The manganese efflux transporter SLC30A10 is essential for gastrointestinal manganese excretion

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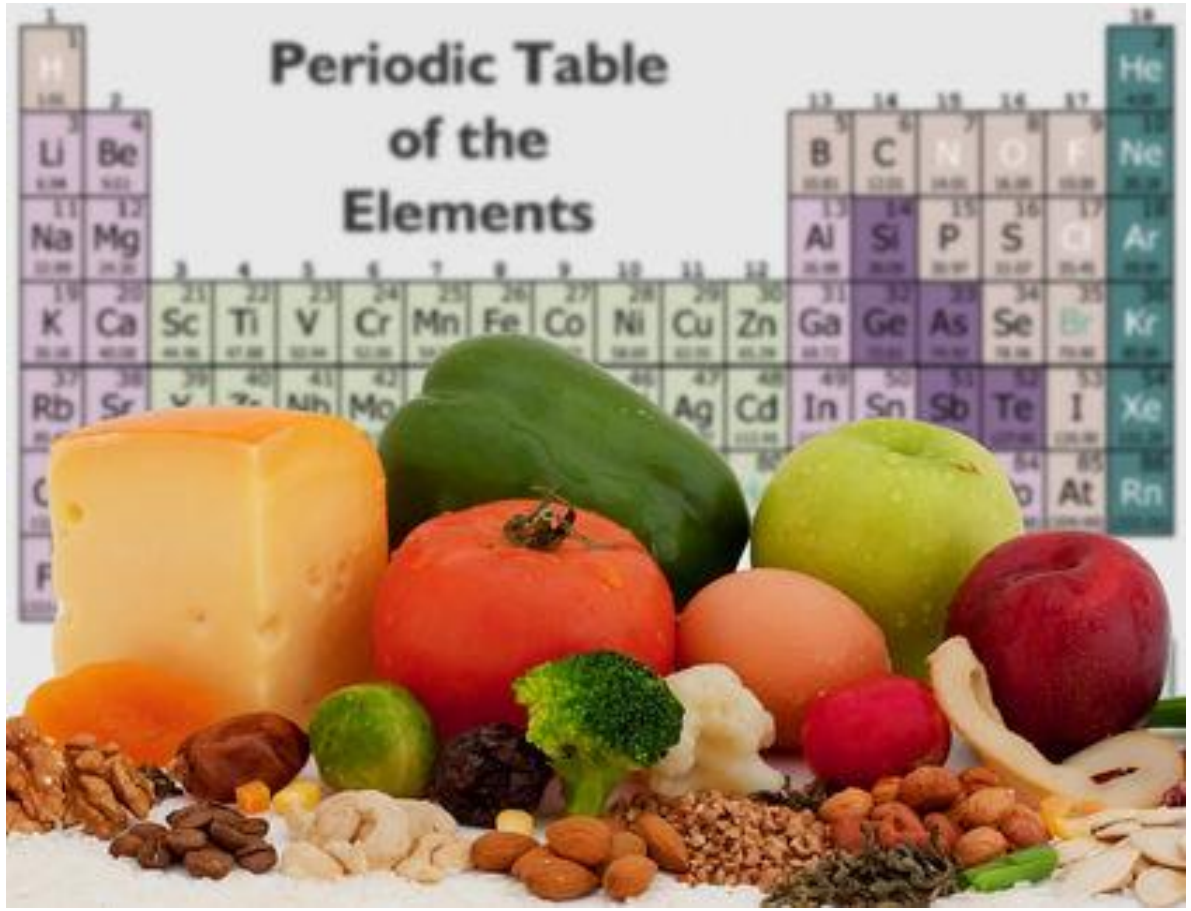
Acquisition of Manganese (Mn)



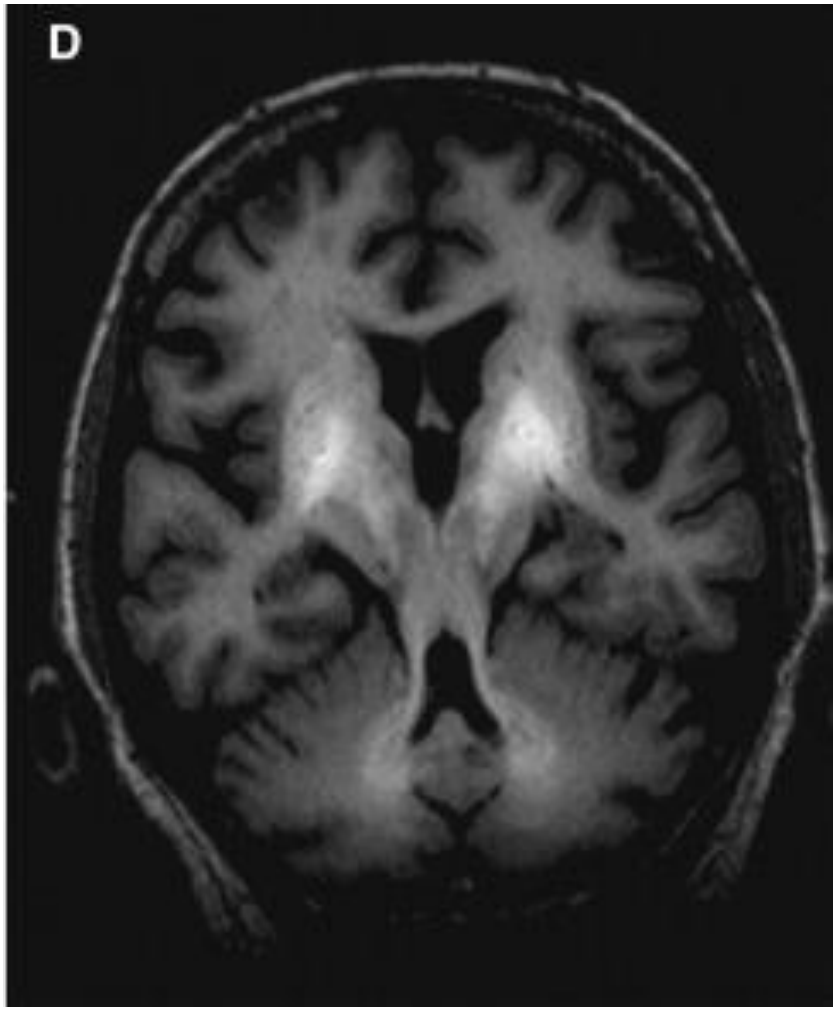
http://www.chemistryexplained.com/elements/L-P/Manganese.html

- Cofactor of essential proteins
- Oxidant defense, bone growth, immunity
- Men and women require 2.3 and 1.8 mg/day, respectively
- Plentiful dietary sources
- Only 3-5% of dietary Mn is absorbed
- Mn deficiency is very rare
- Mn related diseases are often diseases of excess

Manganese in excess is toxic

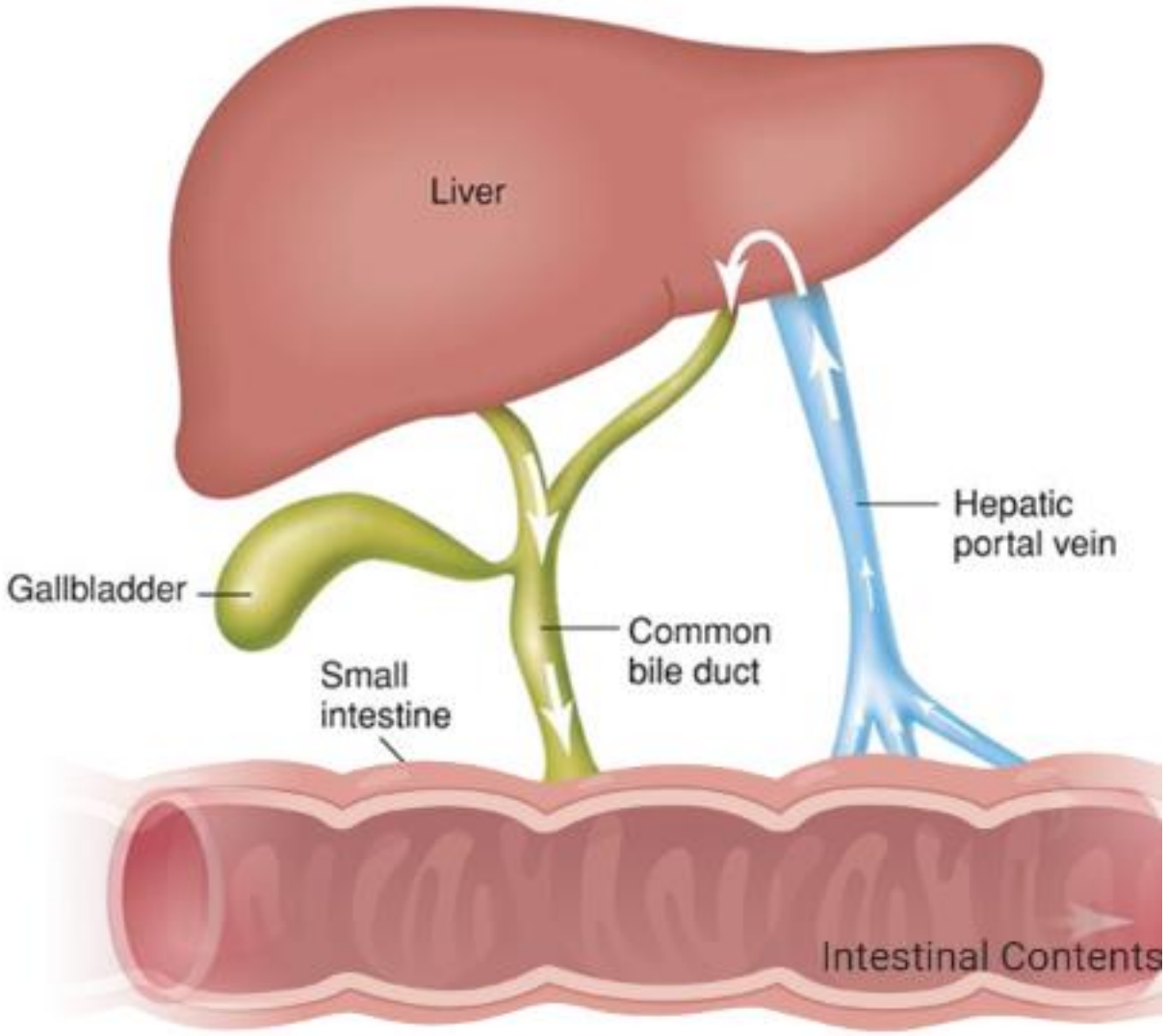
- Mitochondrial dysfunction, compromised antioxidant defense mechanisms

- Manganism: Parkinson's- like disorder
  - Behavioral changes, slow and clumsy movements, tremors, cock-walk gait



Quadri et al., 2012. *J. Human Genetics*

Physiological Mechanisms of Mn Homeostasis



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Manganese excess: Acquired vs. Inherited

[Mn]

Deficiency

inherited

SLC39A8 Deficiency

acquired

?

