Supplemental Tables

Supplemental Table 1. A general linear mixed model was used to compare AST and ALT between disorders. AST and ALT were transformed used a natural logarithm for analysis. The regression model included fixed effects for baseline age, disorder, time (continuous), and a disorder-time interaction term. The baseline visit was assumed to be time 0 for each participant. The model also included a random intercept and slope to model repeated measures within an individual over time. Statistical significance for model coefficients was assessed at the 0.05 level. Pairwise differences between disorders were assessed at the adjusted 0.05 level using Tukey's method.

Pairwise Comparisons	P Value (AST)	P Value (ALT)	P value (INR)
OTCD (F) vs. OTCD (M)	0.069	0.760	0.081
ASS1D vs. OTCD (M)	0.812	0.342	1.00
ASLD vs. OTCD (M)	**<0.001**	**<0.001**	0.998
ARG1D vs. OTCD (M)	**0.001**	**<0.001**	**<0.001**
Other UCDs vs. OTCD (M)	1.00	0.816	1.00
ASS1D vs. OTCD (F)	**<0.001**	**<0.001**	**0.022**
ASLD vs. OTCD (F)	**<0.001**	**<0.001**	**0.001**
ARG1D vs. OTCD (F)	**<0.001**	**<0.001**	**<0.001**
Other UCDs vs. OTCD (F)	0.14	0.04	0.111
ASLD vs. ASS1D	**0.004**	**<0.001**	1.00
ARG1D vs. ASS1D	**0.049**	**0.009**	**<0.001**
Other UCDs vs. ASS1D	1.00	1.00	1.00
ARG1D vs. ASLD	1.00	1.00	**0.001**
Other UCDs vs. ASLD	**0.006**	**0.002**	1.00
Other UCDs vs. ARG1D	**0.025**	**0.032**	**0.005**

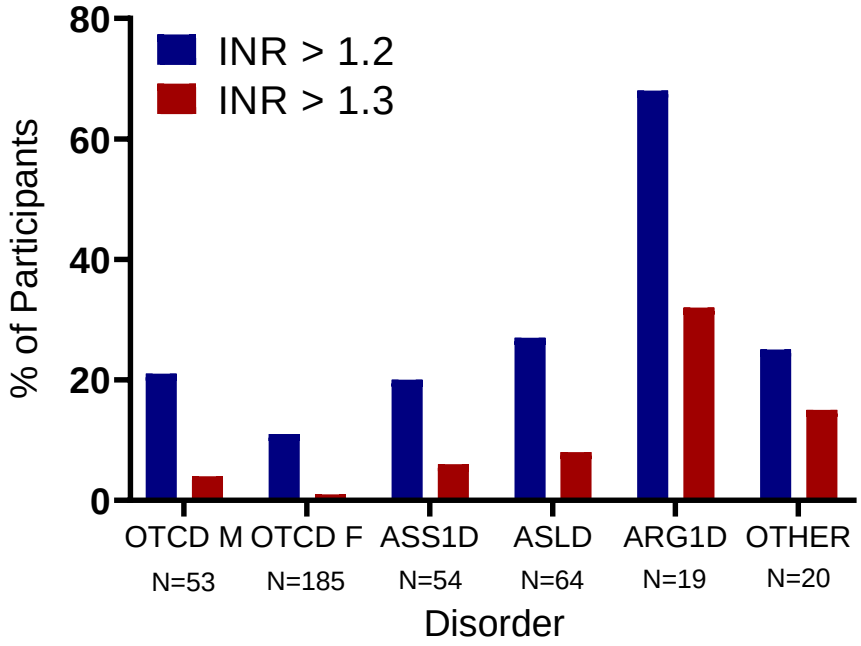
Supplemental Table 2. Pathogenic variants in participants with ASLD in the Longitudinal Study of Urea Cycle Disorders. The impact of variants in ASL has been summarized and reviewed elsewhere (29). The range of AST and ALT were provided for any participant who was scored as having chronic hepatocellular injury based on definitions used in this study. NA = fewer than two AST or ALT results recorded.

