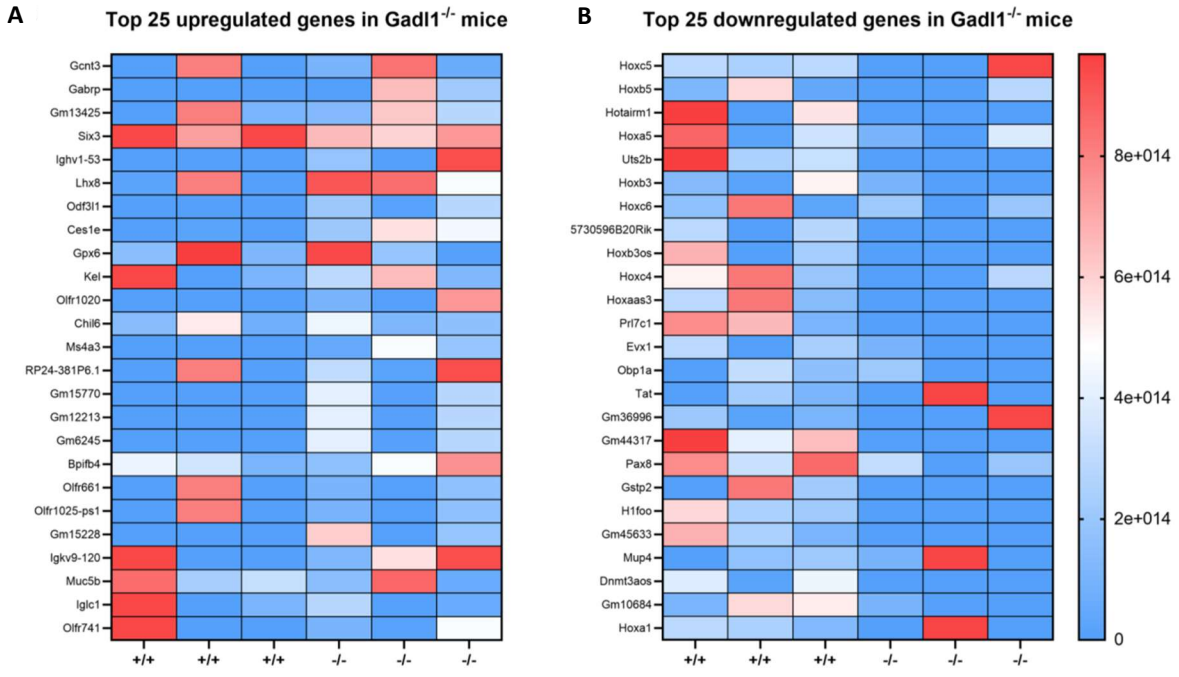