Sufficiency

Excess

acquired

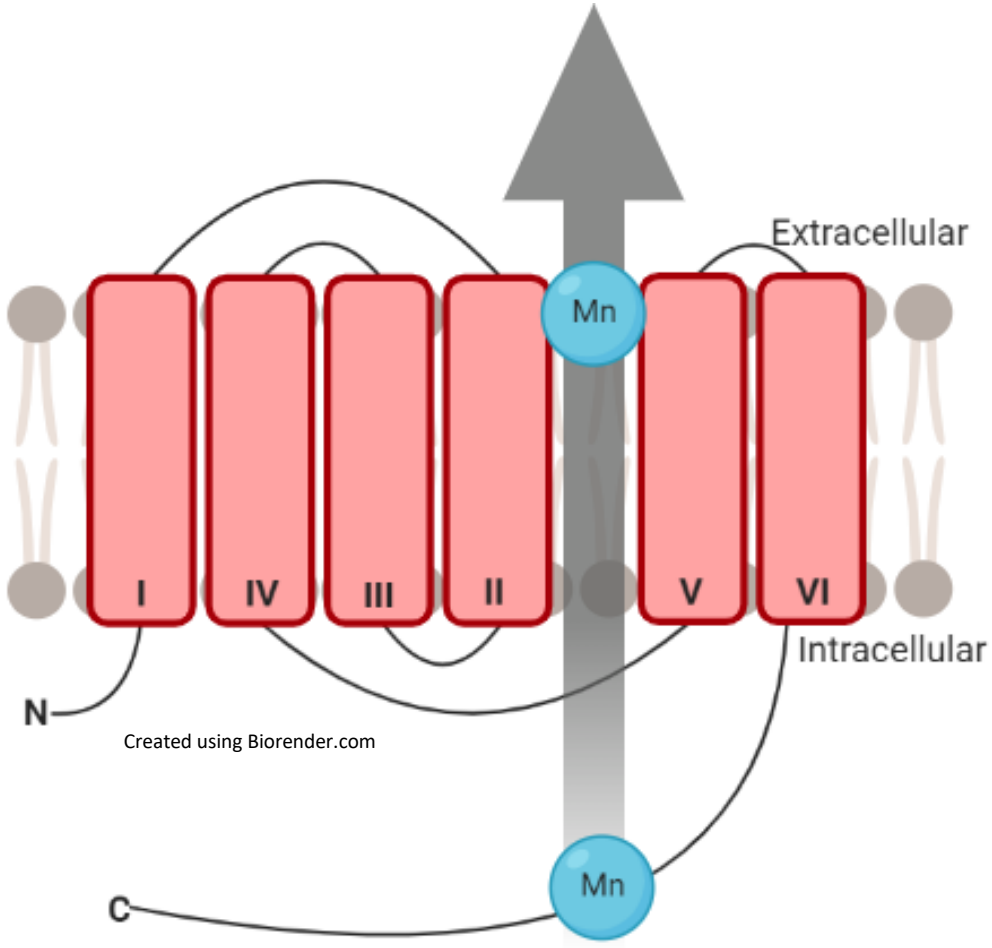
Occupational

inherited

SLC30A10 or SLC39A14 Deficiency

Park et al 2015 Am J Hum Genet; Tuschl et al 2016 Nat Commun

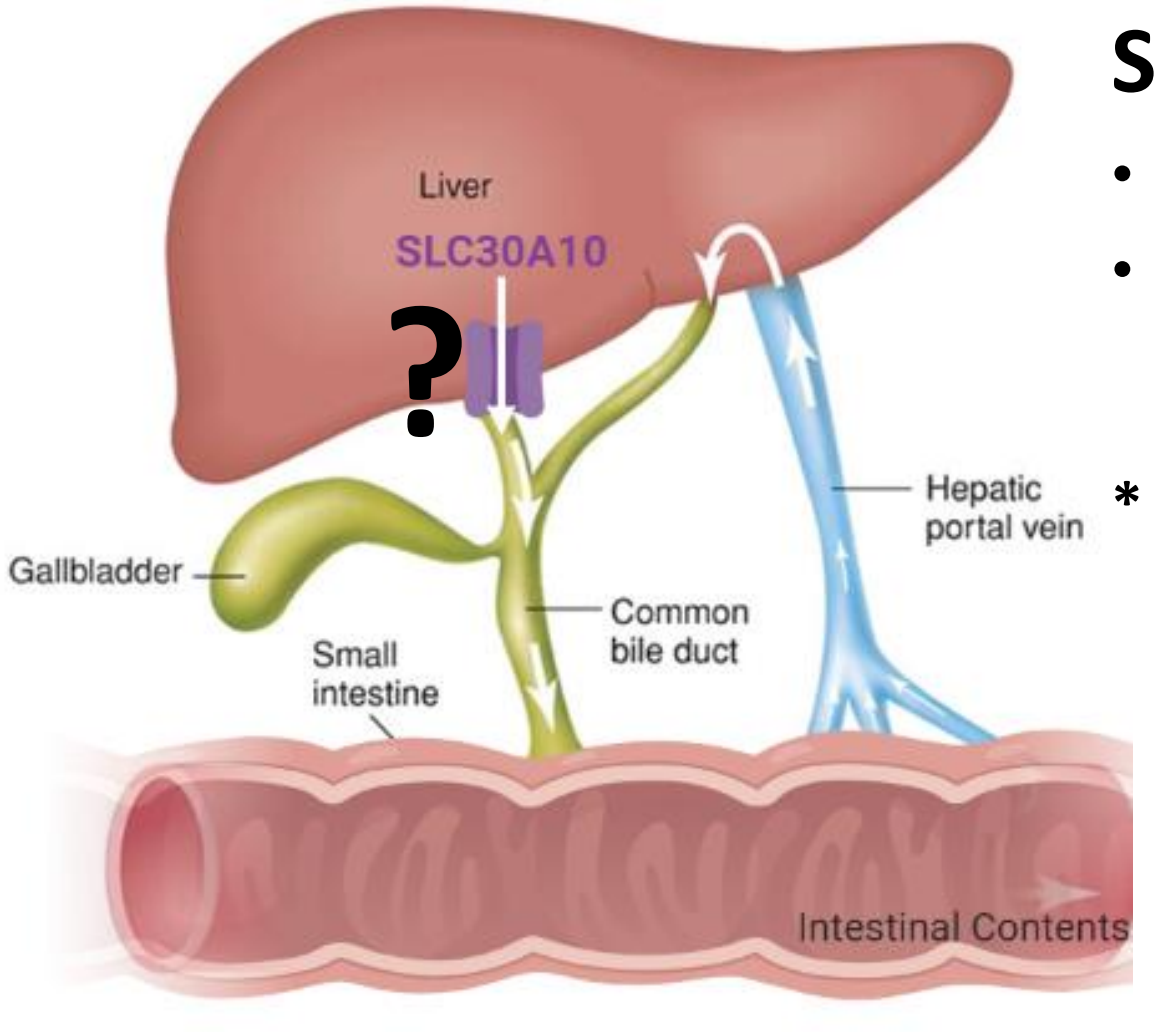
Manganese excess: Acquired vs. **Inherited**



SLC30 family of proteins

- Originally thought to be a zinc transporter (Znt10)
- SLC30 proteins- cation diffusion facilitator superfamily of metal transporters
  - Transport divalent metal cations (Fe, Zn, Cu, Ni, Co, Cd, Mn)
  - Efflux metals from cytosol to extracellular space
- 6 transmembrane domains with a cytoplasmic N and C termini

Manganese excess: Acquired vs. **Inherited**



SLC30A10 deficiency

- Autosomal recessive
- Mutations in ***SLC30A10*** identified in patients with hepatic cirrhosis, polycythemia, manganism, and high Mn levels

*** No history of environmental Mn exposure**

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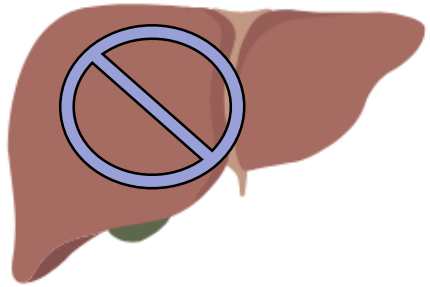
Generating Slc30a10-deficient mice

