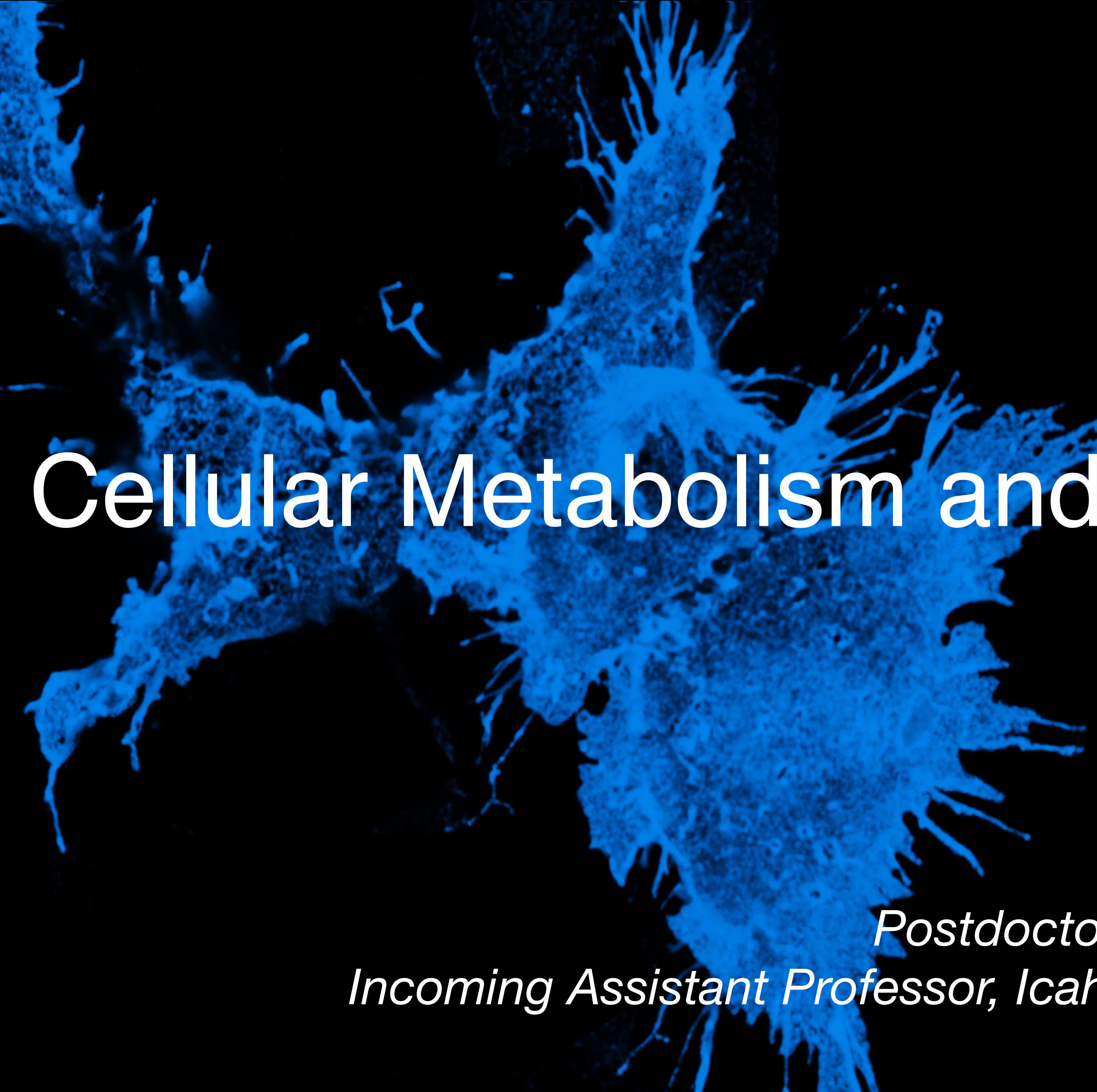




Cellular Metabolism and Nutrient Transport

Timothy C. Kenny, PhD