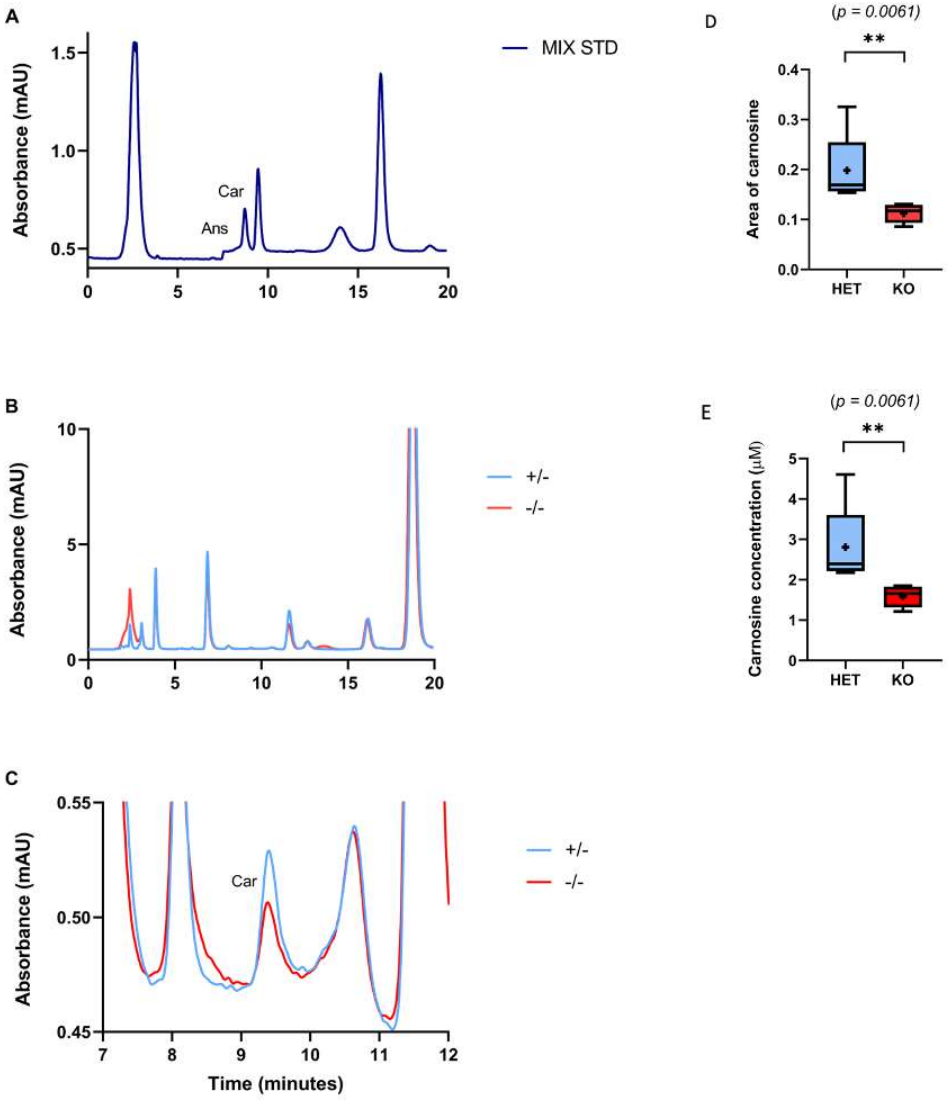
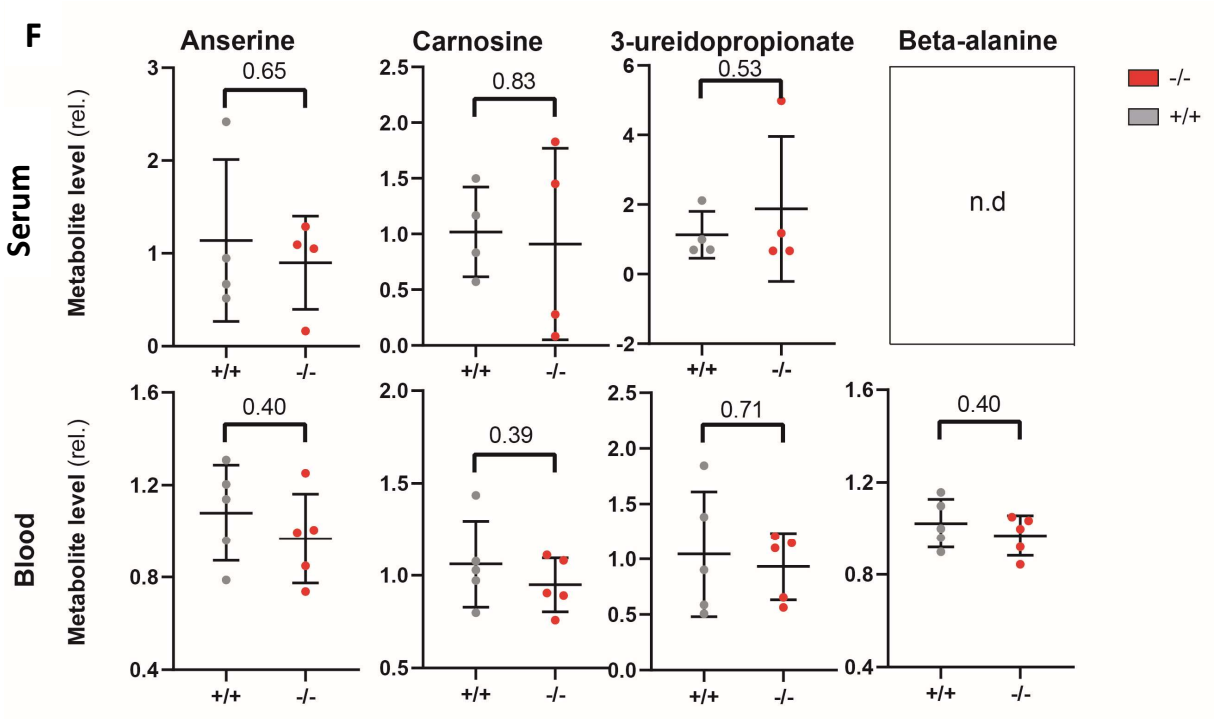
