

Supplementary information

Glutaric aciduria type 3 is a naturally occurring biochemical trait in inbred mice of 129 substrains

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Supplemental figure legends

Figure S1. Identification of a GA3 trait and SUGCT deficiency in mice of the 129 substrain. (A) Quantitative proteomics data for liver expression of selected proteins in the 8 founder laboratory strains of the Collaborative Cross as extracted from Table S1 in Chick et al [1]. Abundance data are displayed for proteins associated with biochemical phenotypes reported in the C57BL/6J and 129S1/SvImJ strains. This analysis confirmed several previously described mild inborn errors of metabolism including deficiencies of DHTKD1, BCKDHB, D2HGDH, COX7A2L and NNT in C57BL/6J, and deficiencies of IVD and GLYCTK in 129S1/SvImJ. Other strains include all data from A/J, NOD/ShiLtJ, CAST/EiJ, NZO/HILtJ, WSB/EiJ and PWK/PhJ. (B) Mapping of *Sugct* (*5033411D12Rik*; Probeset ID 1421422_at) liver expression data from the hybrid mouse diversity panel using the systems genetics resource at UCLA (<https://systems.genetics.ucla.edu/>) [2, 3]. (C) Expression analysis of *Sugct* in liver cDNA of C57BL/6J, DBA/2J and 129S2/SvPasCrl mice. *Rplp0* served as control gene.

Figure S2. Association of the GA3 trait with the *Sugct*^{129/129} genotype in a B6129F2 population. (A) Plasma C5-carnitine and urine 2-hydroglutaric acid in samples of B6129F2 mice. For plasma C5-carnitine the mice were genotyped at the *Ivd* locus, and for urine 2-hydroglutaric acid the mice were genotyped at the *D2hgdh* locus. (B) Immunoblot analysis of SUGCT in kidney samples of B6129F2 mice with *Sugct*^{B6/B6}, *Sugct*^{B6/129} and *Sugct*^{129/129} genotypes. (C) Quantification of urine adipic acid in samples of B6129F2 mice with *Sugct*^{B6/B6}, *Sugct*^{B6/129} and *Sugct*^{129/129} genotypes. The P value indicates the result of an ANOVA test. **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.

Figure S3. The biochemical consequences of SUGCT deficiency in GA1 mice. (A) Plasma C5DC, urine glutaric acid, 3OH-glutaric acid, C5DC and 2-oxoadipate, and kidney C5DC in GA1 mice. Mice are segregated according to their genotype at the *Dhtkd1* locus. The P values indicate the result of an ANOVA test and a Tukey's multiple comparisons test. Ns, not significant; ****, P < 0.0001. (B) Urine adipic acid for male and female GA1 mice. Mice are segregated according to their genotype at the *Sugct* locus. (C) Liver and brain C5DC in GA1 mice. Data are displayed for the same cohort of animals (Fig. 4 and Fig. S3A), segregated according to their genotype at the *Sugct* locus. The table displays the result of a two-way ANOVA.

Supplemental tables

Table S1. Genotype distribution in an intercross of *Gcdh*^{+/-} *Sugct*^{129/B6} *Dhtkd1*^{129/B6} mice. Provided as an Excel table.

Table S2. Biochemical and phenotypic data in mice of an F2 population of the parental C57BL/6J and 129S2/SvPasCrl strains (B6129F2). Provided as an Excel table.

Table S3. Biochemical and phenotypic data in the GA1 mice of an F2 population of the parental C57BL/6J and 129S2/SvPasCrl strains (B6129F2). Provided as an Excel table.

Table S4. List of selected defects due to spontaneous mutations in (commonly used) inbred mouse strains.

