

Supplemental Tables

Parent A	Parent B	Expected	Observed	<i>p</i> -value
<i>Htt^{fl/+};Alb^{cre/+}</i>	<i>Htt^{fl/+};Alb^{cre/+}</i>	2.1875	2	0.89
<i>Htt^{fl/+};Alb^{cre/+}</i>	<i>Htt^{fl/+};Alb^{cre/cre}</i>	4.375	1	0.11
<i>Htt^{fl/fl};Alb^{cre/cre}</i>	<i>Htt^{fl/+};Alb^{cre/cre}</i>	34.5	36	0.97

Table S1. Mendelian ratios with expected and observed homozygote pups. Pearson's chi-squared test *p*-values are reported for each pairing.

Tissue	<i>Htt</i> ^{+/+}	<i>Htt</i> ^{LKO/LKO}	<i>p</i> -value
Weight, g (SD)	26.5 (2.4)	24.4 (1.5)	0.04
Liver, mg (SD)	1128.2 (179.3)	1033.2 (195.8)	0.28
White adipose, mg (SD)	719.4 (239)	649 (150.8)	0.5
Brown adipose, mg (SD)	50.1 (8.3)	42.1 (6.8)	0.09
Spleen, mg (SD)	84.2 (16.7)	81.6 (16.7)	0.73
Brain, mg (SD)	495.5 (12.2)	496.2 (16.6)	0.92

Table S2. Organ weights from 13-month mice. Significant t-test values are in bold.

Analyte (Unit)	<i>Htt</i> ^{+/+}	<i>Htt</i> ^{LKO/LKO}	p-value
Glucose (mg/dL)	184.2	186.0	0.921
BUN (mg/dL)	17.7	22.8	0.002
Creatinine (mg/dL)	0.5	0.5	0.175
BUN:creatinine ratio	38.2	45.6	0.027
Phosphorus (mg/dL)	6.7	7.2	0.359
Total Protein (g/dL)	3.1	3.3	0.185
Albumin (g/dl)	1.5	1.6	0.465
Globulin (g/dL)	1.6	1.8	0.165
Alb:Glob ratio	1.0	0.9	0.363
Bilirubin (mg/dL)	0.1	0.2	0.123
GGT (U/L)	0.8	0.4	0.359
ALT (U/L)	105.5	114.6	0.886
AST (U/L)	214.8	229.5	0.838
AST:ALT ratio	3.1	2.5	0.440
Cholesterol (mg/dL)	41.2	55.6	0.003

Table S3. Analytes from clinical chemistry screen. Significant t-test comparisons ($p < 0.05$) are in bold. Abbreviations: blood urea nitrogen (BUN), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST).

Measure	<i>Htt</i> ^{+/+}	<i>Htt</i> ^{LKO/LKO}
Lipid accumulation	0	0
Hepatocyte swelling	0	0
Fibrosis	0	0
Necrosis	0	0
Immune cell infiltration	1	1
Total score	1	1

Table S4. Median liver pathology scores. Scores: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Analyte (Unit)	LLOQ	<i>Htt</i> ^{+/+}		<i>Htt</i> ^{LKO/LKO}		<i>p</i> -value
		6 mo	13 mo	6 mo	13 mo	
CCL6 (ng/mL)	0.039	5.91	7.11	10.24	8.11	0.029
CRP (ug/mL)	0.33	3.19	4.02	4.03	4.26	0.129
Eotaxin (pg/mL)	9.4	4458.33	3526.67	4048.89	2917.78	0.021
GCP-2 (ng/mL)	0.35	1.15	0.78	1.31	1.06	0.177
GM-CSF (pg/mL)	1.2	8.24	2.59	11.51	1.62	0.462
IL-12p40 (ng/mL)	0.85	18.28	16.88	16.74	17.28	0.818
IL-17A (pg/mL)	12	74.6	27.32	117.02	23.26	0.268
IL-1 α (pg/mL)	50	38.47	24.48	61.36	28.29	0.241
IL-28 (pg/mL)	6	71.7	10.23	86.12	9.99	0.529
IL-5 (pg/mL)	47	45.52	57.08	53.8	50.68	0.68
IP-10 (pg/mL)	23	58.45	52.82	63.44	44.58	0.15
KC/GRO (pg/mL)	6.7	89.62	67.92	61.16	63.69	0.096
MCP-1 (pg/mL)	19	28.37	23.53	29.36	44.7	0.115
M-CSF-1 (ng/mL)	0.06	0.61	0.52	0.52	0.47	0.248
MDC (pg/mL)	1.4	316.33	237.33	370.89	235.11	0.573
MIP-1 β (pg/mL)	0.88	10.83	11.98	11.01	10.84	0.599
MIP-1 γ (ng/mL)	0.17	13.13	12.87	13.79	14.46	0.141
MMP-9 (ng/mL)	1.2	4.64	4.92	4.15	10.76	0.373
SAP (ug/mL)	2.6	65.23	90.42	80.39	95.91	0.132
SCF (pg/mL)	62	140.48	118.62	168.78	99.06	0.997
TIMP-1 (ng/mL)	0.62	1	0.67	1.25	1.05	0.026
TNF α (pg/mL)	14	134.92	23.53	214.67	24.1	0.148
TSLP (pg/mL)	5.3	20.35	6.39	29.18	4.97	0.445
VCAM-1 (ng/mL)	2.2	593.67	715.83	603.78	846.89	0.053
VEGF-A (pg/mL)	4.2	11.31	11.27	13	9.28	0.851