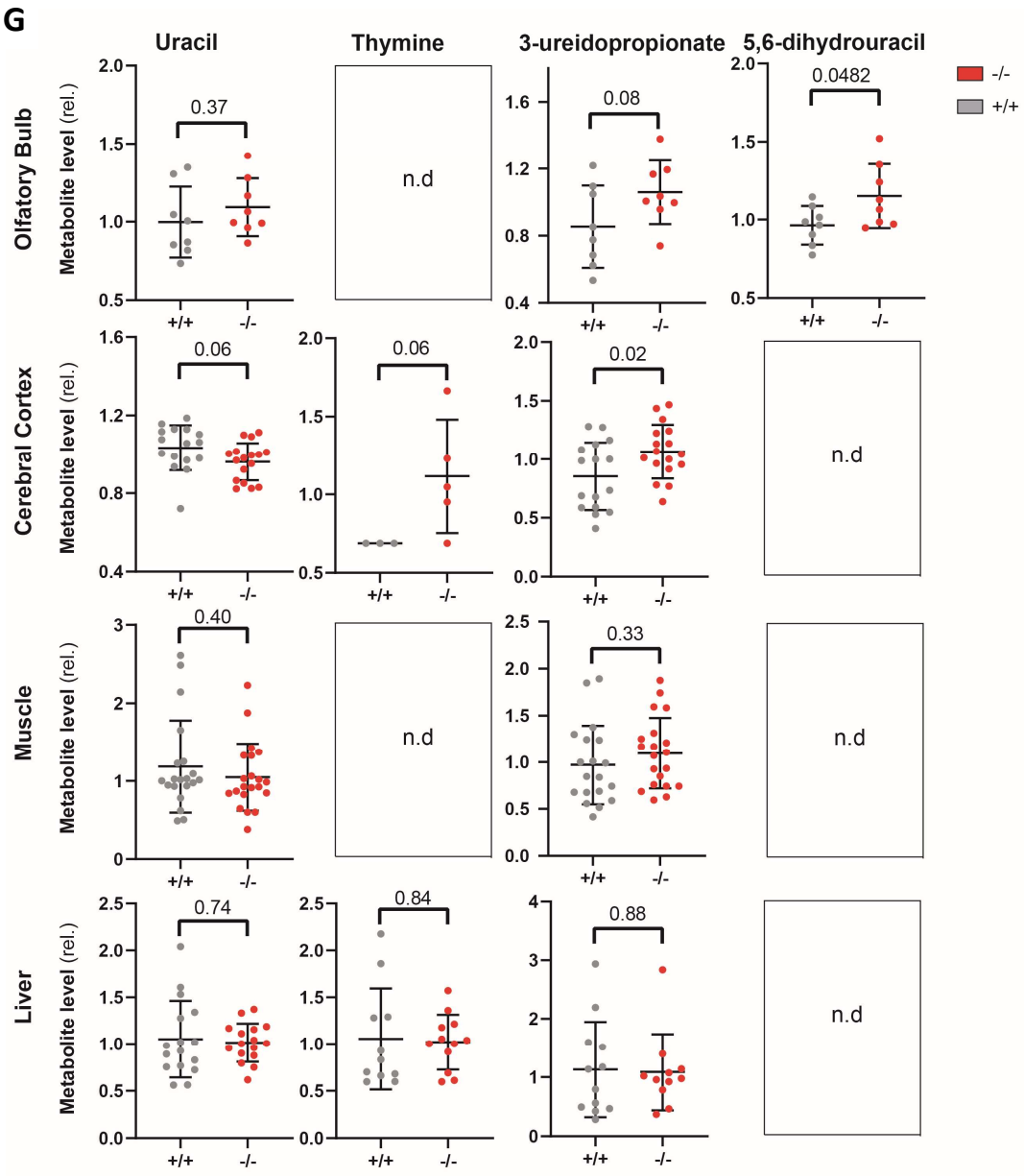