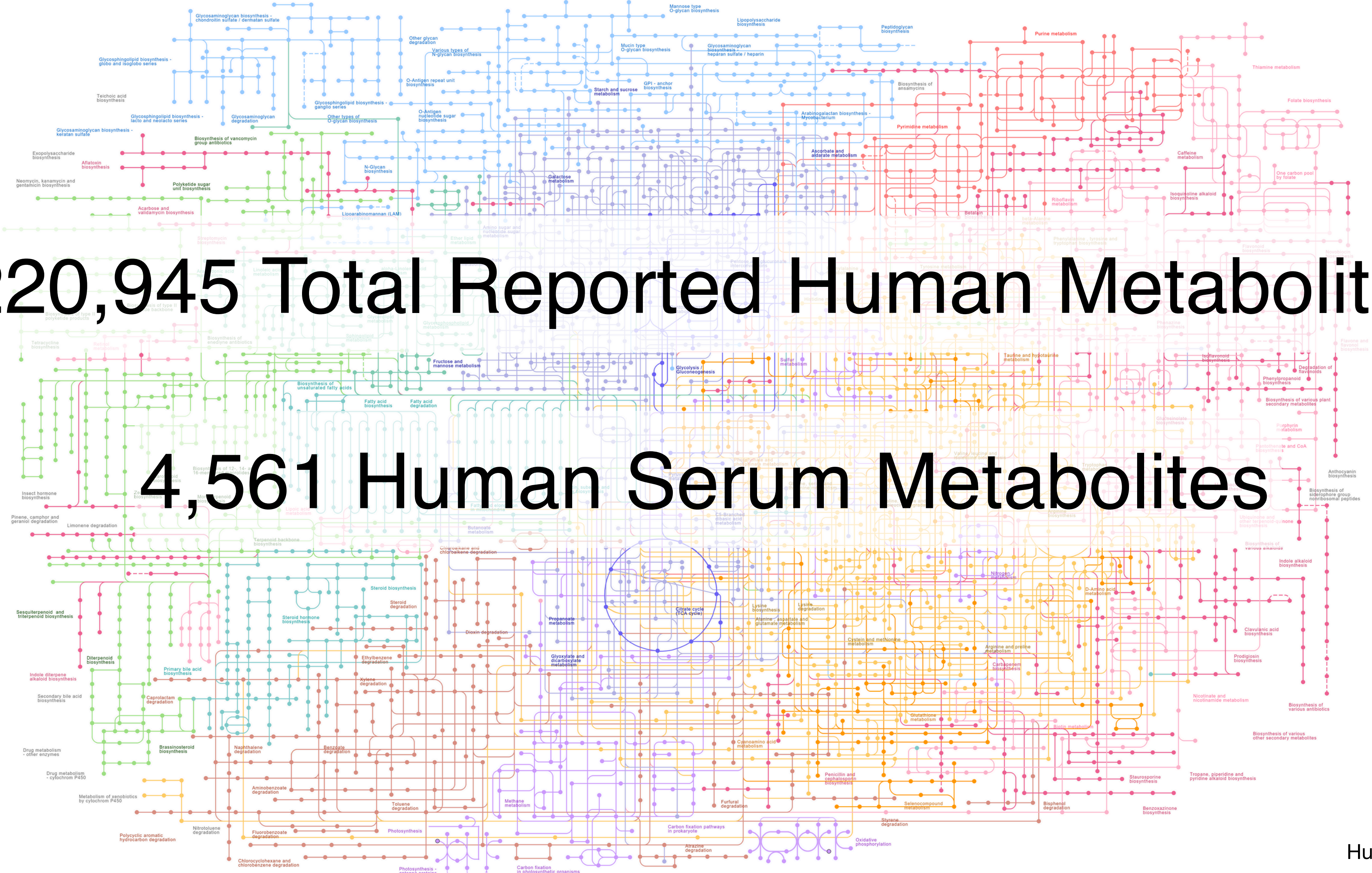
Postdoctoral Fellow, The Rockefeller University

