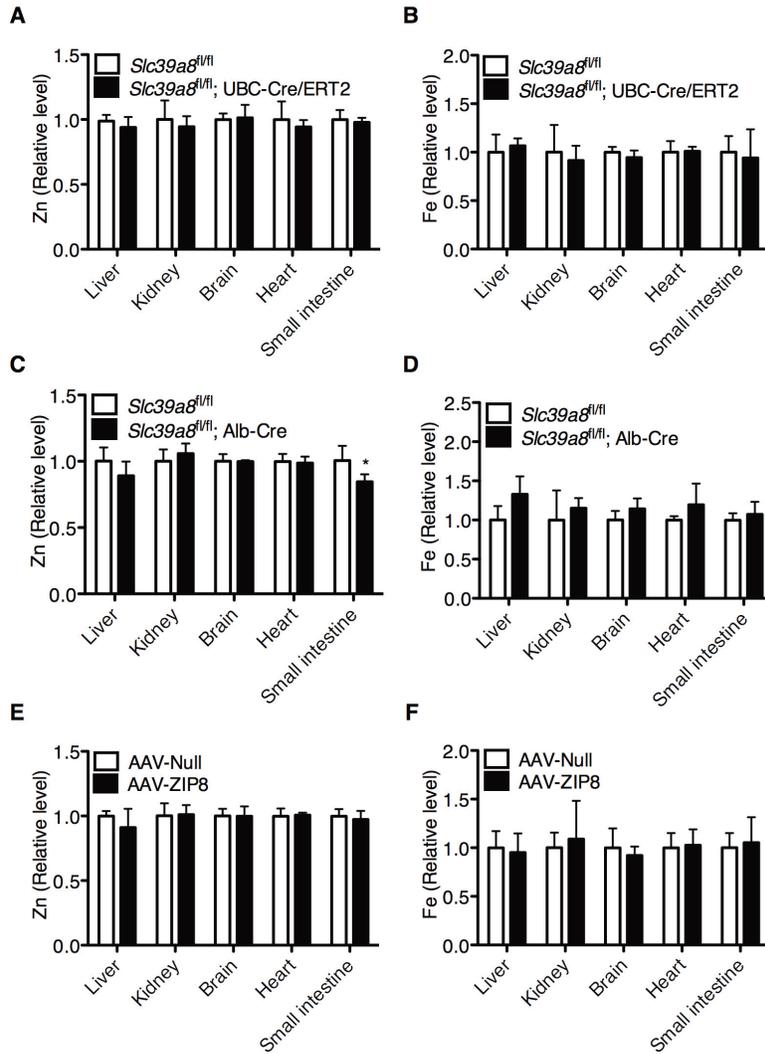
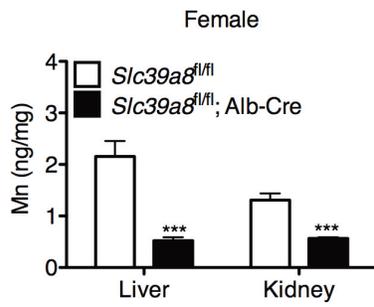