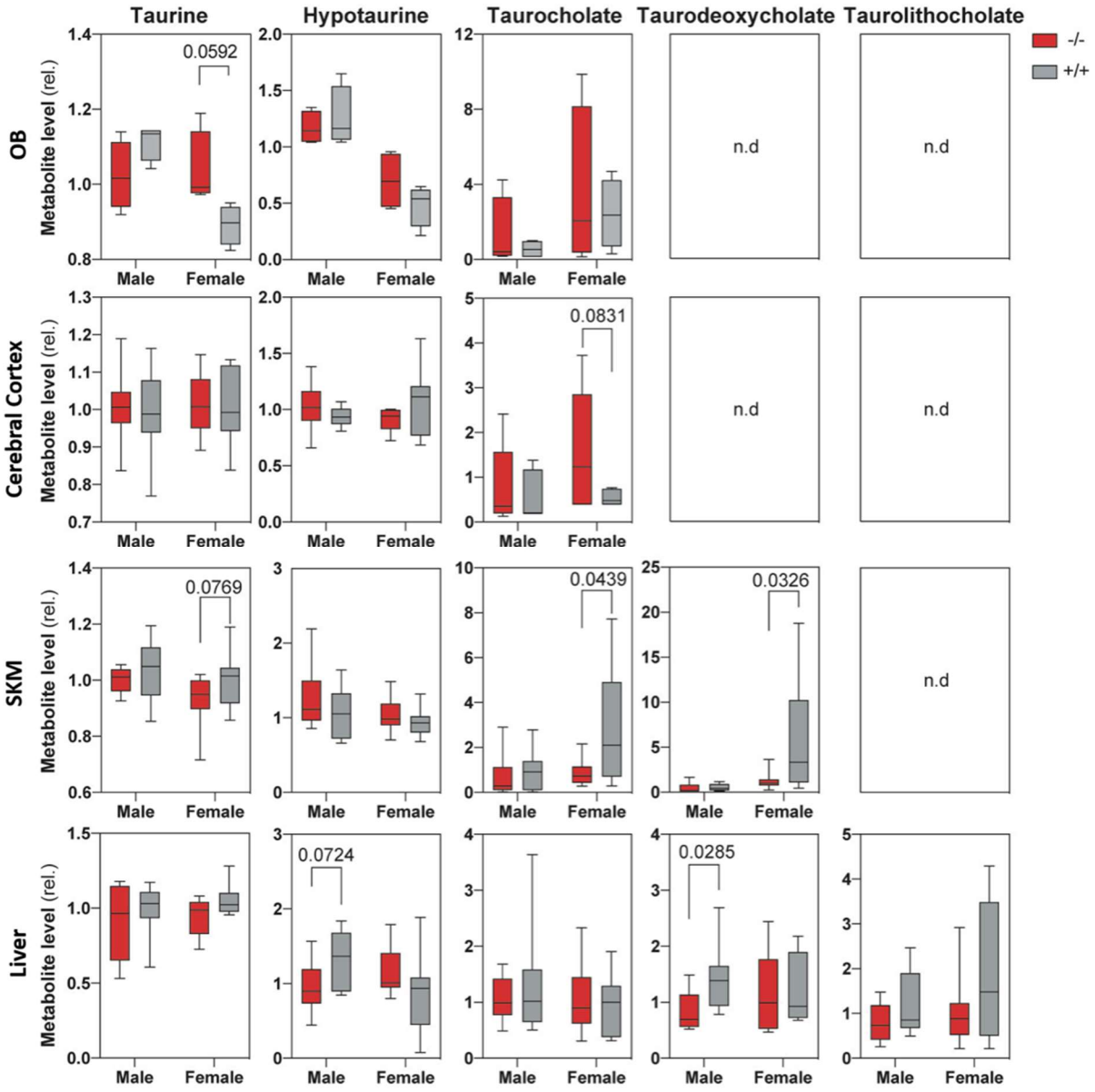
Fig. S3. Top 25 up (A) and down (B) regulated genes in olfactory bulb when comparing *Gadl1*$^{-/-}$ (n =3) to *Gadl1*$^{+/+}$ (n = 3).