Incoming Assistant Professor, Icahn School of Medicine at Mount Sinai

Metabolism is the sum of all chemical reactions in a biological system

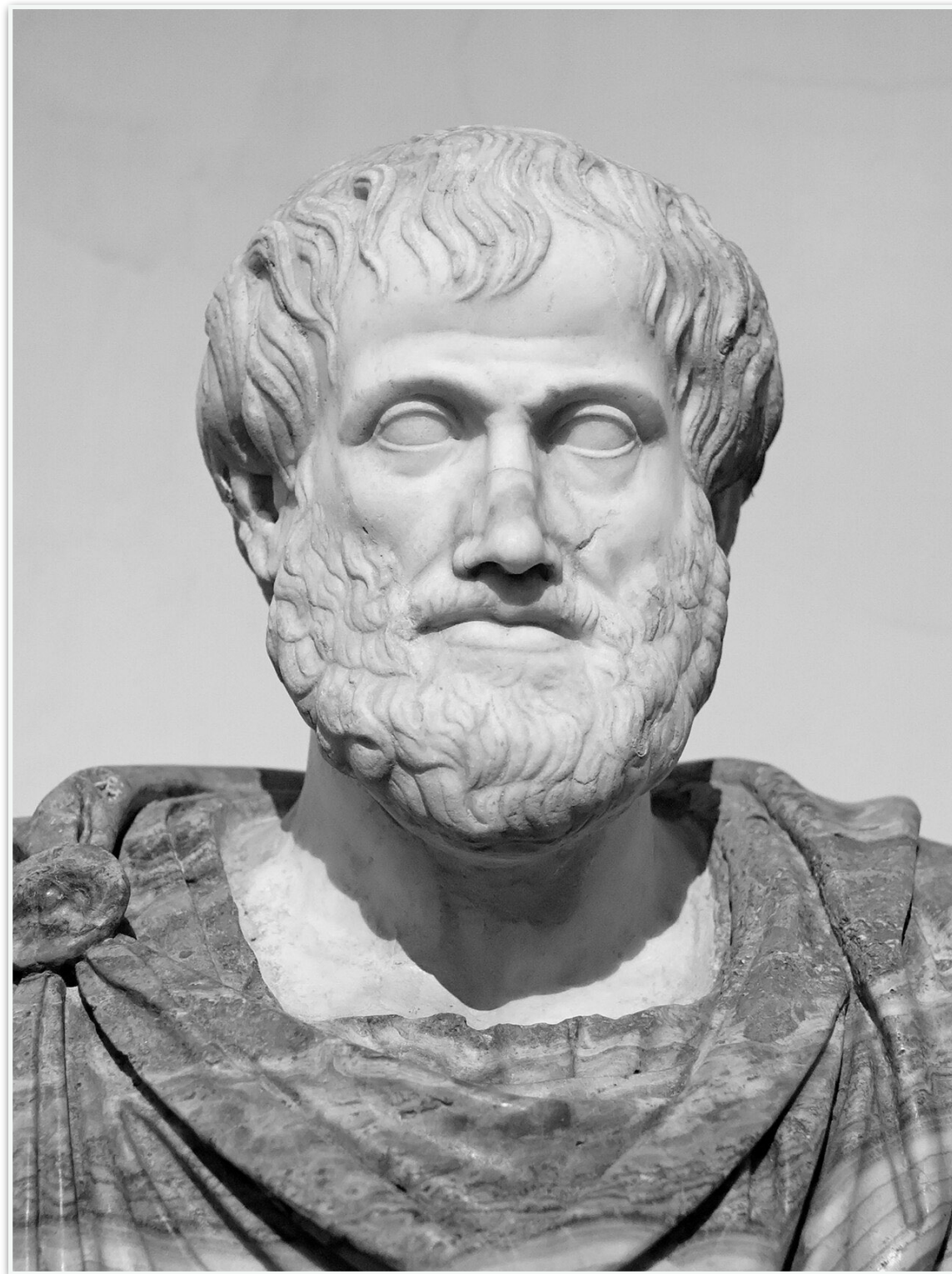
220,945 Total Reported Human Metabolites