ID	Age (yrs)	ALT	AST	Variant 1	Published effect(29)	Mutation 2	Published effect(29)
1	0.7	No	No	p.Glu59Lys	Unknown	p.Val178Met	Mild
2	1.1	No	No	p.Gln460X	Severe	p.His160Asn	Unknown
3	1.2	No	No	p.Arg217X	Severe	p.Asp120Glu	Severe
4	1.2	No	No	p.Arg193Gln	Unknown	p.Val178Met	Mild
5	1.5	No	No	c.447-1G>A	Unknown	p.Ala205Val	Unknown
6	1.5	Yes (70 – 573)	Yes (28 – 217)	p.Arg113Trp	Severe	p.Val349Cysfs*72	Severe
7	2.5	No	No	p.Arg193Trp	Unknown	p.Arg385His	Unknown
8	2.7	No	No	p.Arg217X	Severe	p.Ser447Asn	Unknown
9	2.8	No	No	c.446+1G>A	Severe	p.Arg379Cys	Mild
10	2.9	Yes (27 – 1575)	Yes (32 – 345)	p.Val349Cysfs*72	Severe	p.Asp237Asn	Severe
11	3.4	No	No	p.Val178Met	Mild	p.Leu419Valfs*54	Unknown
12	3.7	NA	NA	p.Val349Cysfs*72	Severe	p.Arg379Cys	Mild
13	4.5	No	No	p.Val178Met	Mild	p.Met256Thr	Unknown
14	4.7	No	No	p.Arg193Trp	Unknown	p.Arg385His	Unknown
15	5.1	Yes (27 – 212)	No (28 – 87)	p.Arg186Gln	Severe	p.Arg193Gln	Unknown
16	5.9	Yes (33 – 226)	No (47 – 114)	c.834-1G>A	Severe	Not identified	
17	6.8	Yes (38 – 396)	Yes (27 – 202)	p.Gln286Arg	Severe	p.Gln286Arg	Severe
18	11.5	Yes (70 – 1175)	Yes (57 – 440)	c.524+2T>G	Severe	p.Ala444Val	Unknown
19	12.9	No	No	p.Glu189Gly	Mild	Not identified	

20	14.7	No	No	p.Arg12Gln	Mild	p.Gly280Glufs*4	Unknown
21	17.6	Yes (82 – 146)	No (42 – 79)	p.Gln286Arg	Severe	p.Gln286Arg	Severe
22	17.8	No	No	p.Arg12Gln	Mild	p.Gly280Glufs*4	Unknown
23	24.7	No	No	p.Asp231Glu	Unknown	p.Asp231Glu	Unknown
24	37.4	No	No	p.Val178Met	Mild	c.918+5G>A	Unknown

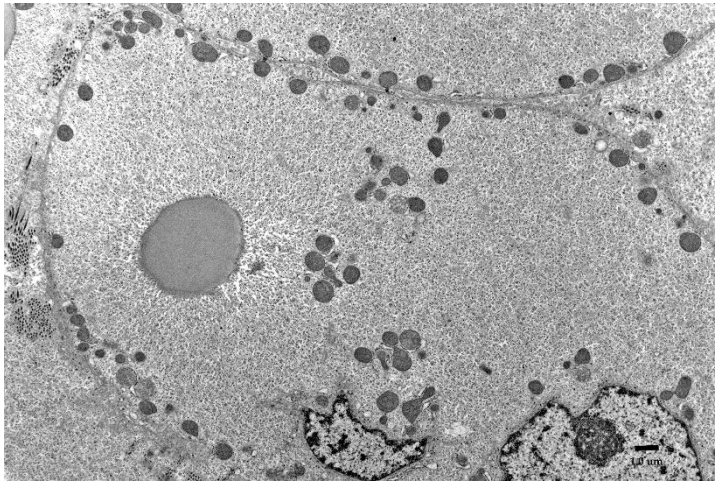
Supplemental Table 3. Clinical information for individuals with ASLD and liver transplantation at Texas Children's Hospital. HA = hyperammonemia. APRI = AST to platelet ratio = ((AST in U/L / 40 U/L) / Platelet count)

ID	Age at Transplant (yrs)	Mutations	History of HA	AST/ALT (units/L)	Platelets 10^9/L	APRI	Pathology[1]
1	5.9	Not available	Yes	278 / 797	411	1.69	Stage 4 Fibrosis; Glycogen Deposition
2	2.3	Not available	Yes	114 / 179	N/A	N/A	Stage 3 Fibrosis; Glycogen Deposition
3	1.7	Heterozygous p.Arg385Cys; Heterozygous p.Thr131Met	Yes	144 / 381	476	0.76	Stage 1 Fibrosis; Glycogen Deposition
4	2.6	Homozygous p.Gln354X	Yes	69 / 112	438	0.39	Stage 3-4 Fibrosis; Glycogen deposition



Supplemental Figure 1. International Normalized Ratio (INR) in UCDs. The percentage of participants with each disorder who had two or more INR values above the indicated threshold are shown. Abbreviations: OTCD = ornithine transcarbamylase deficiency; ASS1D = argininosuccinate synthetase deficiency; ASLD = argininosuccinate lyase deficiency; ARG1D = arginase deficiency; OTHER = other urea cycle disorders; M = male, F = female

A.