A
Absorbance (mAU)
1.5
1.0
0.5
0
5
10
15
20
Car
Ans
MIX STD
B
Absorbance (mAU)
10
5
0
+/-
-/-
C
Absorbance (mAU)
0.55
0.50
0.45
7
8
9
10
11
12
Car
Time (minutes)
+/-
-/-
D
(p = 0.0061)
**
Area of carnosine
0.4
0.3
0.2
0.1
0.0
HET
KO
E
(p = 0.0061)
**
Carnosine concentration (µM)
5
4
3
2
1
0
HET
KO

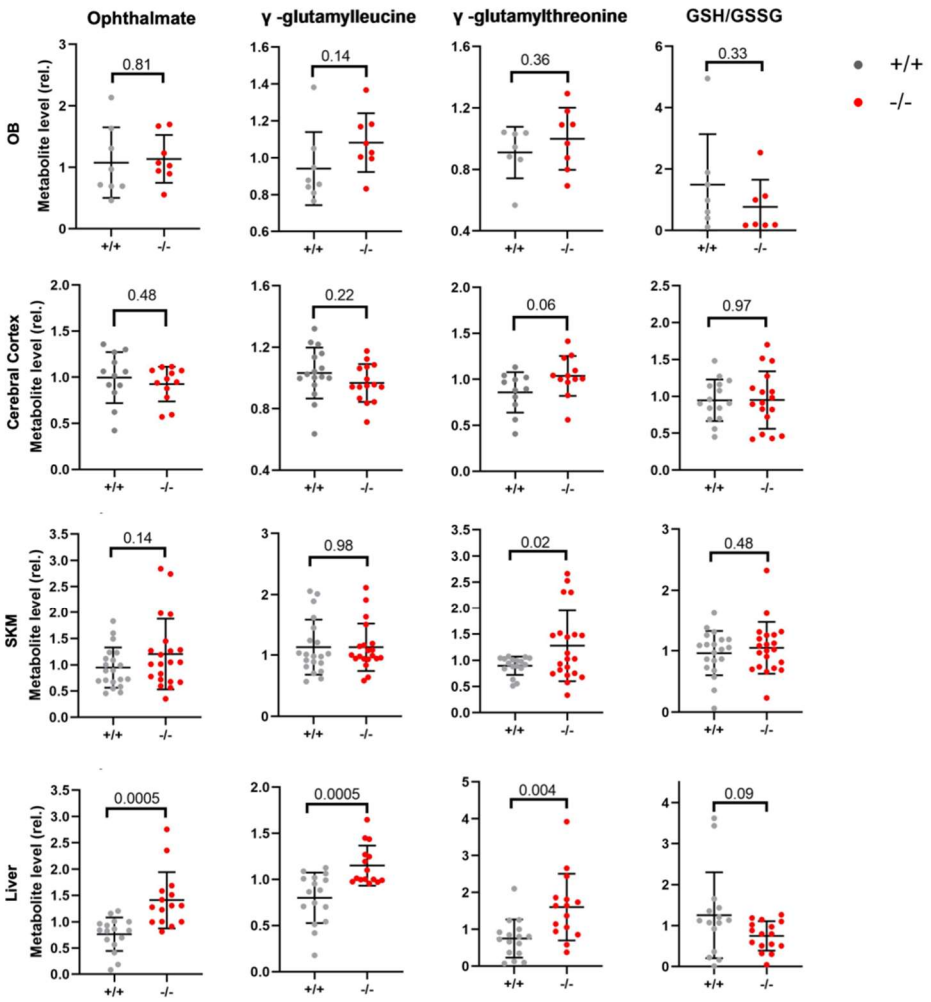

F
Anserine
Carnosine
3-ureidopropionate
Beta-alanine
Serum
Blood
Metabolite level (rel.)
0.65
0.83
0.53
n.d
0.40
0.39
0.71
0.40
+/+
-/-
-/-
+/+