4,561 Human Serum Metabolites



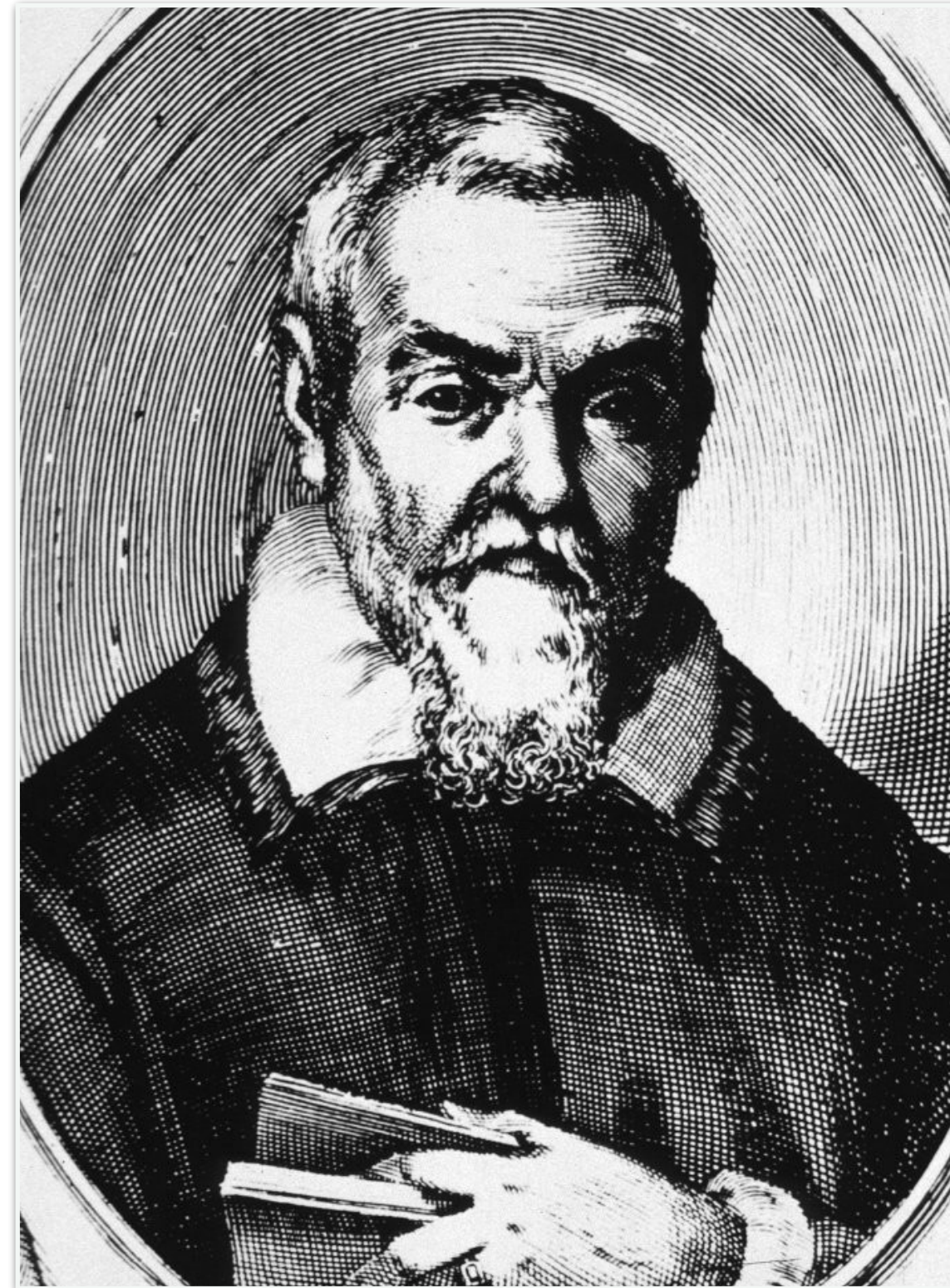
How is metabolic homeostasis maintained?