Whole body Slc30a10 deficiency

Slc30a10$^{KO/KO}$

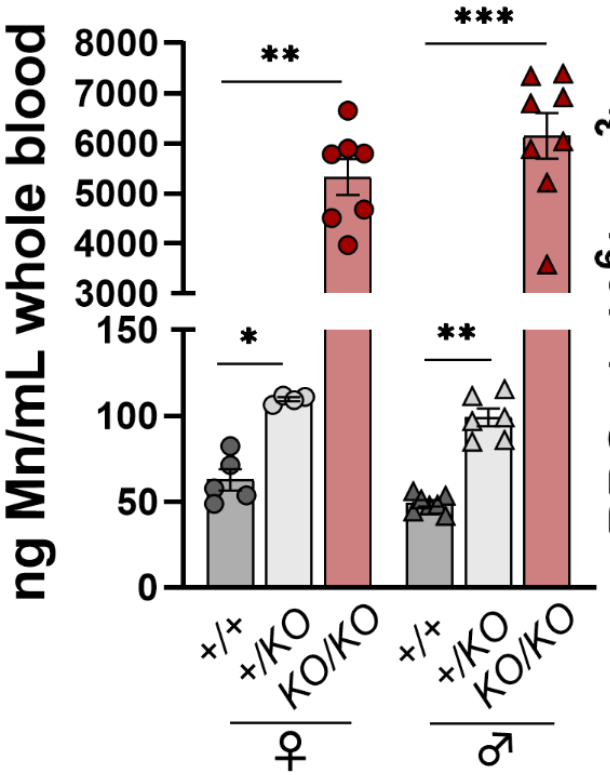
Hepatic
Slc30a10 deficiency

Slc30a10$^{lox/lox}$ Alb

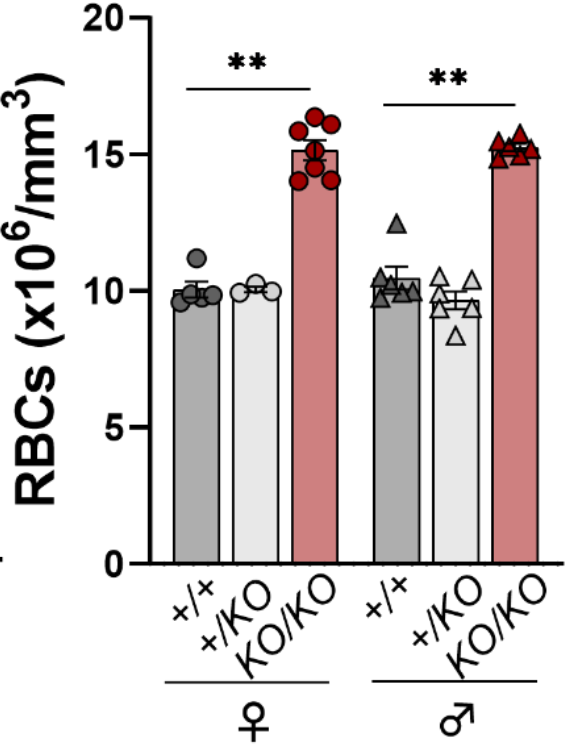


Slc30a10-deficient mice recapitulate human disease phenotypes

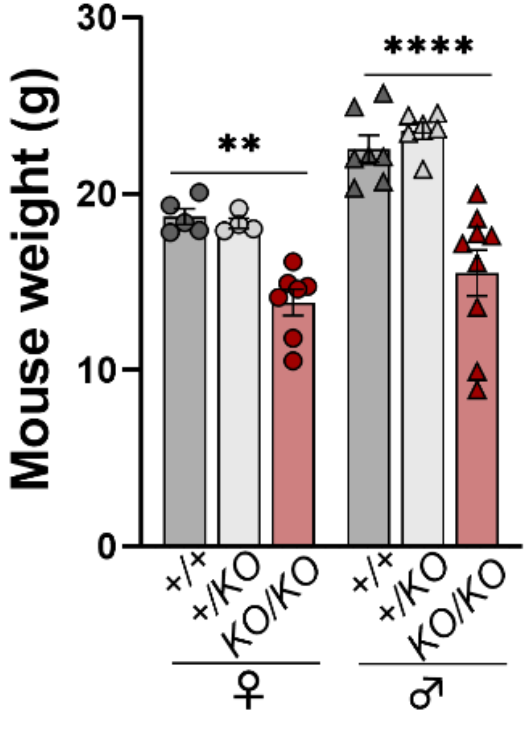
Hypermanganesemia

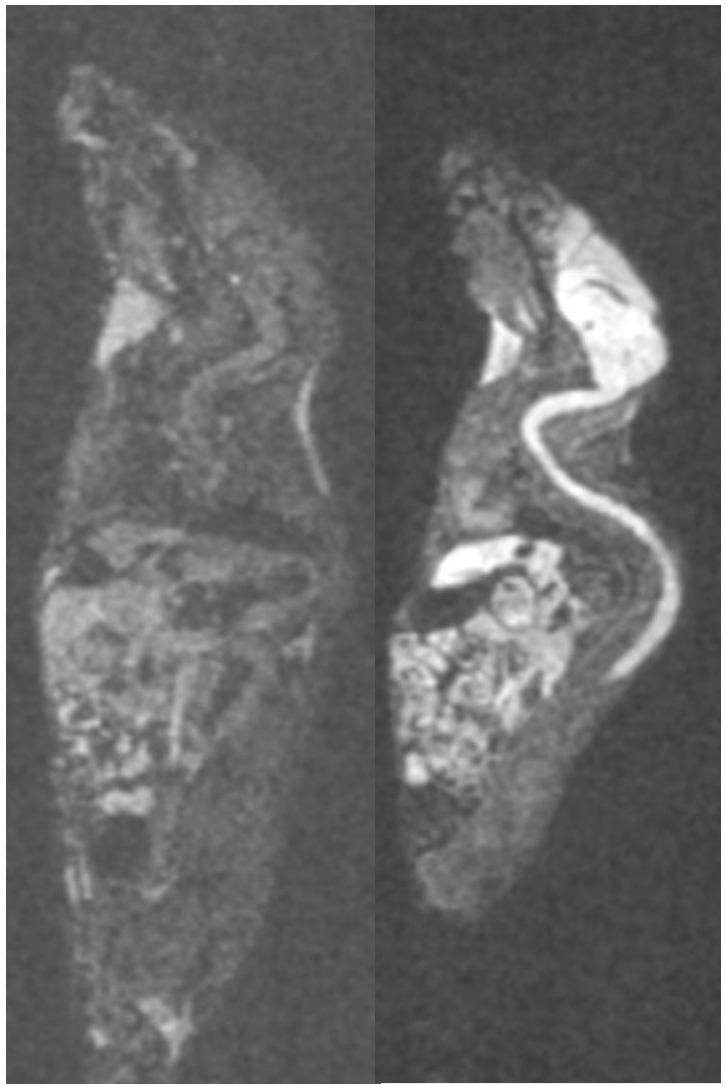


Polycythemia

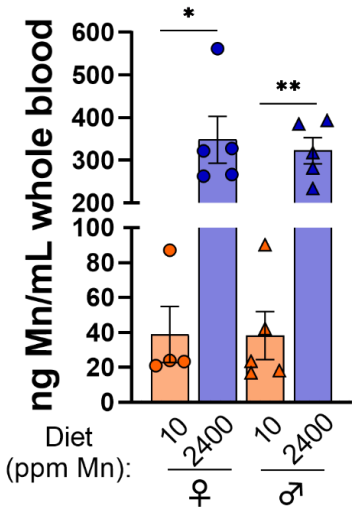


Decreased weight



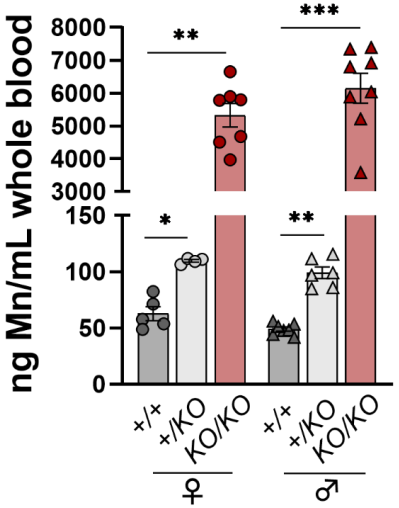


Wild-type mice on high Mn diet accumulated high Mn levels

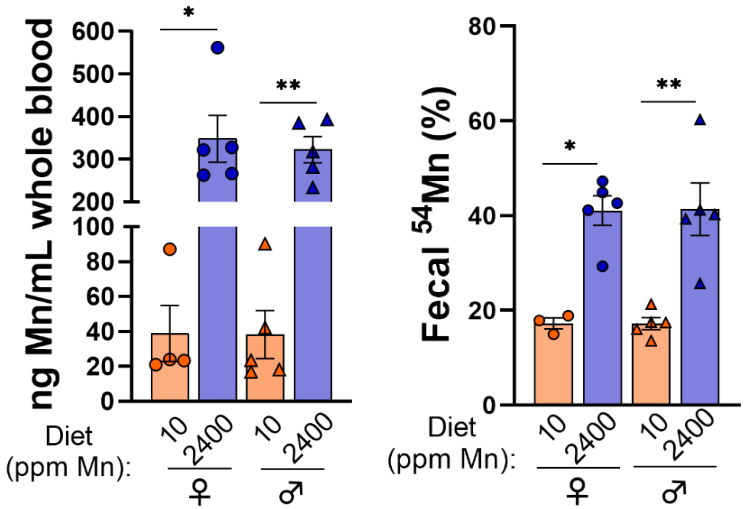