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#	Gene	Full name	Causal variant	Strain(s)	MIM	References
1	<i>a</i>	nonagouti	Many	Many	611742	[4]
2	<i>Acads</i>	Short-chain acyl-CoA dehydrogenase (SCAD)	Deletion Chr5:115,110,929-115,111,207	BALB/cByJ	201470	[5]
3	<i>Alpl</i>	alkaline phosphatase	Unknown	C57BL/6J	146300 241500 241510	[6]
4	<i>Bckdhb</i>	branched chain keto acid dehydrogenase E1 subunit beta	Insertion Chr9:83,942,547-83,949,878	C57BL/6J	248600	[7-9]
5	<i>Casp4</i>	caspace 4, apoptosis-related cysteine peptidase	Deletion Chr9:2,328,429:2,328,433 skipping of exon 7 p.P304fsX309 rs235337590	129 substrains		[10]
6	<i>Cdh23</i>	cadherin 23	c.753G>A in-frame skipping of exon 7	Many strains including the C57BL/6 substrains	601386 601067 617540	[11]
7	<i>Cdt1</i>	chromatin licensing and DNA replication factor 1	c.265-282delAGCCCTCCAGCTGACCCT p.S89_P94del rs232721151	129 substrains LP/J	613804	[12]
8	<i>Cox7a2l</i>	supercomplex assembly factor I	c.216_221delGCCCAT p.F72delinsLPI	C57BL/6 substrains 129S5/SvEvBrd BALB/cJ	Not reported	[9, 13]

9	<i>D2hgdh</i>	D-2-hydroxyglutarate dehydrogenase	Unknown	C57BL/6J	600721	[9] This paper
10	<i>Dhtkd1</i>	dehydrogenase E1 and transketolase domain containing 1	Insertion chr2:5,924,595-5,925,150	C57BL/6J A/J AKR/J FVB/NJ NOD/LtJ NZO/HILtJ	204750 245130	[7, 8]
11	<i>Disc1</i>	disrupted in schizophrenia 1	c.1583-1607delACCAGGCTCCCTTCCAGGTGGAGCC p.Q529LfsX141	129 substrains FVB/NJ LP/J	604906	[14, 15]
12	<i>Dock2</i>	dedicator of cytokinesis 2	duplication in exons 28 and 29	C57BL/6NHsd	616433	[16, 17]
13	<i>Eci3</i>	enoyl-Coenzyme A delta isomerase 3	Unknown	DBA/2J	Not applicable	[18]
14	<i>Glyck</i>	glycerate kinase	c.196dupA p.R66KfsX143 rs243632237	129 substrains LP/J	220120	[19, 20]
15	<i>Gpnmb</i>	glycoprotein (transmembrane) nmb	c.448C>T p.R150X rs47598337	DBA/2J	Not reported	[21]
16	<i>Ivd</i>	isovaleryl-CoA dehydrogenase	c.1068G>A p.K356K rs27440099	129S1/SvImJ 129S2/SvPasCrl 129P2/OlaHsd 129S5/SvEvBrd BTBR T ⁺ Itpr3 ^{fl} /J BUB/BnJ	243500	[7] This paper

				LP/J		
17	<i>Lep</i>	Leptin (Obese)	c.313T>C p.R105X	<i>Ob/Ob</i>	614962	[22, 23]
18	<i>Mlycd</i>	malonyl-CoA decarboxylase	Insertion 5313bp Chr8:119,402,361	DBA/2J SM/J	248360	Our unpublished data
19	<i>Nnt</i>	nicotinamide nucleotide transhydrogenase	Deletion 17.8 kbp Chr13:119,375,448	C57BL/6J	614736	[24, 25]
20	<i>Slc3a1</i>	solute carrier family 3 member 1 (rBAT)	c.1232G>A p.E383K	129S2/SvPasCrl Later reported as not present in 129S1/Sv or 129S2/SvPas mice, which was confirmed by our lab	220100	[26]
21	<i>Slc11a1</i>	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1 natural resistance- associated macrophage protein 1 (<i>Nramp1</i>)	c.506A>G p.D169G rs47476426	129P2/OlaHsd 129S1/SvImJ 129S5SvEvBrd C3H/HeJ most other strains		[27-31]
22	<i>Slc22a5</i>	high-affinity sodium- dependent carnitine cotransporter (OCTN2)	c.1055T>G p.L352R	juvenile visceral steatosis (Jvs)	212140	[32]