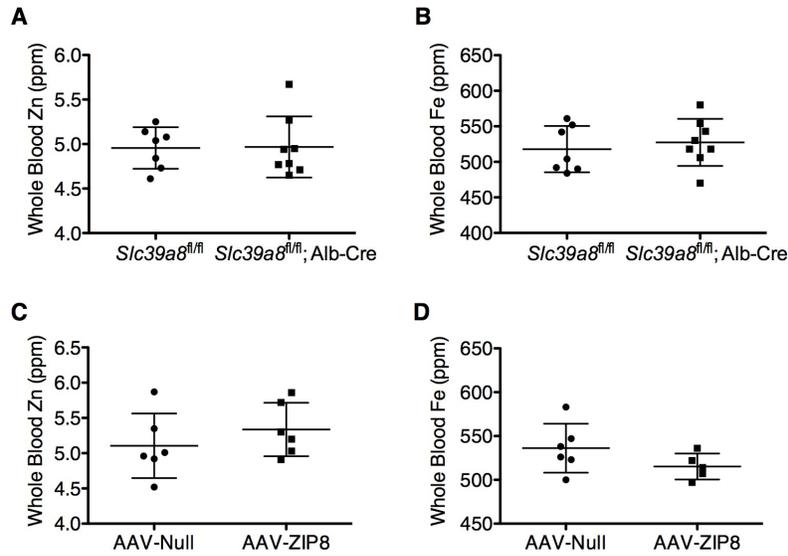
Supplementary Materials



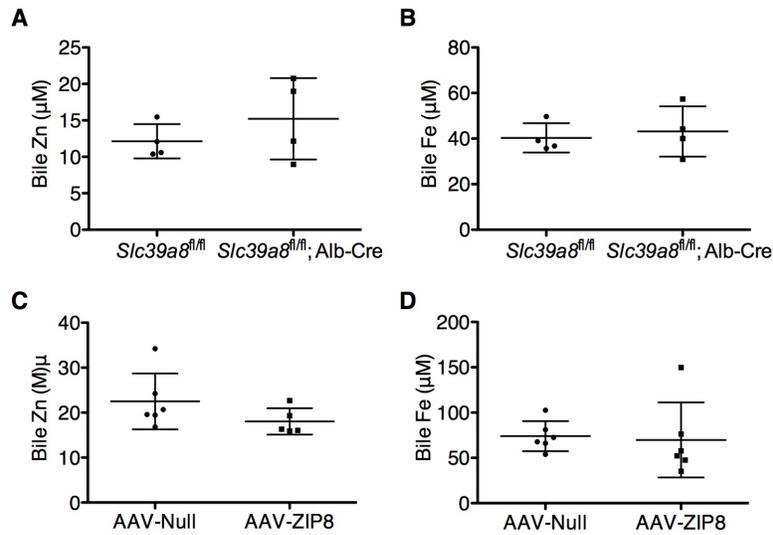
Supplementary Figure 1. Zn and Fe in *Slc39a8* mouse models (A and B) ICP-OES analysis of Zn and Fe in male *Slc39a8*^{fl/fl} and *Slc39a8*^{fl/fl}; UBC-Cre/ERT2 mice injected with tamoxifen at 8 weeks of age and sacrificed 5 weeks after the injection. N=6. (C-D) ICP-OES analysis of Zn and Fe in 12-14 weeks old male *Slc39a8*^{fl/fl} and *Slc39a8*^{fl/fl}; Alb-Cre mice. n=4. (E-F) ICP-OES analysis of Zn and Fe in male B6 mice injected with AAV-Null or AAV-ZIP8 at 10 weeks of age and sacrificed 4 weeks after injection. n=6. ICP-OES results were normalized to wet tissue weight. Zn and Fe levels were normalized to the average of the control group. Absolute Zn and Fe content can be found in supplementary table. All data are shown as the mean \pm SD.



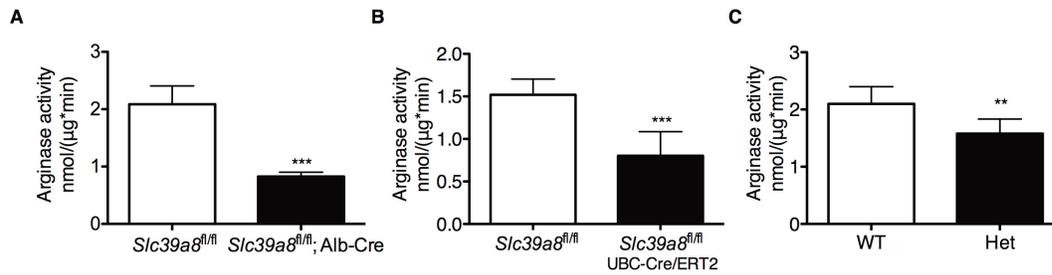
Supplementary Figure 2. ICP-OES analysis of hepatic Mn in 12-14 weeks old female *Slc39a8^{fl/fl}* and *Slc39a8^{fl/fl}; Alb-Cre* mice. n=3 and 6. ICP-OES results were normalized to wet tissue weight. All data are shown as the mean \pm SD. Results were analyzed using Student's t test (***) $p \leq 0.001$)



Supplementary Figure 3. Zn and Fe in the whole blood of *Slc39a8* liver-specific mouse models (A and B) ICP-MS analysis of Zn and Fe in the whole blood of 14-16 weeks old male *Slc39a8*^{fl/fl} and *Slc39a8*^{fl/fl}; Alb-Cre mice. n=7 and 8. (C and D) ICP-MS analysis of Zn and Fe in the whole blood of male B6 mice injected with AAV-Null or AAV-ZIP8 at 8 weeks of age and sacrificed 4 weeks after injection. n=6. All data are shown as the mean ± SD.



Supplementary Figure 4. Zn and Fe in the bile of *Slc39a8* liver-specific mouse models (A and B) ICP-MS analysis of Zn and Fe in the bile of 12-14 weeks old male *Slc39a8*^{fl/fl} and *Slc39a8*^{fl/fl}; Alb-Cre mice. N=4. (C and D) ICP-MS analysis of Zn and Fe in the bile of male B6 mice injected with AAV-Null or AAV-ZIP8 at 8 weeks of age and sacrificed 4 weeks after injection. n=6. All data are shown as the mean \pm SD.