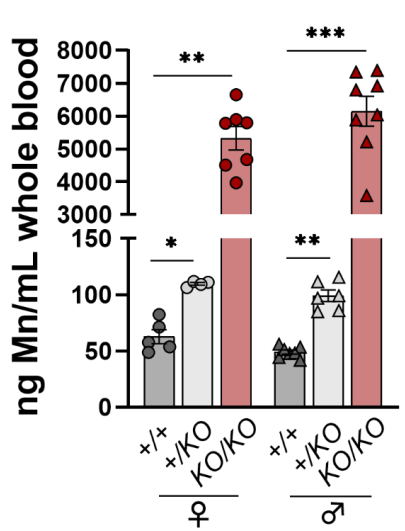
Control Mn diet
10 ppm

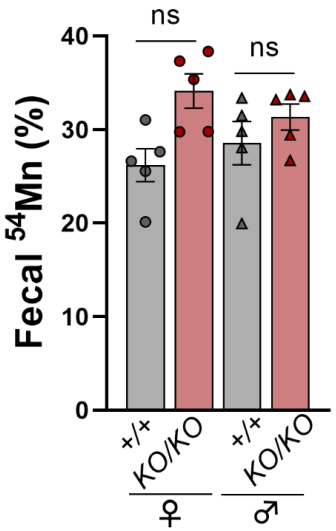
High Mn diet
2400 ppm



Slc30a10-deficient mice have impaired Mn excretion







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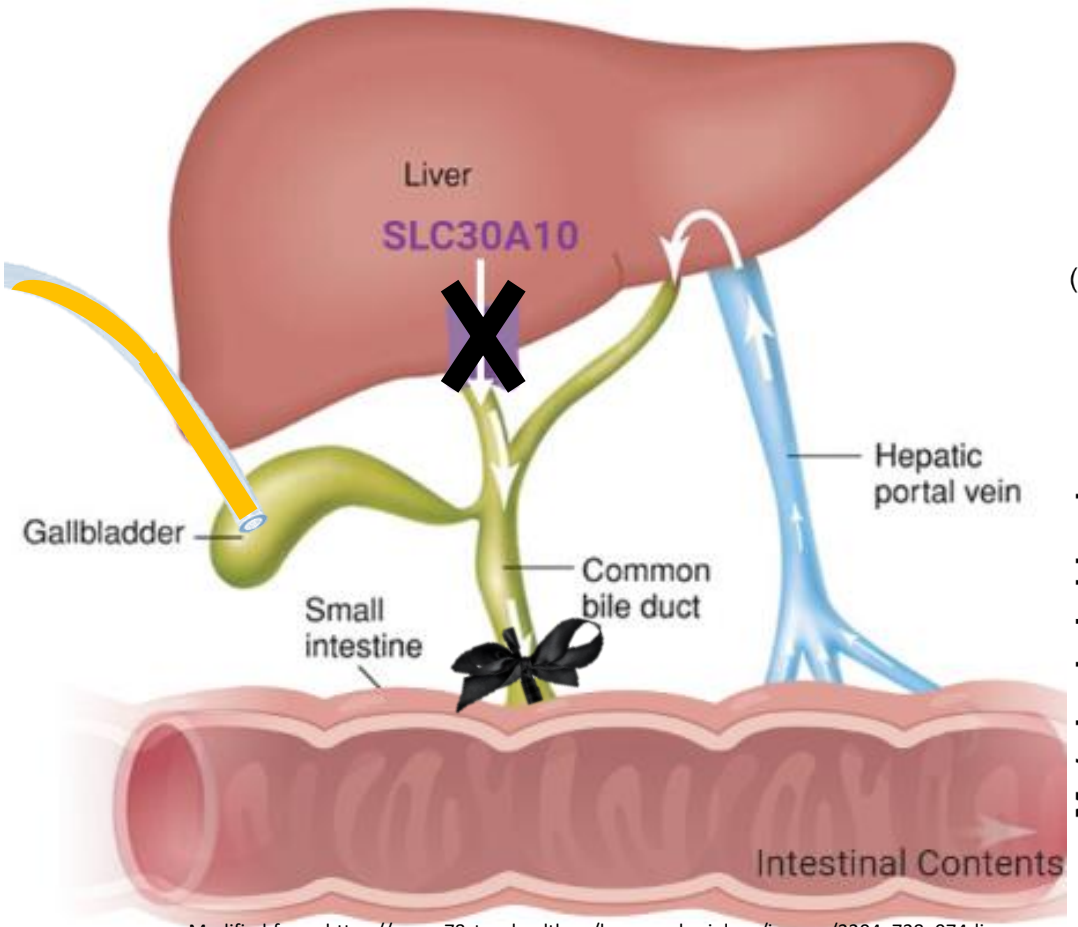
Slc30a10-deficient mice have impaired Mn excretion



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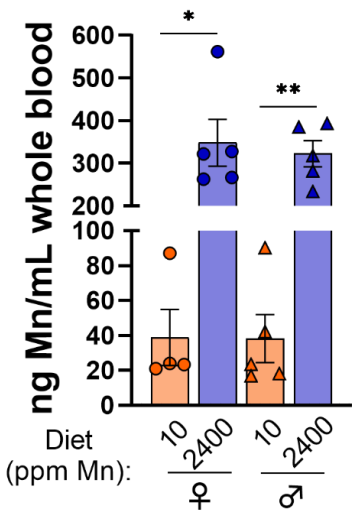
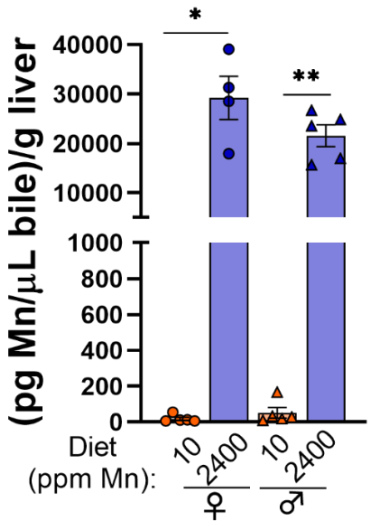
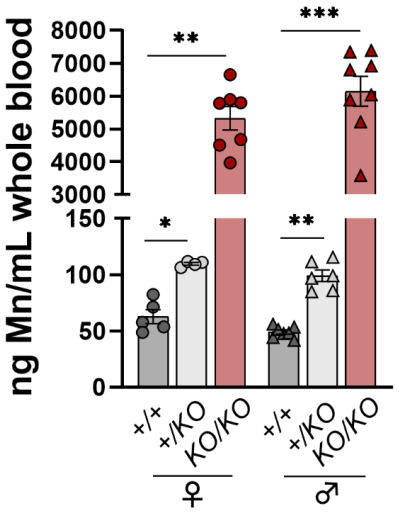
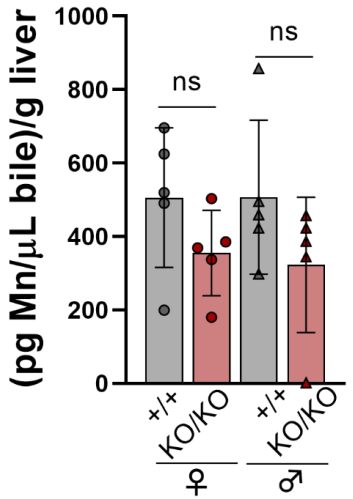