G
Uracil
Thymine
3-ureidopropionate
5,6-dihydrouracil
Olfatory Bulb
Cerebral Cortex
Muscle
Liver
Metabolite level (rel.)
0.37
n.d
0.08
0.0482
0.06
0.06
0.02
n.d
0.40
n.d
0.33
n.d
0.74
0.84
0.88
n.d
+/+
-/-
-/-
+/+

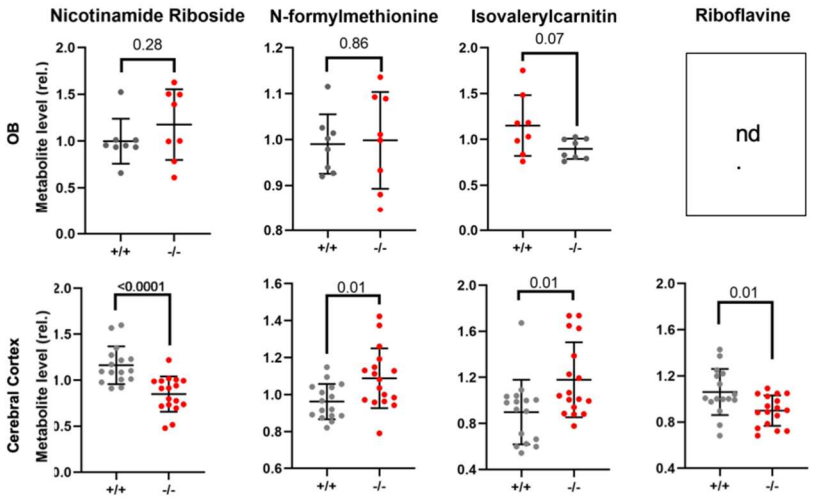
H


Taurine
Hypotaurine
Taurocholate
Taurodeoxycholate
Taurolithocholate
-/-
+/+
OB
Cerebral Cortex
SKM
Liver
Metabolite level (rel.)
0.0592
0.0831
0.0769
0.0439
0.0326
0.0724
0.0285
n.d
Male
Female

I


Ophthalmate
γ -glutamylleucine
γ -glutamylthreonine
GSH/GSSG
+/+
-/-
OB
Cerebral Cortex
SKM
Liver
Metabolite level (rel.)
0.81
0.14
0.36
0.33
0.48
0.22
0.06
0.97
0.14
0.98
0.02
0.48
0.0005
0.0005
0.004
0.09

J


Nicotinamide Riboside
N-formylmethionine
Isovalerylcarnitin
Riboflavine
OB
Cerebral Cortex
Metabolite level (rel.)
0.28
0.86
0.07
nd
<0.0001
0.01
0.01
0.01