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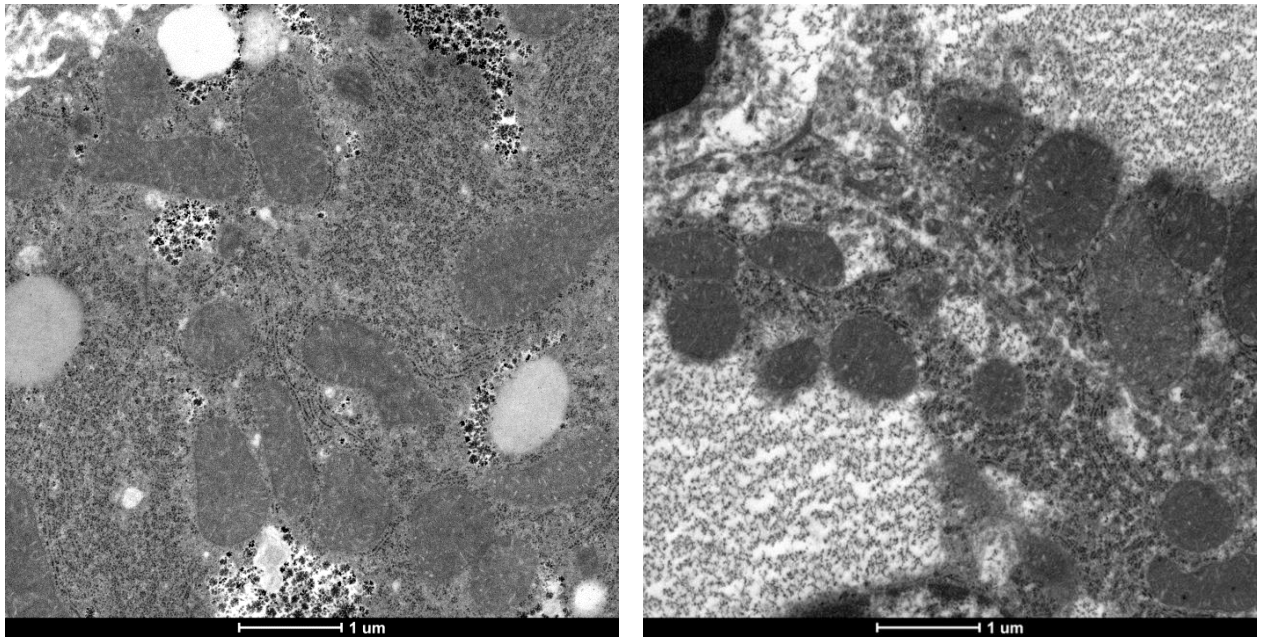