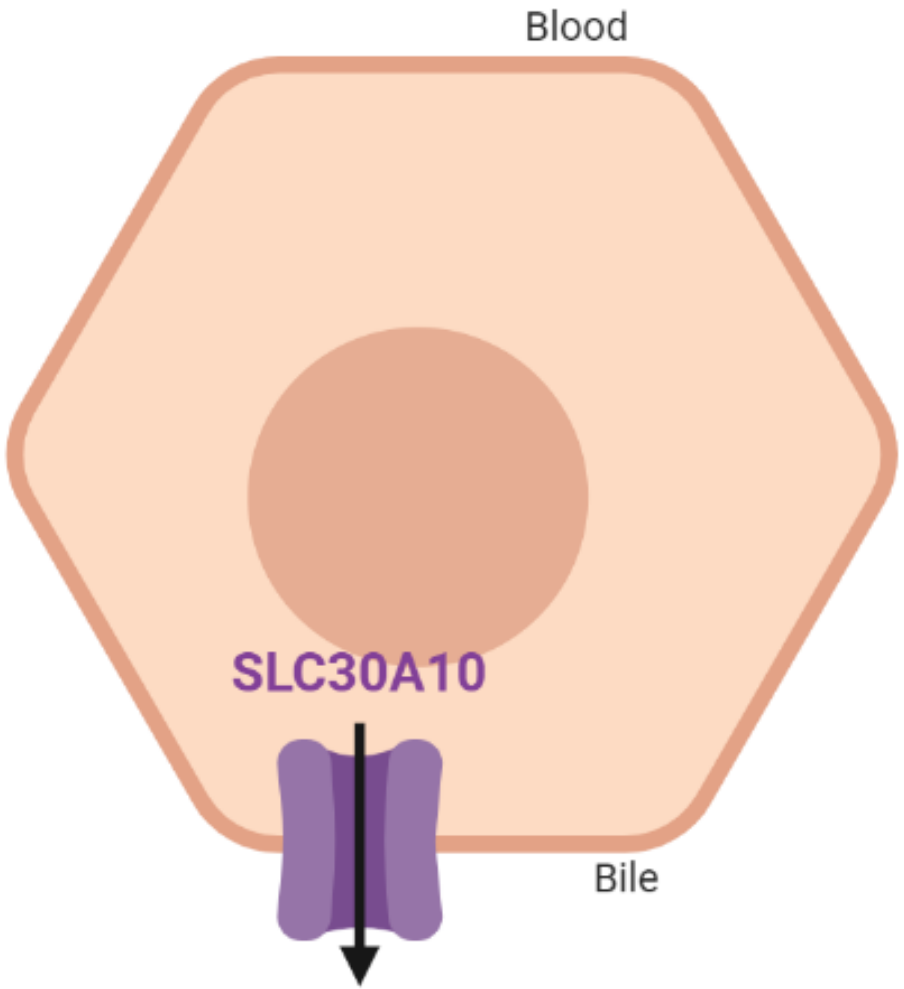




Control Mn diet
10 ppm

High Mn diet
2400 ppm

Hepatic-Slc30a10 deficiency leads to minimal Mn excess



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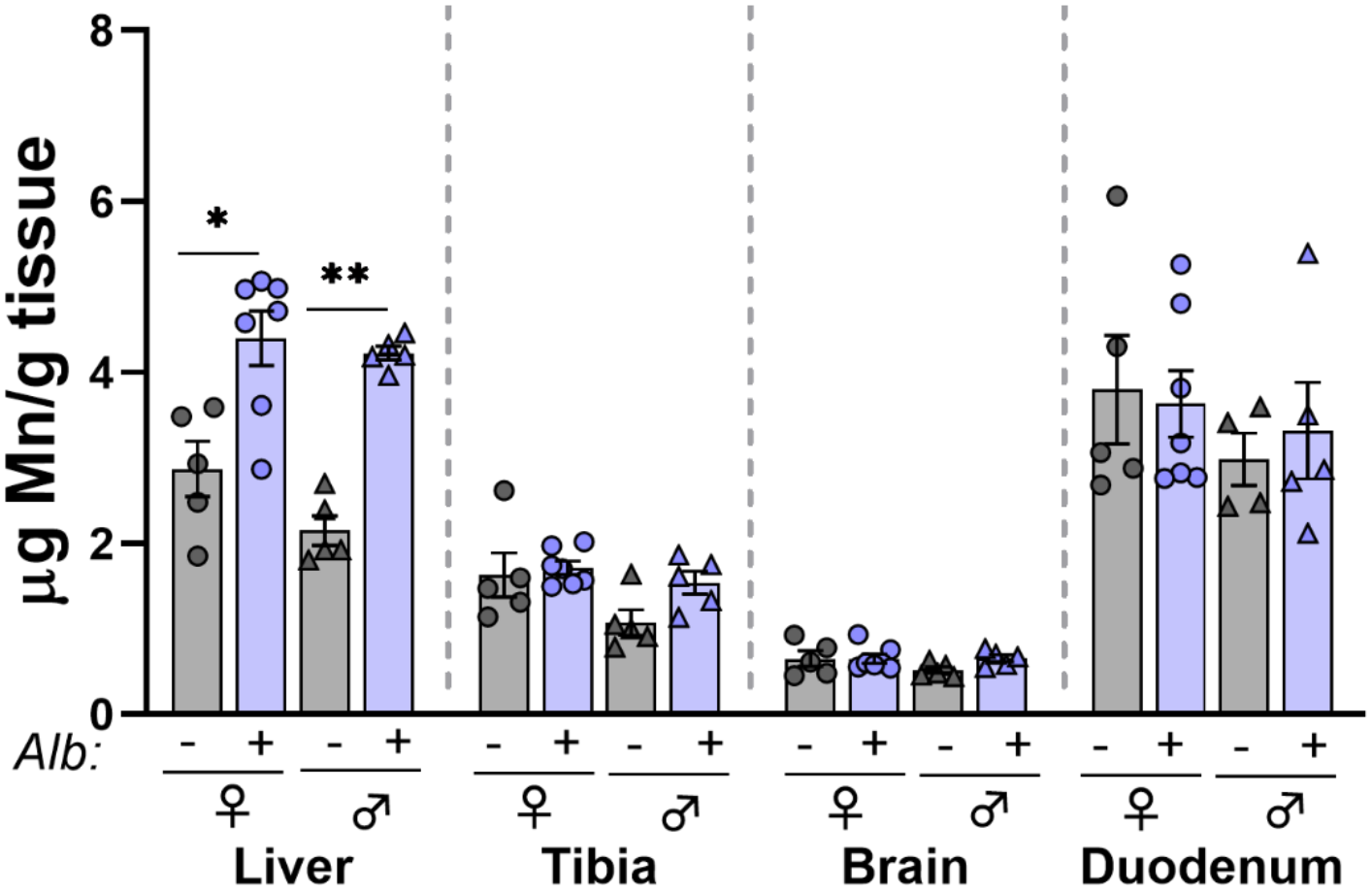
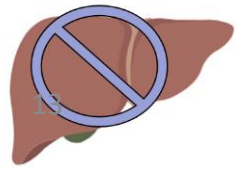
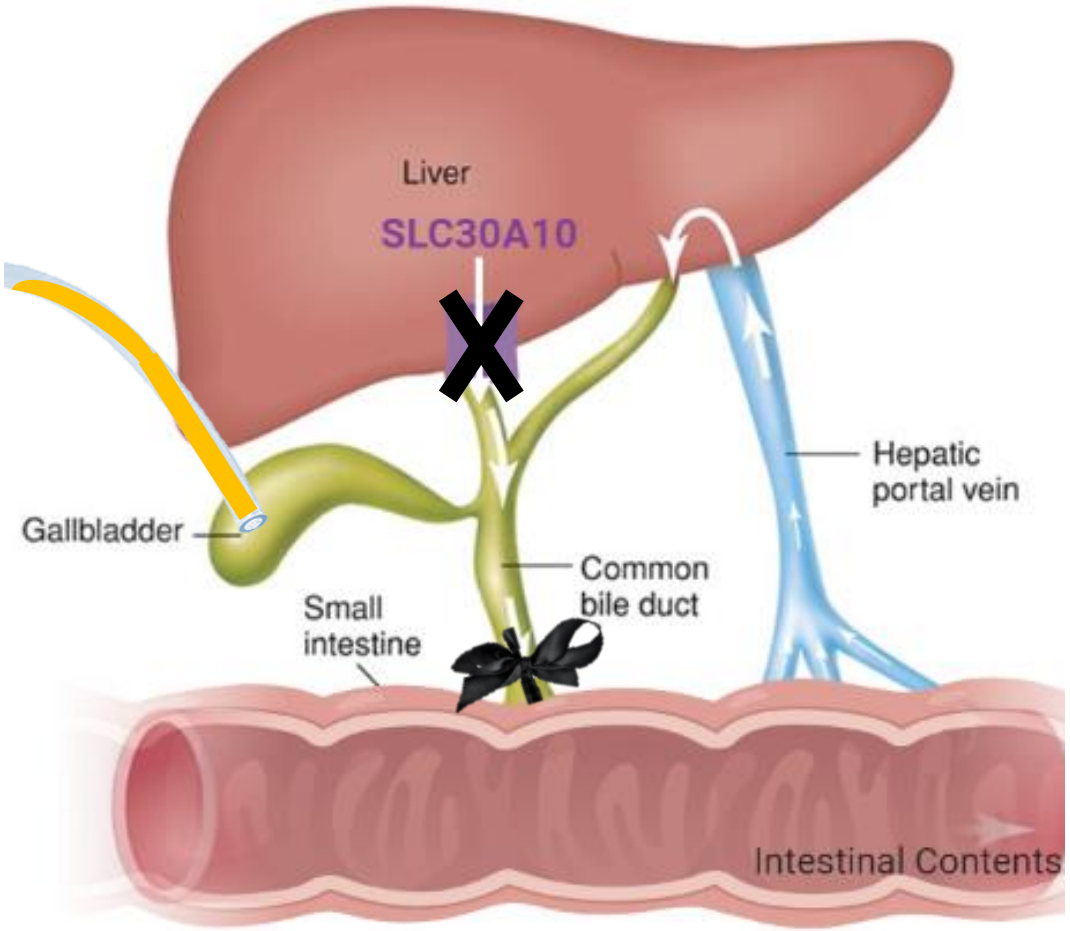




Hepatic Slc30a10-deficient mice have impaired biliary Mn excretion, but minimal Mn excess