23	<i>Sugct</i>	succinyl-CoA:glutarate-CoA transferase	unknown	129 substrains	231690	This paper
24	<i>Trem2</i>	triggering receptor expressed on myeloid cells 2	c.TC>GA p.S148E	129S1/SvImJ PWK/PhJ CASA/RkJ	618193	
25	<i>Ttc7</i>	tetratricopeptide repeat domain 7	An ETn early transposon insertion of 183 bp occurred in intron 14, 57 bp upstream of exon 15.	A/J	243150	[33]
26	<i>Tyr</i>	tyrosinase (albino / c)	c.308G>C p.C103S rs31191169	A/J AKR/J BALB/cJ FVB/NJ NOD/LtJ	203100	[34]
<p>The table lists the official gene name of the affected gene, a commonly used full gene name and abbreviation, the causal variant, the strain in which the variant was first characterized, the MIM number (https://www.omim.org/) of the equivalent human genetic disorder and a selected reference. The Dec. 2011 (GRCm38/mm10) mouse assembly was used.</p>						

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Figure S1

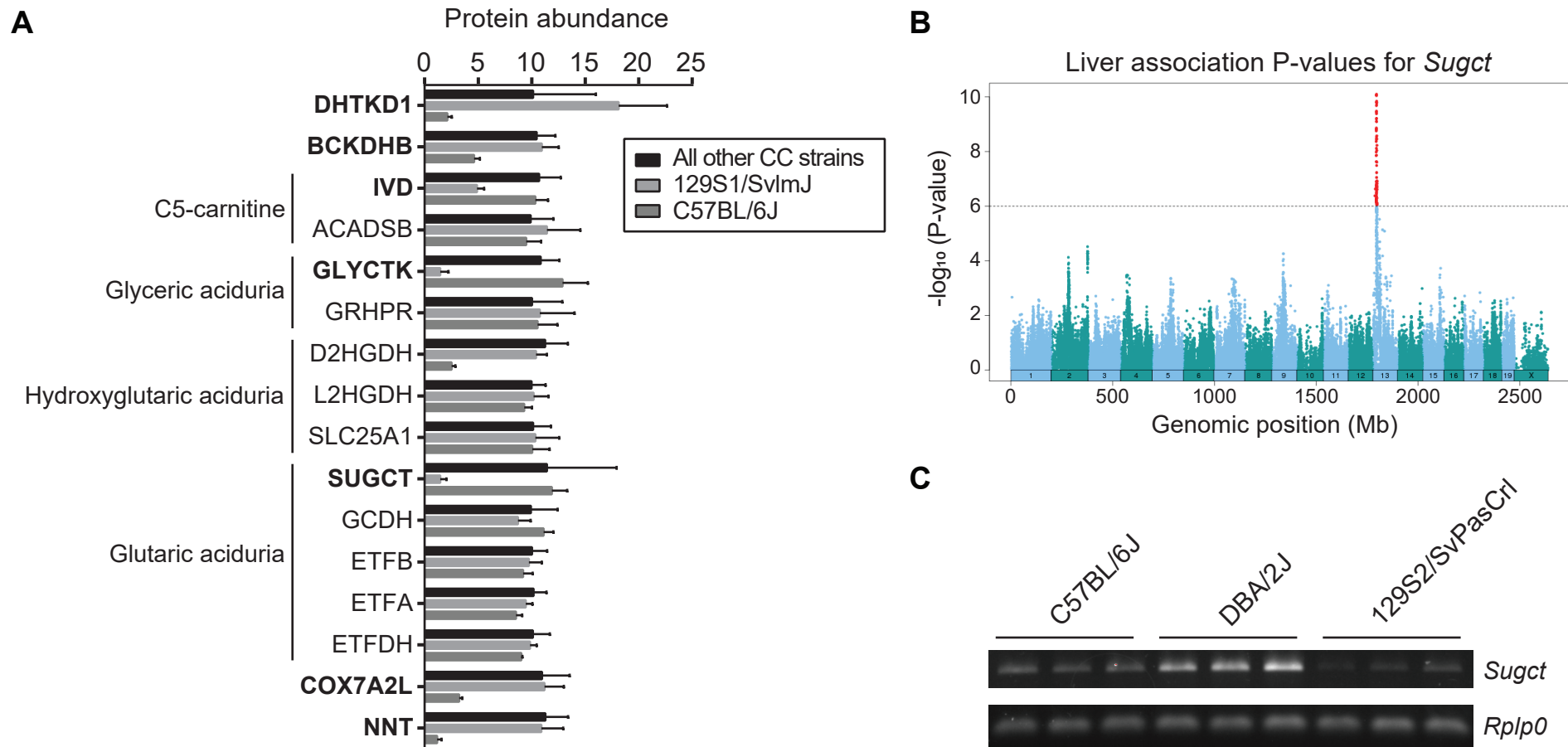
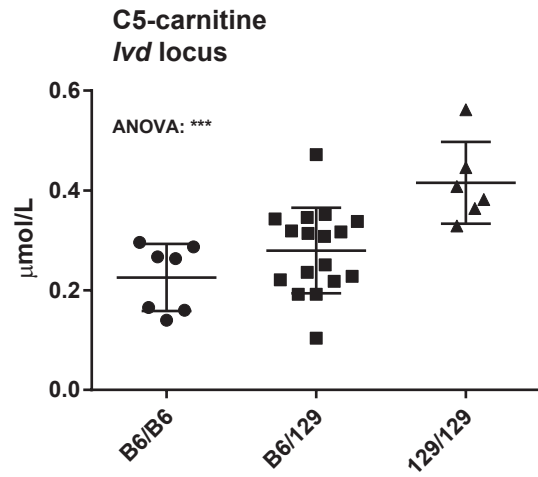
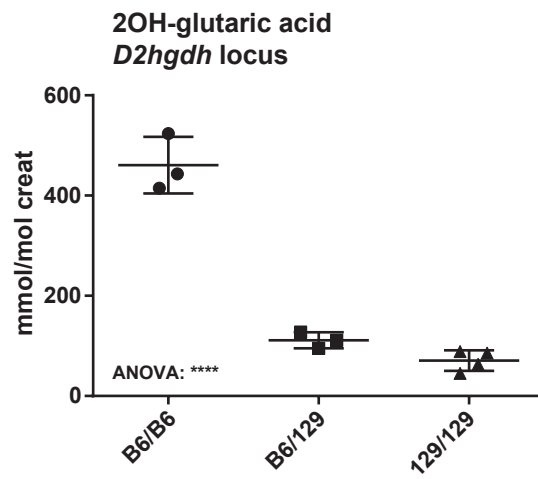
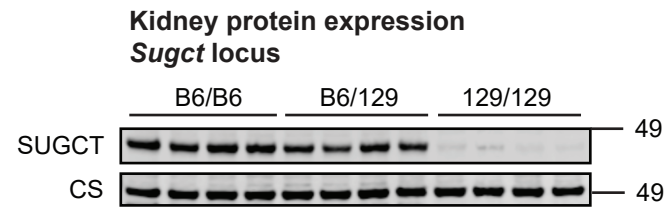