Supplementary Figure 5. Arginase activity in the liver of *Slc39a8* mouse models (A)

Arginase activity in the liver of 12-14 weeks old female *Slc39a8^{fl/fl}* and *Slc39a8^{fl/fl}; Alb-Cre* mice. N=3 and 6. (B) Arginase activity in the liver of male *Slc39a8^{fl/fl}* and *Slc39a8^{fl/fl}; UBC-Cre/ERT2* mice injected with tamoxifen at 8 weeks of age and sacrificed 5 weeks after the injection. N=6. (C) Arginase activity in the liver of 12-14 weeks old male WT and Zip8 Het mice. n=6. All data are shown as the mean ± SD. Comparisons were performed using Student's t test. *** $p \leq 0.001$, ** $p \leq 0.01$.

Supplementary Table. Mn, Zn and Fe levels in liver, kidney, brain, heart and small intestine of *Slc39a8* mouse models

	Mn (ng/mg)		Zn (ng/mg)		Fe (ng/mg)	
	WT	Zip8 iKO	WT	Zip8 iKO	WT	Zip8 iKO
Liver	1.57±0.12	0.36±0.03 ^a	29.6±1.4	28.2±2.4	74.0±13.6	78.8±5.7
Kidney	1.12±0.09	0.54±0.03 ^a	18.8±2.7	17.7±1.5	43.3±12.2	39.7±6.6
Brain	0.39±0.02	0.27±0.02 ^a	15.2±0.7	15.4±1.5	16±0.9	15.1±1.2
Heart	0.97±0.16	0.71±0.08 ^b	16.0±2.2	15.1±0.8	72.0±8.3	72.6±3.4
Small intestine	1.51±0.33	1.23±0.36	17.6±1.3	17.2±0.6	15.5±2.6	14.6±4.6

	Mn (ng/mg)		Zn (ng/mg)		Fe (ng/mg)	
	WT	Zip8 Het	WT	Zip8 Het	WT	Zip8 Het
Liver	1.38±0.23	0.85±0.07 ^a	28.0±1.1	27.9±2.0	44.1±2.0	54.0±4.5
Kidney	1.38±0.10	0.94±0.05 ^b	17.3±0.5	16.8±1.0	40.4±6.5	38.2±5.5
Brain	0.38±0.03	0.29±0.01 ^b	13.3±0.1	13.7±0.6	13.3±1.3	13.3±1.4
Heart	0.55±0.05	0.47±0.02 ^c	14.2±1.2	15.0±0.5	55.0±7.0	70.1±9.7
Small intestine	1.18±0.14	1.58±0.16 ^b	16.3±0.5	16.1±1.1	11.9±2.2	12.0±2.8

	Mn (ng/mg)		Zn (ng/mg)		Fe (ng/mg)	
	WT	Zip8 LSKO	WT	Zip8 LSKO	WT	Zip8 LSKO
Liver	1.49±0.19	0.46±0.04 ^a	27.6±2.9	24.6±3.0	41.4±7.3	55.0±9.5
Kidney	1.39±0.08	0.71±0.14 ^a	15.3±1.3	16.2±1.2	35.9±13.6	41.3±4.6
Brain	0.32±0.01	0.21±0.02 ^a	11.7±0.6	11.6±0.1	12.6±1.5	14.4±1.7
Heart	0.53±0.06	0.28±0.05 ^a	14.0±0.8	13.8±0.7	47.3±2.3	56.5±12.9
Small intestine	1.05±0.04	1.08±0.13	18.1±2.0	15.2±1.0 ^c	10.2±0.9	10.9±1.6

	Mn (ng/mg)		Zn (ng/mg)		Fe (ng/mg)	
	AAV-Null	AAV-ZIP8	AAV-Null	AAV-ZIP8	AAV-Null	AAV-ZIP8
Liver	1.30±0.15	2.45±0.26 ^a	28.4±1.1	25.9±4.1	61.4±10.6	58.3±12.1
Kidney	1.26±0.16	1.54±0.05 ^b	16.4±1.6	16.6±1.2	34.7±5.4	37.8±13.6
Brain	0.33±0.01	0.41±0.04 ^b	12.1±0.7	12.1±0.9	16.4±3.3	15.1±1.5
Heart	0.58±0.04	0.71±0.01 ^a	15.1±0.9	17.3±5.0	63.8±9.7	65.5±10.4
Small intestine	1.01±0.15	1.29±0.26 ^c	15.7±0.9	15.3±1.0	12.9±1.9	13.6±3.4

^ap<0.001; ^bp<0.01; ^cp<0.05

Zip8 iKO and the control WT mice were male, and they were injected with tamoxifen at 8 weeks of age and sacrificed 5 weeks after the injection. N=5-6.

Zip8 Het and the control WT mice were 12-14 weeks old male mice. N=4-5.

Zip8 LSKO and the control WT mice were 12-14 weeks old male mice. N=4.

AAV-ZIP8 and the control AAV-Null mice were male, and they were injected with AAV8 at 10 weeks of age and sacrificed 4 weeks after injection. N=5-6.