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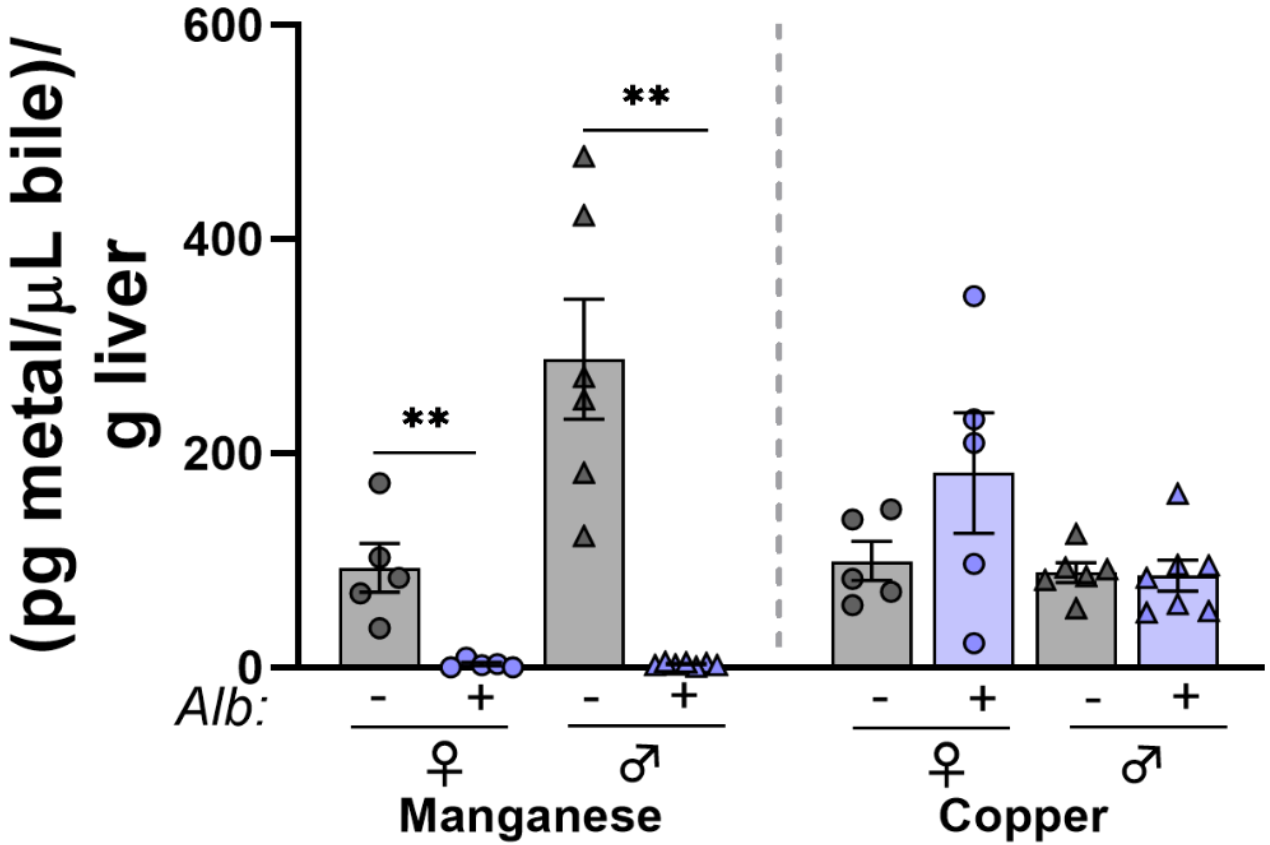
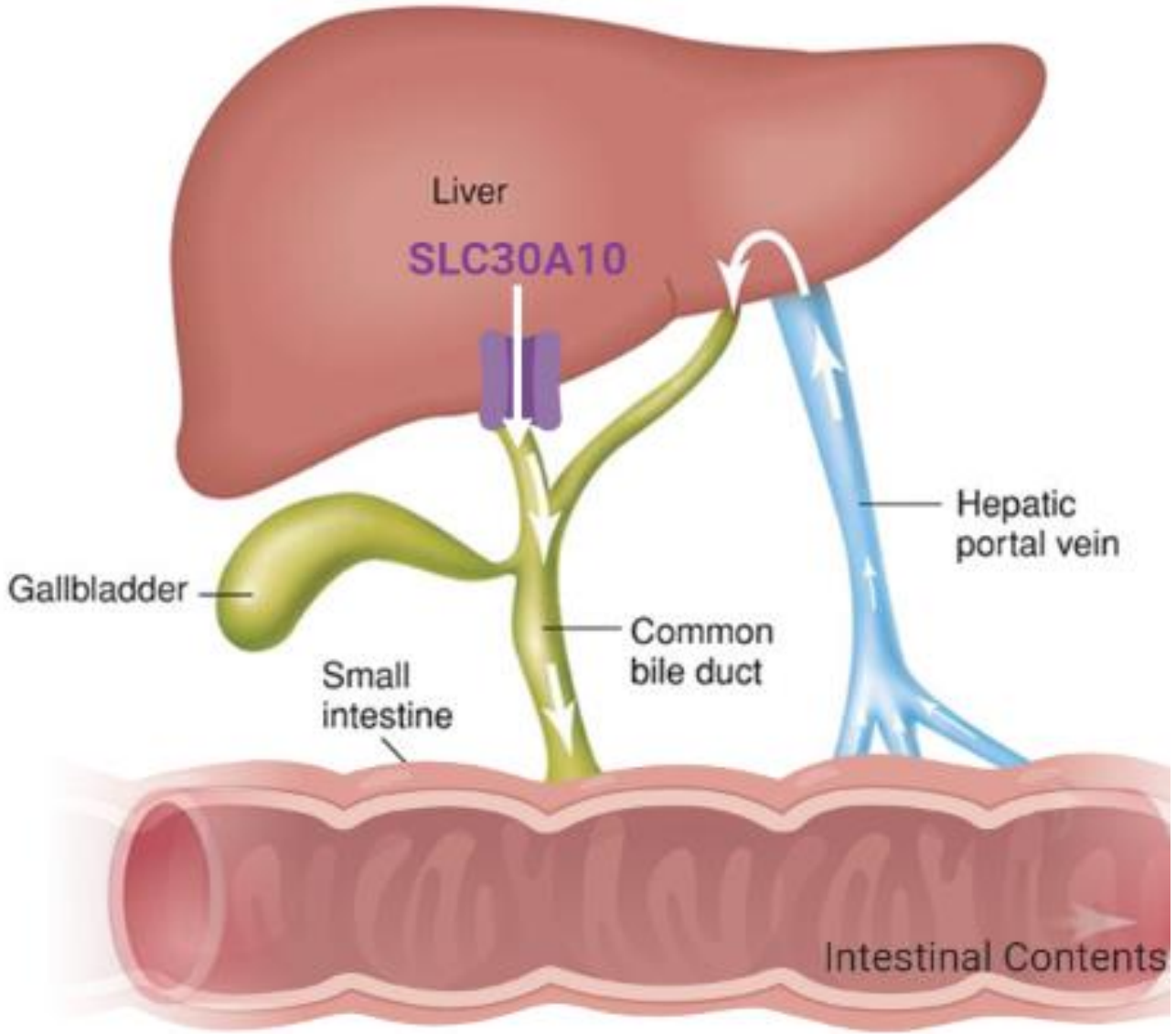


Why do hepatic Slc30a10-deficient mice have minimal Mn excess?

Hepatic Slc30a10 is essential for hepatobiliary Mn excretion, but hepatic Slc30a10 deficiency only results in a minimal Mn excess?

- Late onset of Albumin-Cre transgene (P21)
- Another tissue contributes to Mn excretion



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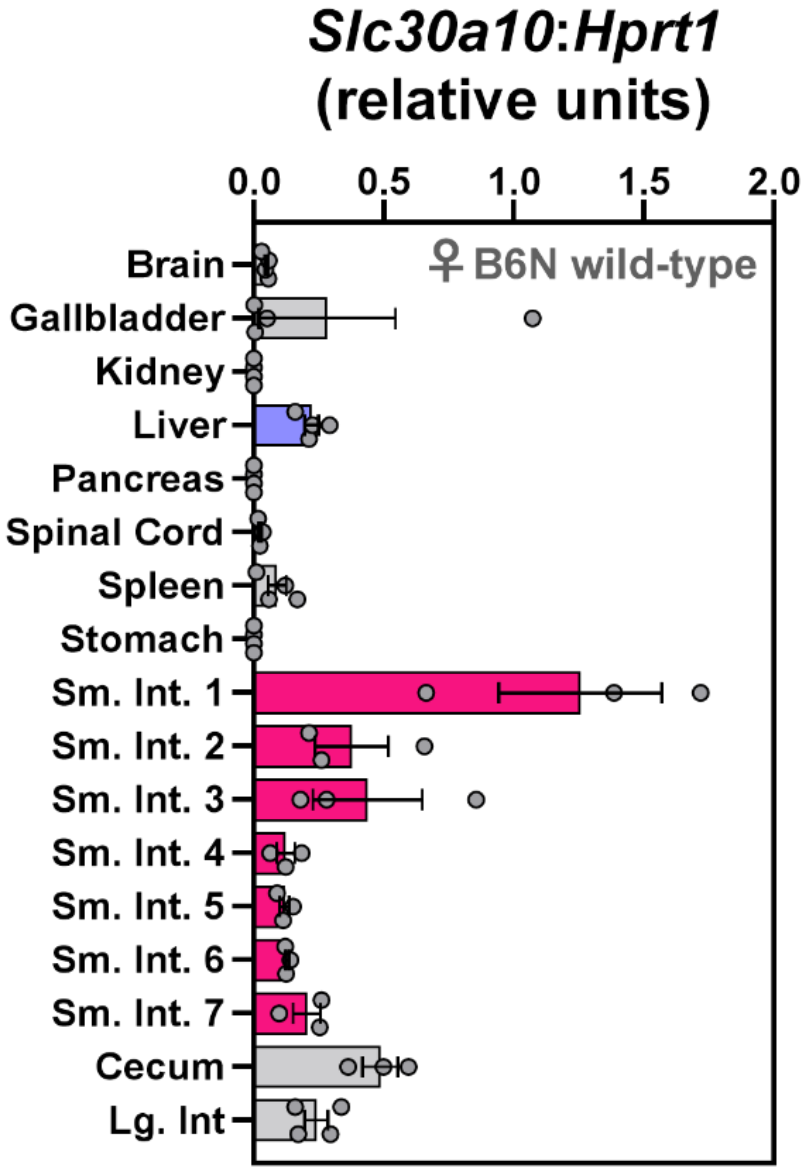
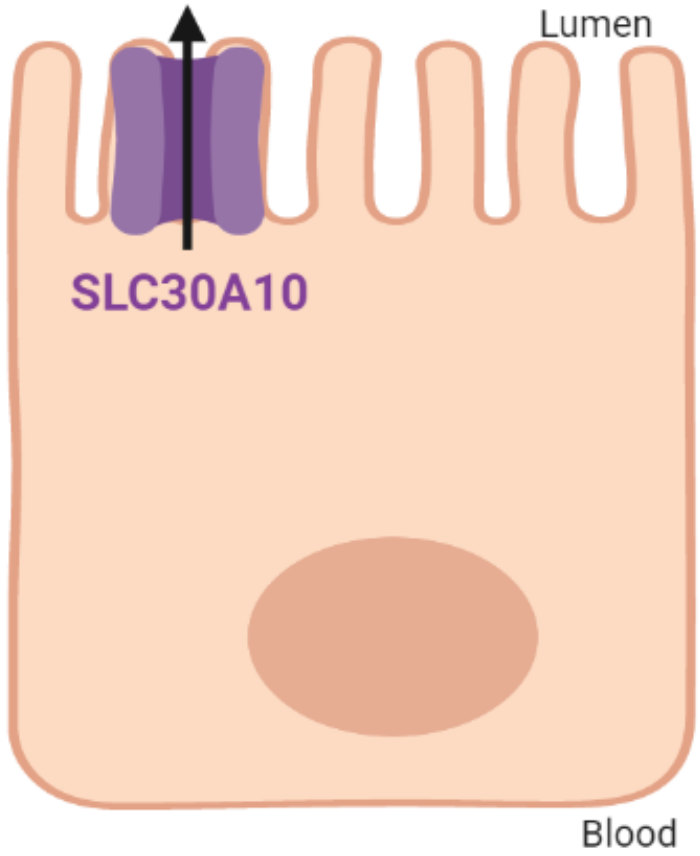
Slc30a10 is highly expressed in intestines





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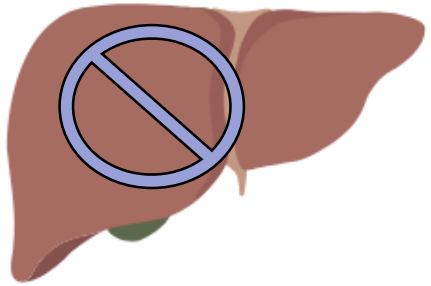
Generating Slc30a10-deficient mice