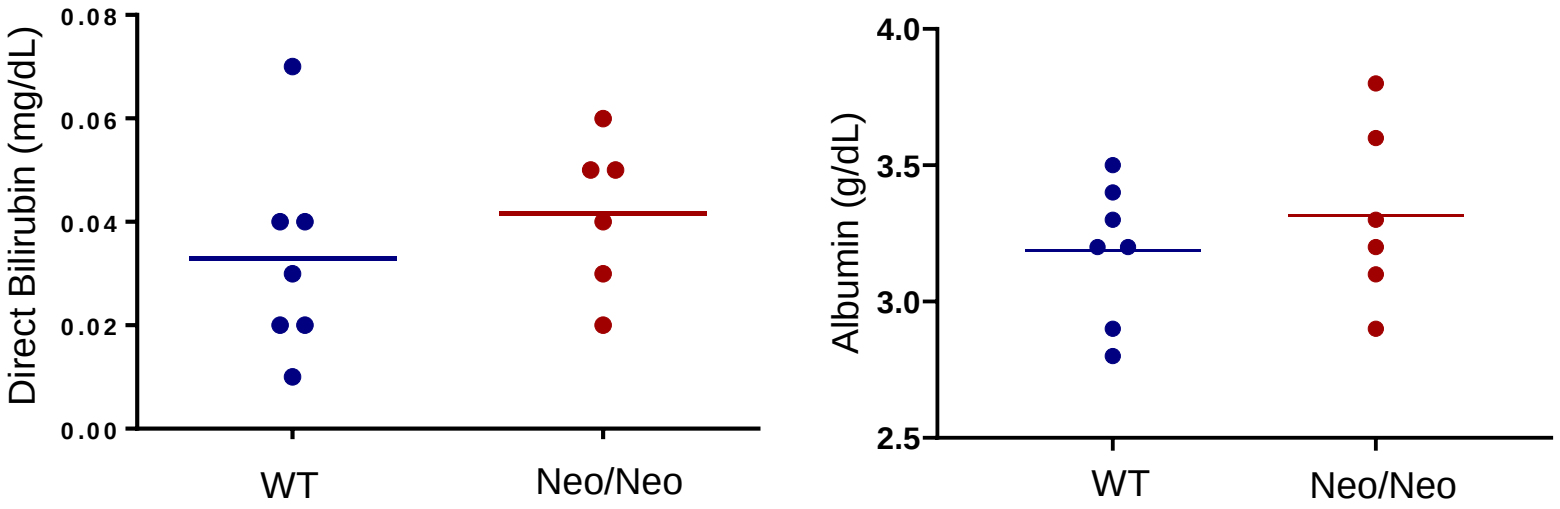
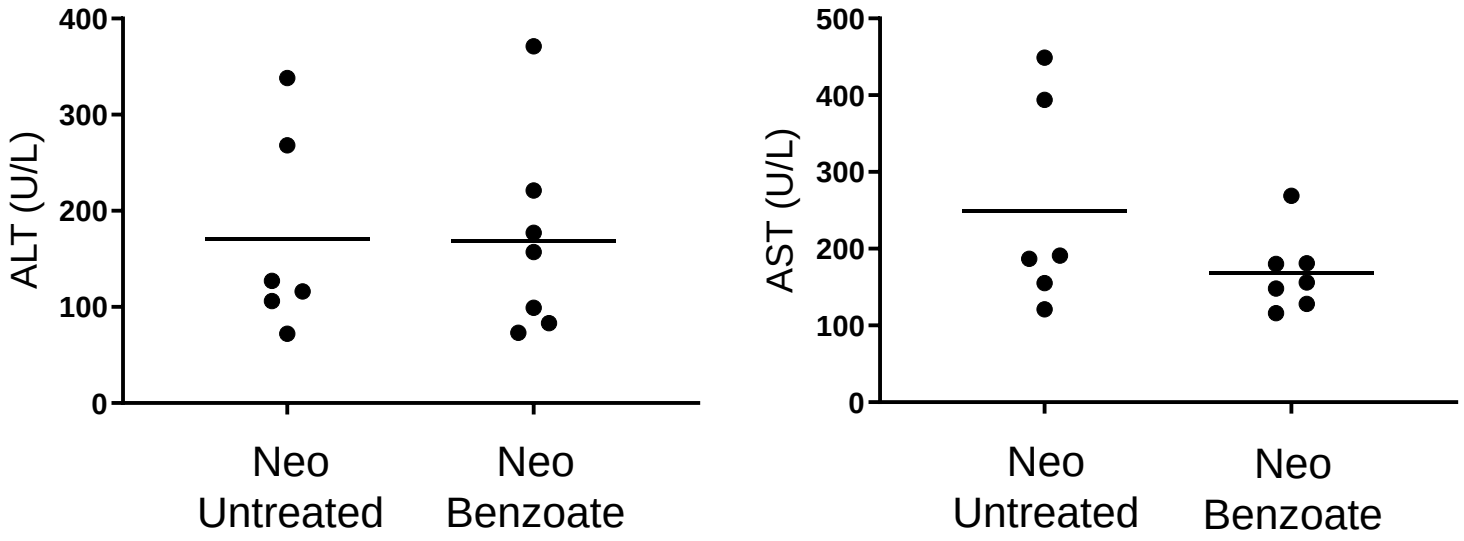