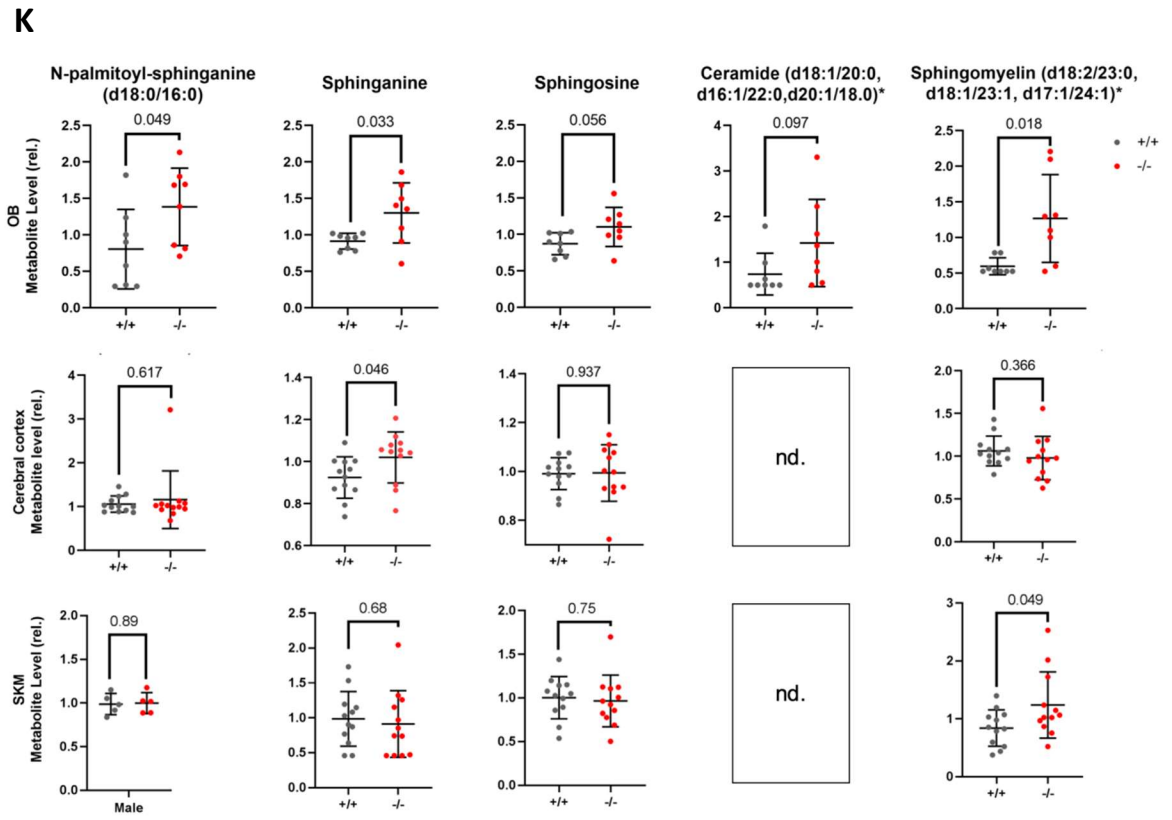


Fig. S4. Metabolite levels in mouse tissues. (A, B, C, D and E) Measurements of carnosine peptides in extracts of cerebral cortex from female *Gadl1*$^{+/-}$ (n=5) and *Gadl1*$^{-/-}$ (n=5) mice (18-22 weeks) using an isocratic RP-HPLC system. Injection of 20µl **(A)** L-anserine nitrate salt and L-carnosine, and **(B and C)** cerebral cortex lysates from female *Gadl1*$^{+/-}$ (n=5) and *Gadl1*$^{-/-}$ (n=5) mice (18-22 weeks). The box plots show **(D)** mean area and **(E)** relative level of carnosine concentration in cortex extracts. The decrease in carnosine levels was 40.46 ± 12.18 % from *Gadl1*$^{+/-}$ to *Gadl1*$^{-/-}$. Median is presented as a line and mean as a plus (+) sign. Whiskers are drawn from min to max value. Statistical significance ($p<0.05$) was determined with a ratio, paired t-test and significant differences are indicated with an asterisk (*). Relative levels of **(F)** 3-ureido-propionate, β-alanine, anserine, and carnosine in whole blood and serum (n=5). Relative levels of various metabolites in OB, cerebral cortex, SKM, and liver tissue extracts from *Gadl1*$^{+/+}$ (grey) and *Gadl1*$^{-/-}$ (red) mice (n=5-21); **(G)** uracil and thymine derivatives, **(H)** taurine and taurine derivatives, **(I)** Glutamate peptides and related oxidative stress markers, **(J)** Nicotinamide riboside, N-formylmethionine, isovalerylcarnitine, riboflavin, **(K)** sphingolipids and ceramide.