Whole body Slc30a10 deficiency

Slc30a10$^{KO/KO}$

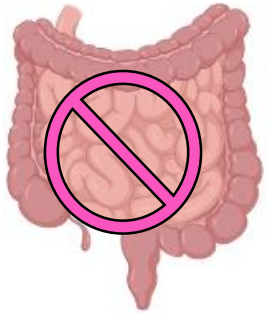
Hepatic
Slc30a10 deficiency

Slc30a10$^{lox/lox}$ Alb



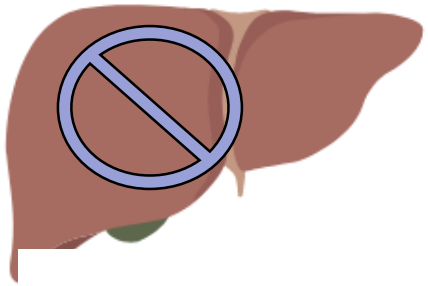
Intestinal
Slc30a10 deficiency

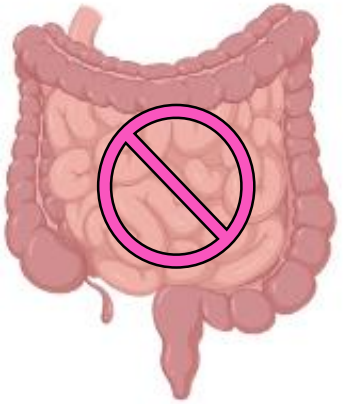
Slc30a10$^{lox/lox}$ Vil



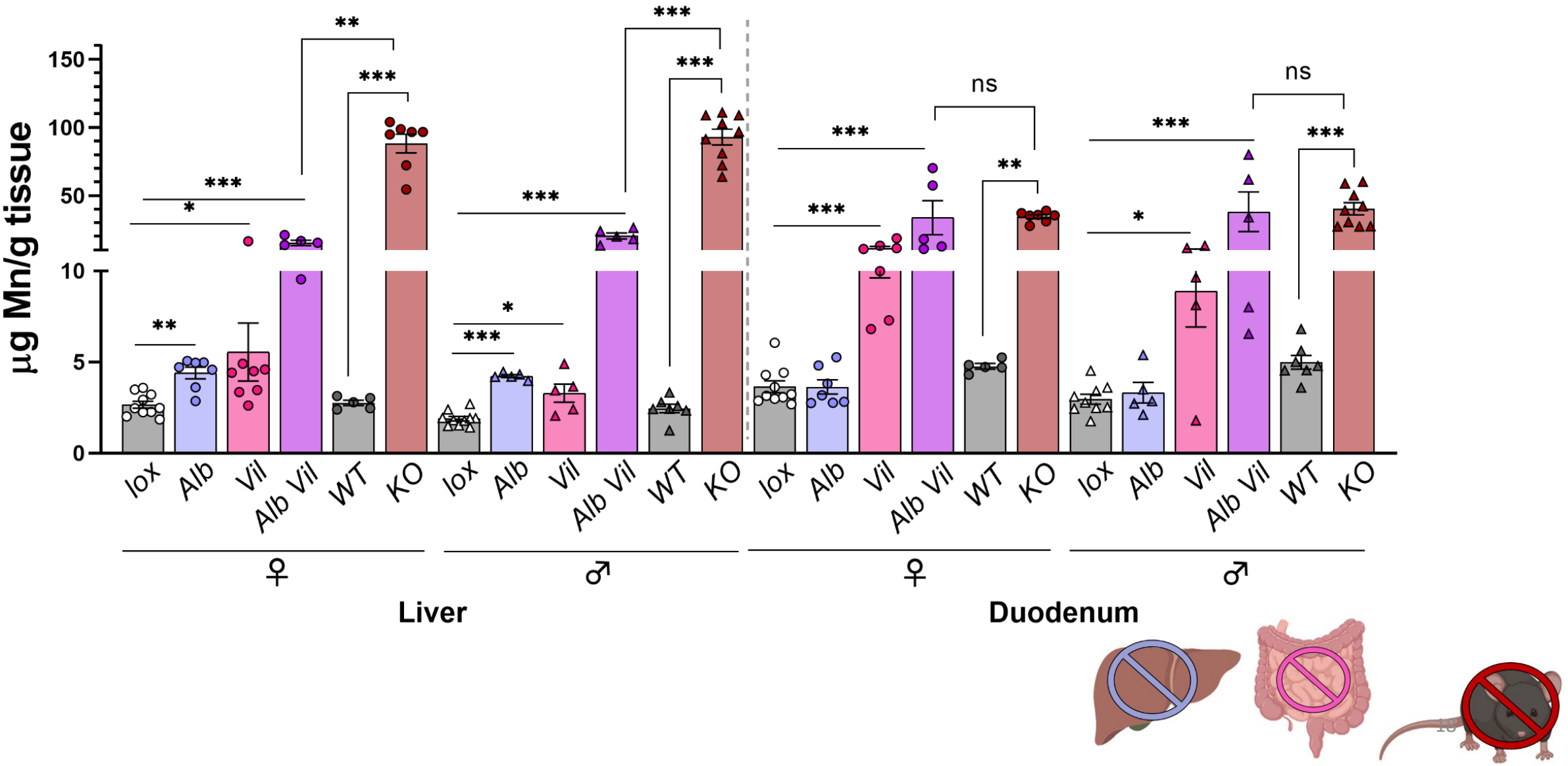
Hepatic and Intestinal
Slc30a10 deficiency