Table S5. Analytes from rodent MAP4.0 (Ampersand Biosciences). Significant genotype ANOVA comparison ($p < 0.05$) are in bold. Abbreviations: Chemokine (C-C motif) ligand (CCL), C-reactive protein (CRP), Granulocyte Chemotactic Protein (GCP), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), interleukin (IL), interferon gamma-induced protein (IP), Growth-Regulated Protein alpha (KC/GRO), monocyte chemoattractant protein (MCP), macrophage colony-stimulating factor (M-CSF), macrophage-derived chemokine (MDC), macrophage inflammatory proteins (MIP), Matrix metalloproteinase (MMP), Serum Amyloid P component (SAP), Stem Cell Factor (SCF), tissue inhibitor of metalloproteinase (TIMP), Tumor Necrosis Factor (TNF), Thymic stromal lymphopoietin (TSLP), Vascular cell adhesion protein (VCAM), vascular endothelial growth factor-A (VEGF-A). Inflammation markers measured below lower limit of quantitation (LLOQ with LLOQ listed: IFN β (112 pg/mL), IFN γ (1.1 pg/mL), IL-10 (5.7 pg/mL), IL-12p70 (21 pg/mL), IL-18 (208 pg/mL), IL-1 β (3 pg/mL), IL-2 (11 pg/mL), IL-23 (35 pg/mL), IL-27 (28 pg/mL), IL-4 (2.8 pg/mL), IL-6 (3.9 pg/mL), IL-9 (132 pg/mL), Insulin (40 mUI/ml), MIP-1 α (221 pg/mL), PAI-1 (0.26 ng/mL), RAGE (0.42 ng/mL), TPO (0.046 ng/mL).

Experiment	Age	N/group	Sex	Statistical tests
Bodyweight	3-12 months	11 WT, 20 LKO	Female	Repeated measure ANOVA
Medelian ratio	1 month	See Table S1	Mixed	Pearson's chi-squared
HTT protein blots	12 month	4	Mixed	T-test, bonferroni adjustment
Organ weights	13 months	See Table S2	Female	T-test
Liver pathology scoring	6 months	5 WT, 11 LKO	Female	N/A
Plasma chemistry	6 months	11	Female	T-test
Bile acid measurement	2 months	163 WT, 34 LKO	Female	T-test
GTT	6, 13 months	10	Female	T-test
ITT	6, 13 months	10	Female	T-test
PTT	6, 13 months	10	Female	T-test
Liver blistering	3-9 months	variable	Mixed	N/A
RNAseq - DEGs	9 months	6	Female	Moderated T-test
EnrichR Pathways	9 months	6	Female	Odds ratio
IHC - CYP1A2	6-months	6	Male	T-test
IHC - CYP2E1	6-months	6	Male	T-test
IHC - CDH1	6-months	6	Male	T-test
IHC - CDH2	6-months	3	Male	T-test
APAP challenge	6-months	9 WT, 7 LKO	Male	T-test

Table S6. Summary of age, N, sex, and statistical test for each experiment.