*Food makes body
and heat*



Aristotle
4th Century BCE

*Measurement of
consumption*



Sanctorius
17th Century AD

*Cellular metabolite
transport*



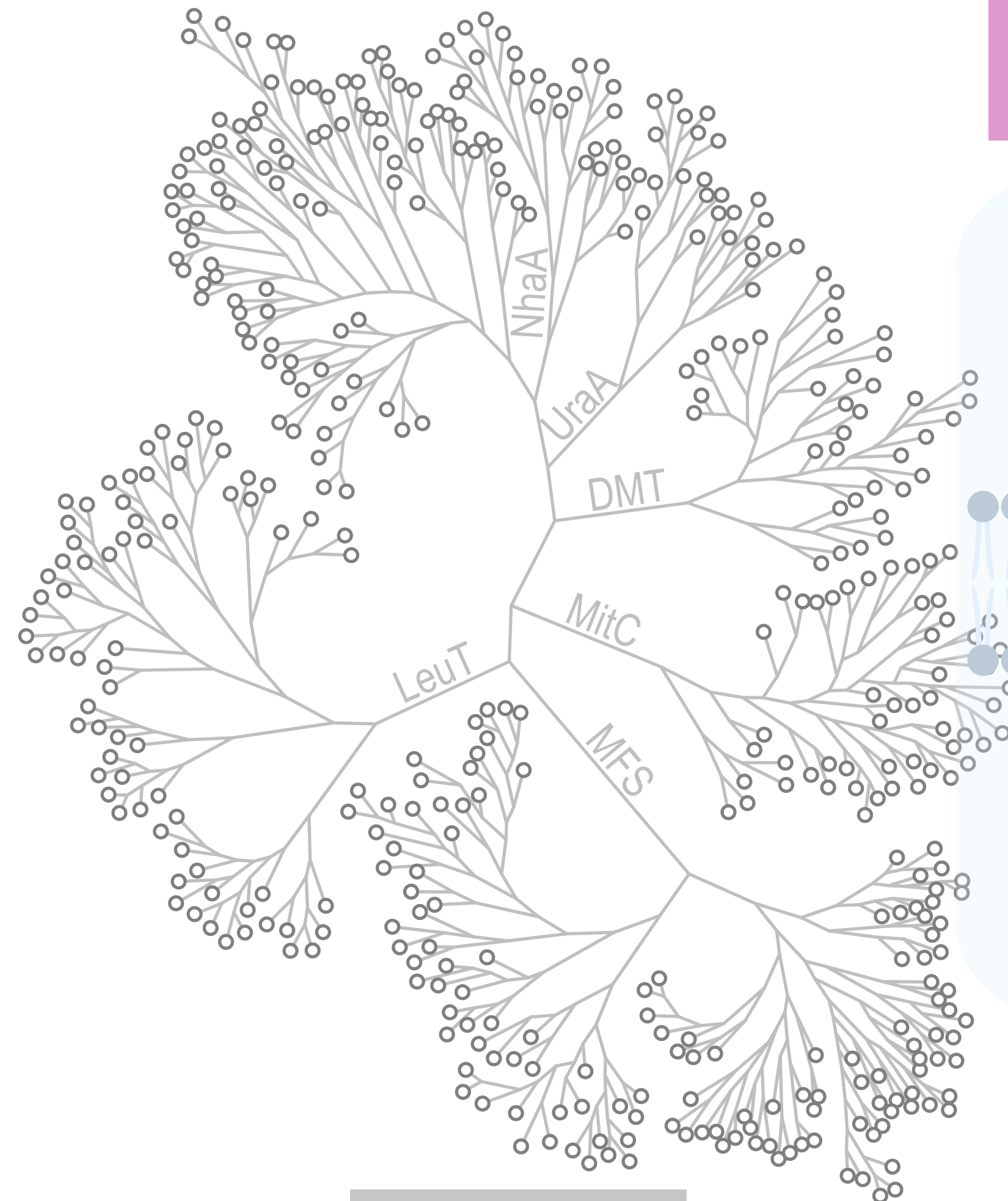
Ernest Overton
19th Century AD

Transporters are the gatekeepers of metabolism