Slc30a10$^{lox/lox}$ Alb Vil

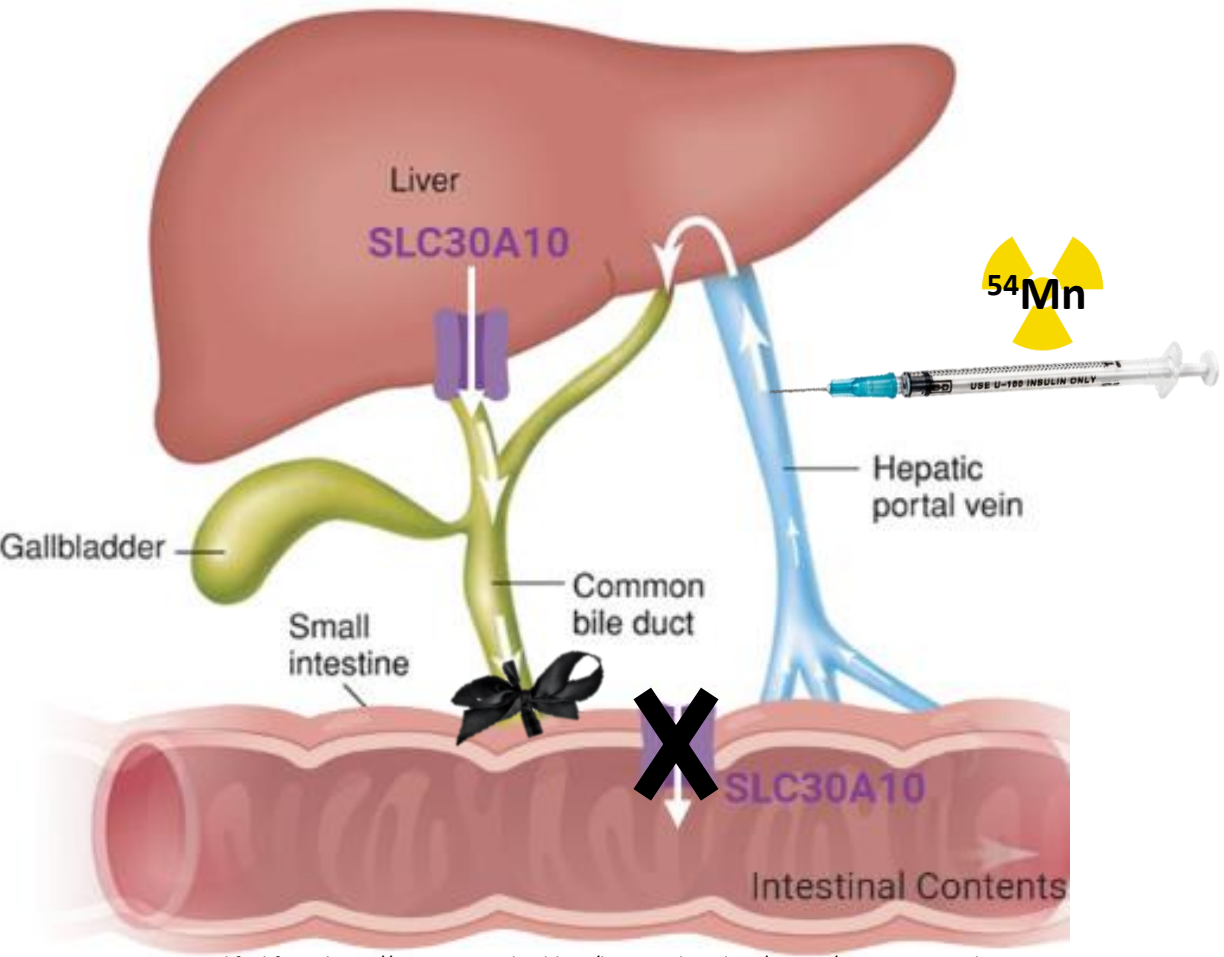




Intestinal and hepatic Slc30a10 contribute to Mn homeostasis



Intestinal Slc30a10 contributes to intestinal Mn excretion



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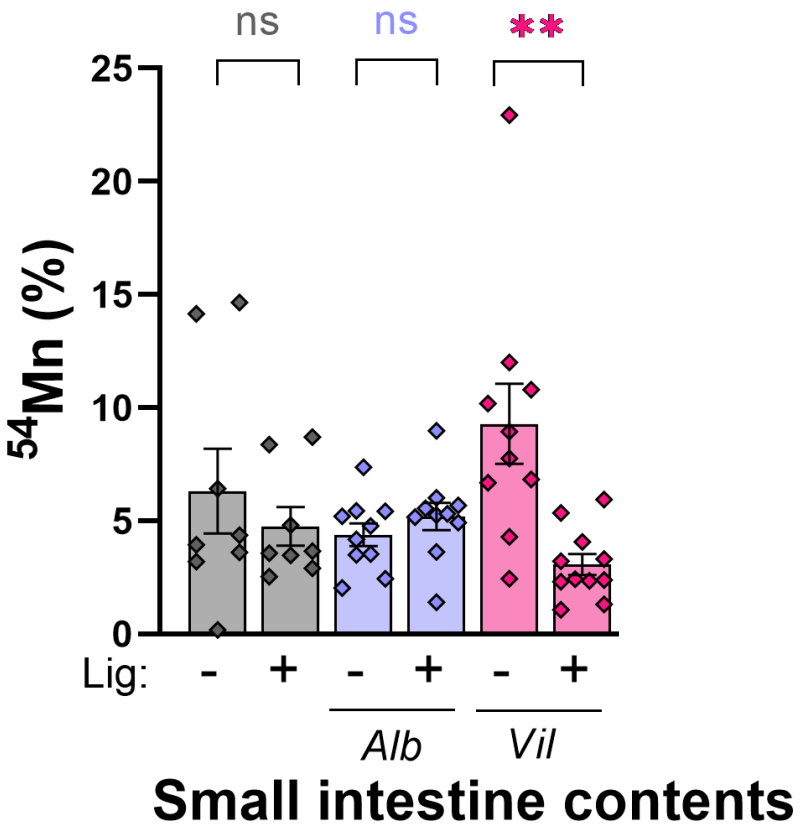
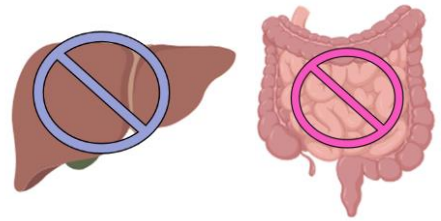
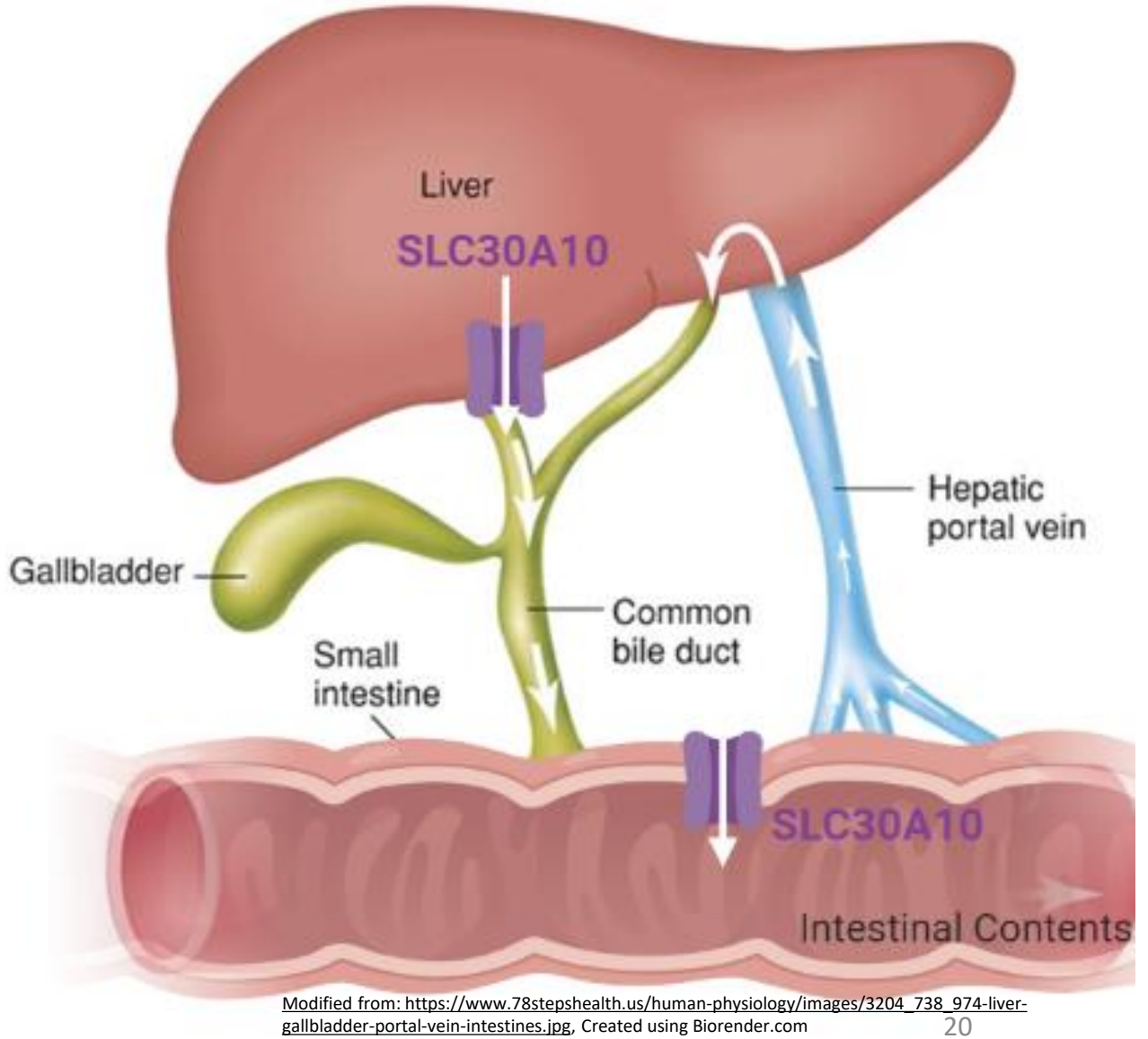




Conclusions

- Slc30a10-deficient mice have impaired Mn excretion
- Hepatic Slc30a10 is essential for hepatobiliary Mn excretion
- Hepatic and intestinal Slc30a10 contribute to manganese homeostasis
- Intestinal Slc30a10 contributes to excretion of Mn into intestinal lumen



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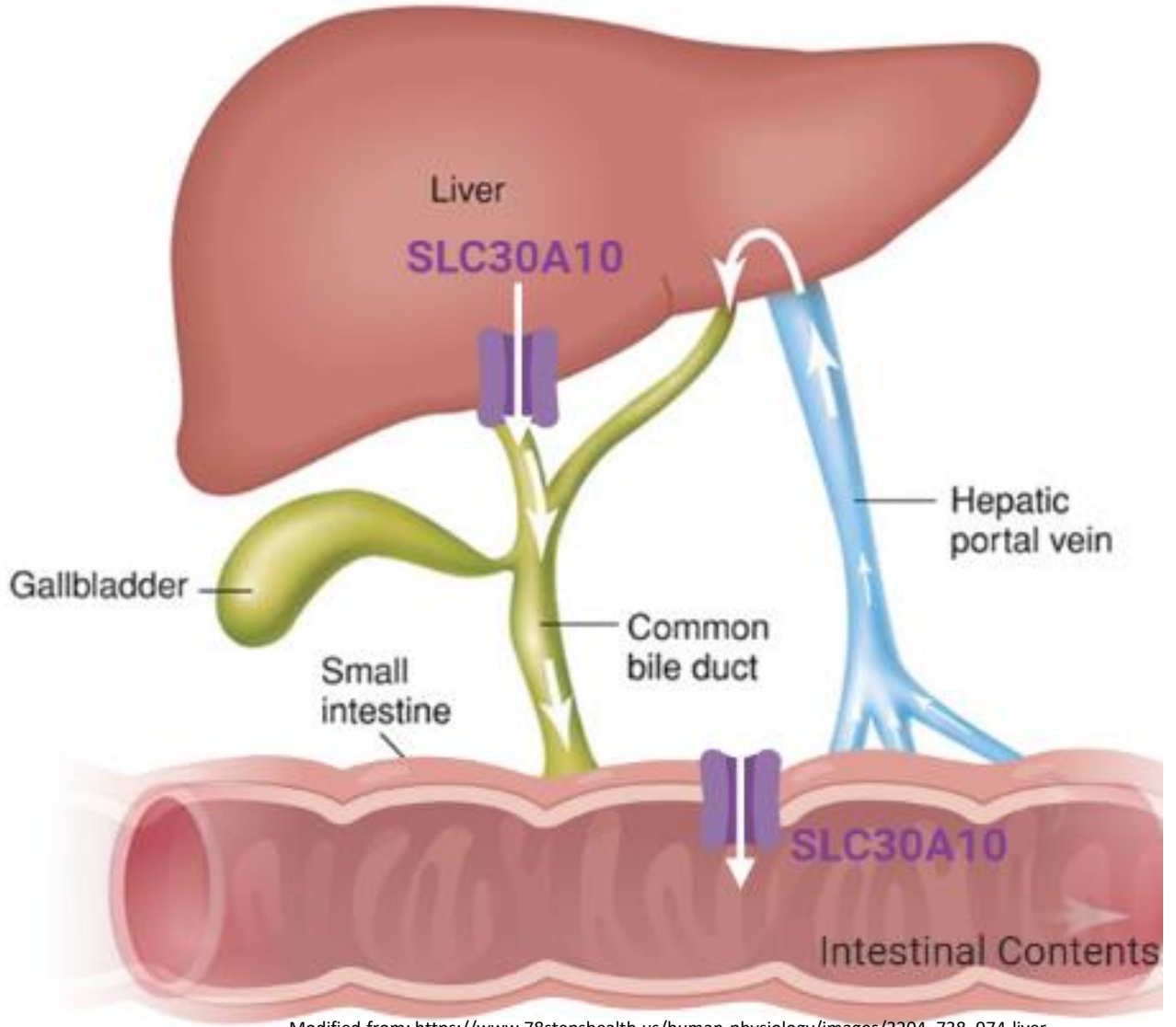
Future Directions

- Determine the contribution of Slc30a10 to Mn homeostasis in developing mice
- Determine the role of Slc30a10 in cecum and large intestine to Mn homeostasis
- What about Mn absorption?



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Acknowledgments

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