WT Neo

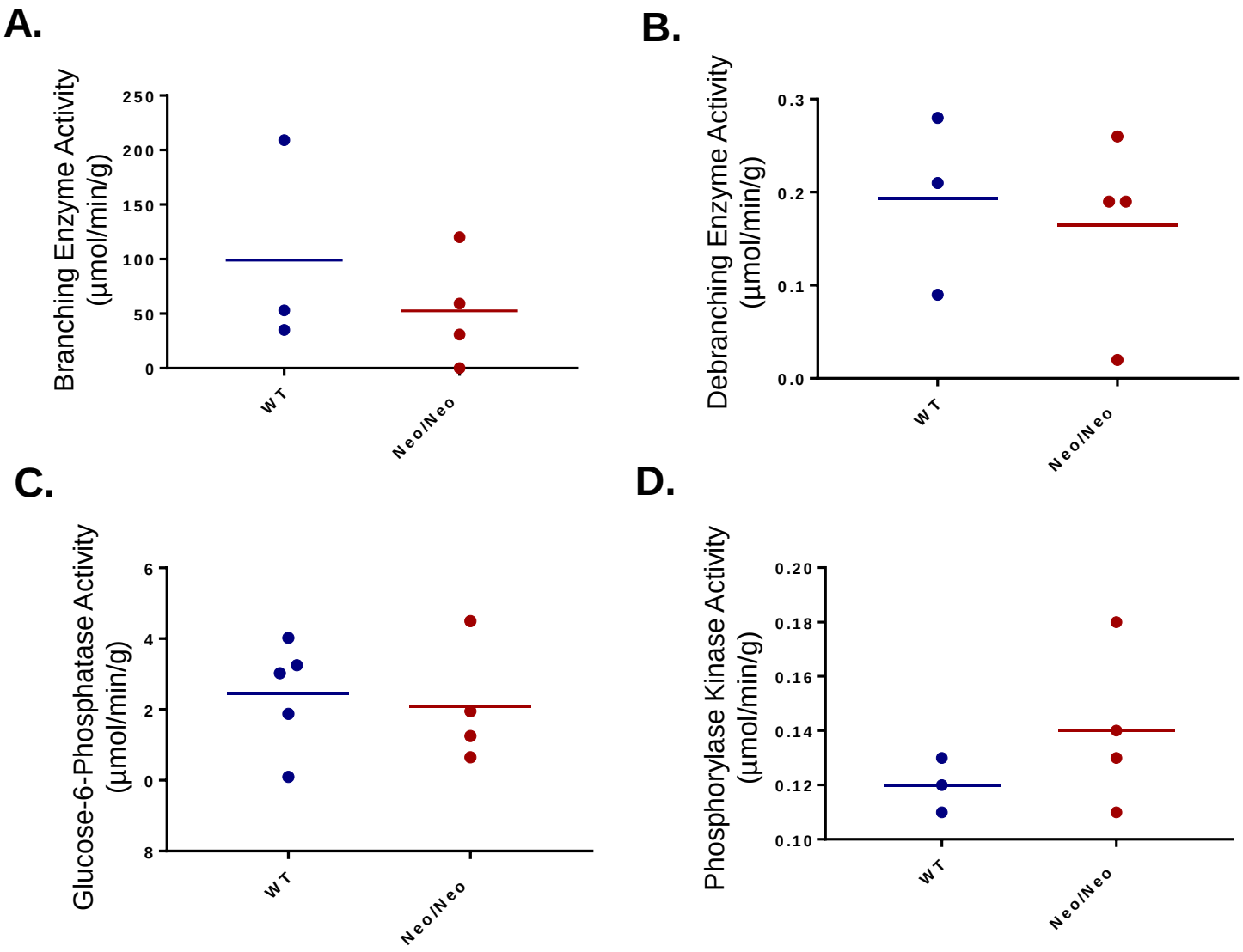
Supplemental Figure 2. A. Electron microscopy demonstrates glycogen deposition within hepatocytes in explant tissue from a 5 year 11 month old individual with ASLD. B. Electron microscopy demonstrates increased glycogen deposition within hepatocytes of *Asl*$^{Neo/Neo}$ mice causing displacement of organelles to the cell membrane. The hepatic glycogen in the wild-type mouse (WT) is more consistent with the alpha-rosette configuration whereas the hepatic glycogen in the *Asl*$^{Neo/Neo}$ mouse (Neo) appeared to be more consistent with beta-particles.



Supplemental Figure 3. Direct bilirubin and albumin are similar in wild-type (WT) vs. *Asl*$^{Neo/Neo}$ mice. A Student's independent two sample t-test was used for the analysis.



Supplemental Figure 4. Hepatic aminotransferase levels in *Asl*$^{Neo/Neo}$ mice treated with sodium benzoate and arginine supplementation in drinking water. Drinking water supplemented with sodium benzoate and arginine from the time of conception until completion of the study at 3-4 weeks of age. The mice were fasted for 3-4 hours prior to sample collection. A Student's independent two sample t-test was used for the comparison.



Supplemental Figure 5. Activity of enzymes involved in glycogen metabolism in liver tissue. A. Branching enzyme activity (3 hour fast). B. Debranching enzyme activity (3 hour fast). C. Glucose-6-phosphatase activity (3 hour fast). D. Phosphorylase kinase enzyme activity (3 hour fast). A Student's independent two sample t-test was used for the analyses.

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