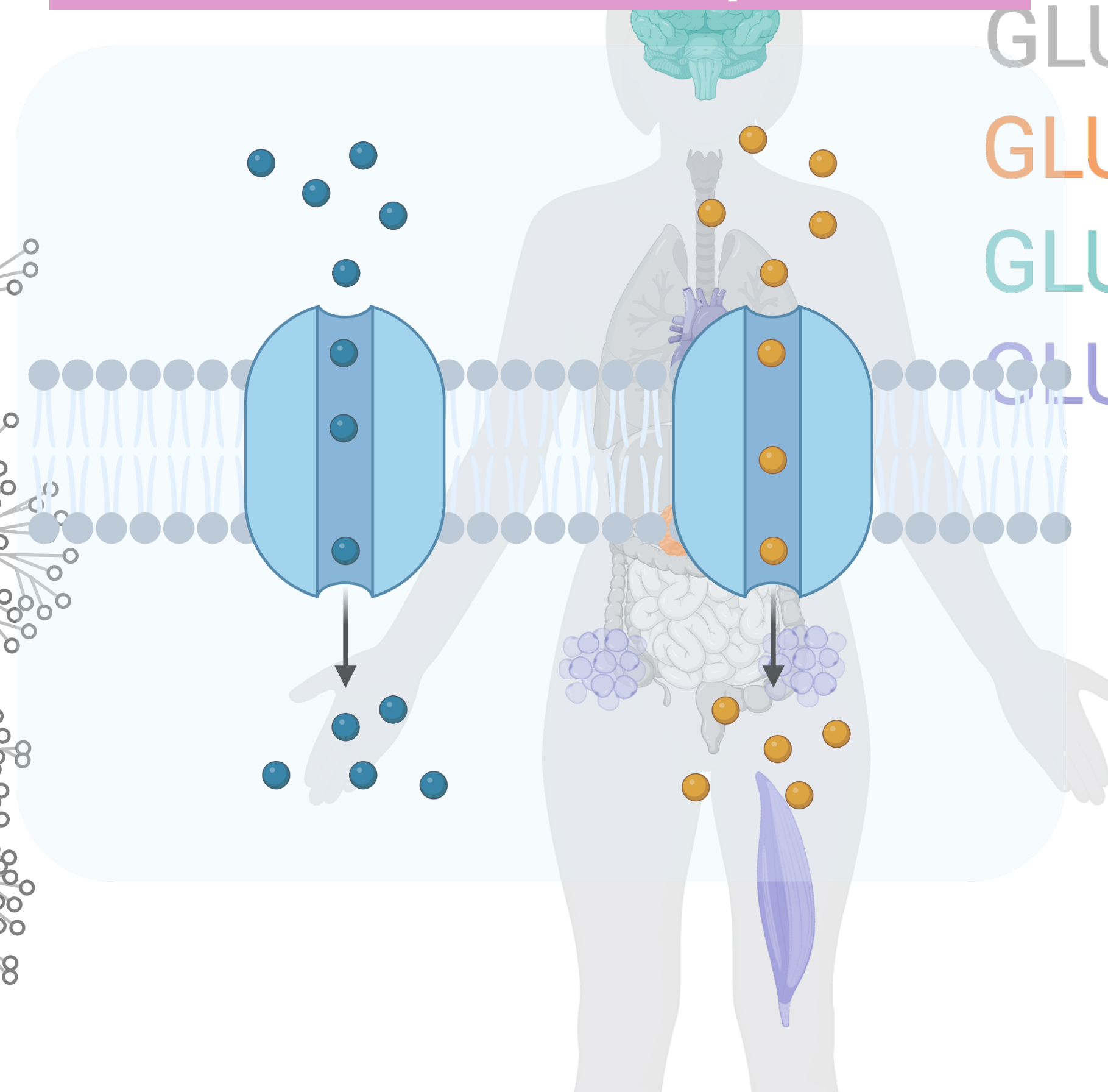
Solute Carrier (SLC) superfamily
of metabolic transporters

Paralogs evolved to fine-tune
organismal metabolism

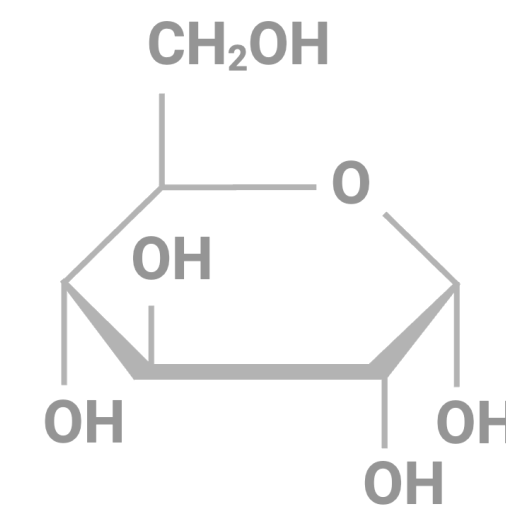
10% of the genome
encodes for transporters