Figure S2

A



B



C

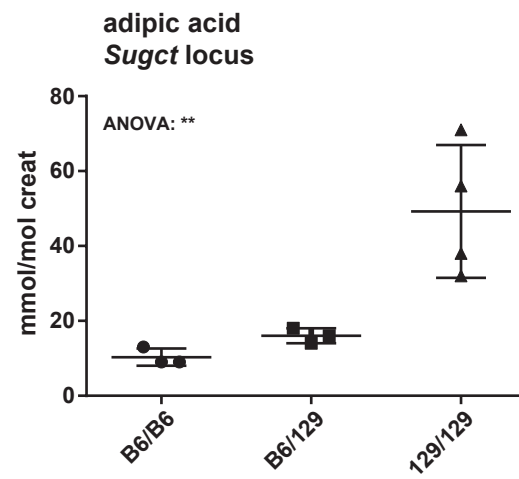
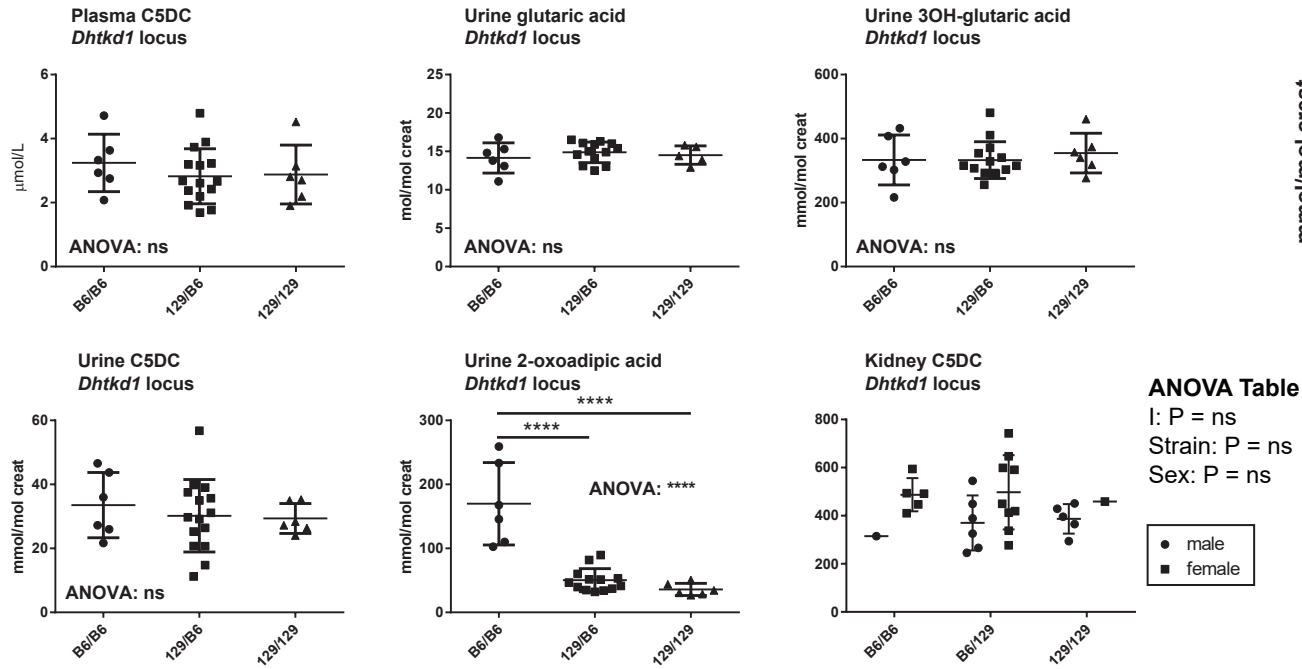
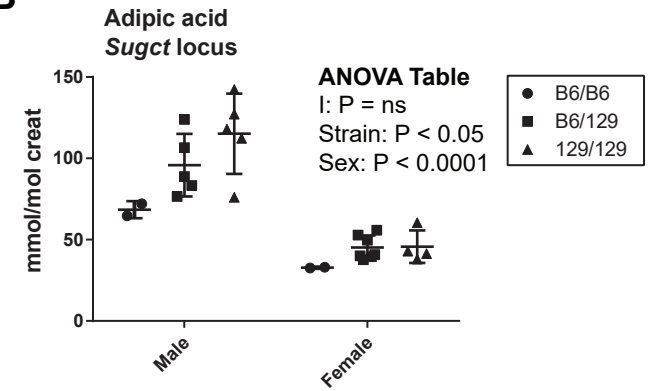


Figure S3

A



B



C