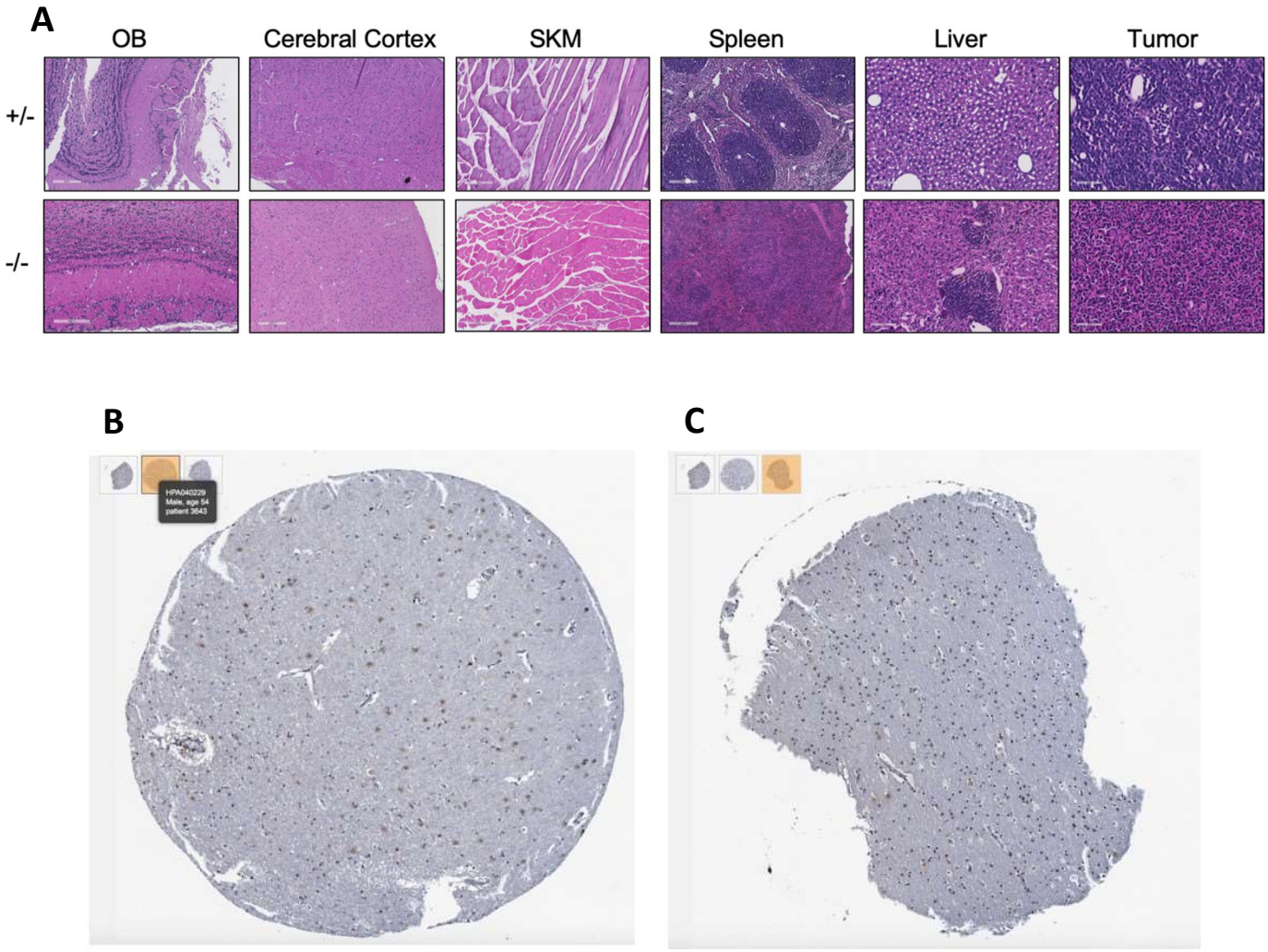


Fig. S5. Tissue distribution of GADL1 (A) Hematoxylin and Eosin (HE) staining of mouse *Gadl1* $^{+/-}$ and *Gadl1*$^{-/-}$ OB, cerebral cortex, SKM, spleen, liver and tumor. (B-C) Immunohistochemistry for GADL1 of (B) grey and (C) white matter using commercial antibody adapted from Human Protein Atlas.

Links to databases:
Human Protein Atlas
https://www.proteinatlas.org/ENSG00000144644-GADL1/tissue

alliance of genome resources
http://www.informatics.jax.org/marker/MGI:1920998

REFERENCES AND NOTES

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