456 Genes

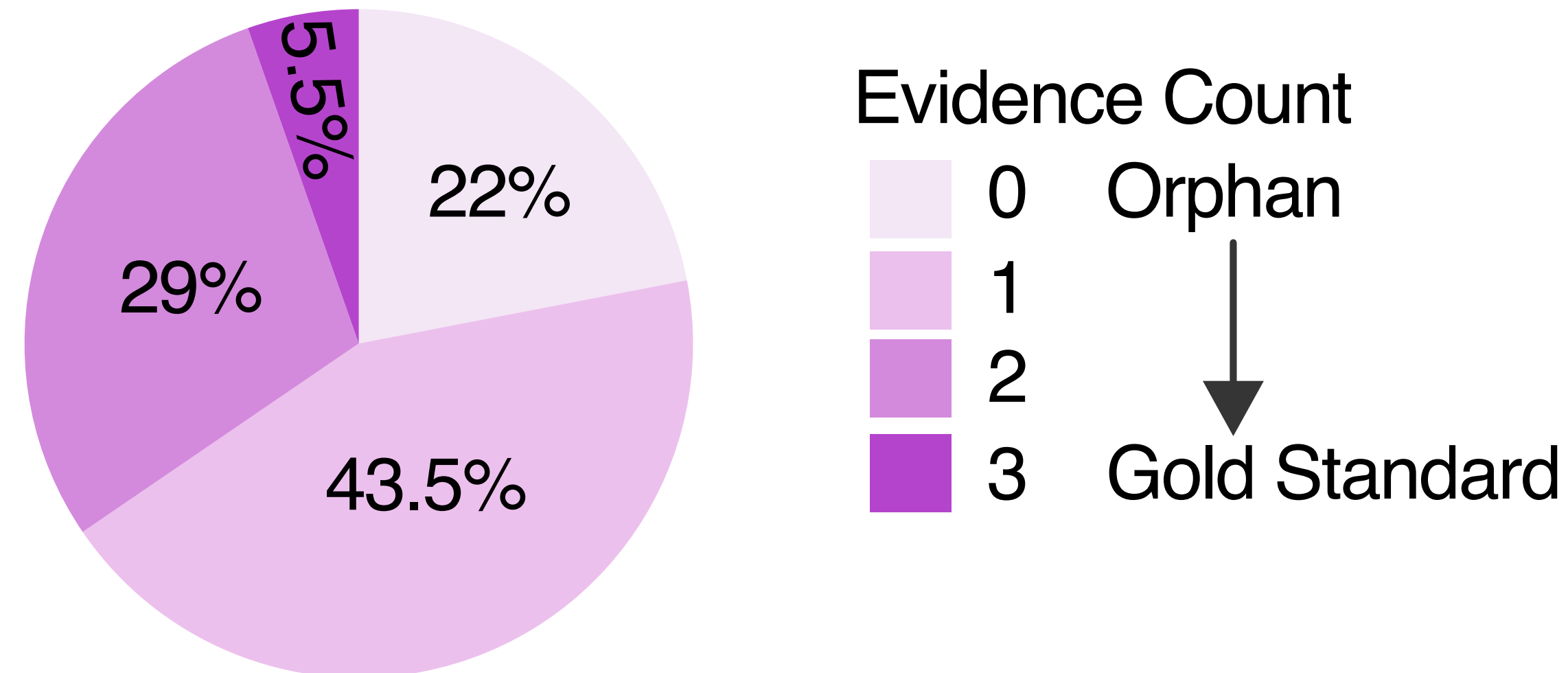


GLUT1/SLC2A1	Ubiquitous expression, Lower affinity
GLUT2/SLC2A2	Pancreatic Beta cells, Low affinity
GLUT3/SLC2A3	Neuronal expression, High affinity
GLUT4/SLC2A4	Adipose tissue and muscle, High affinity



SLC transporters are implicated in disease but poorly understood

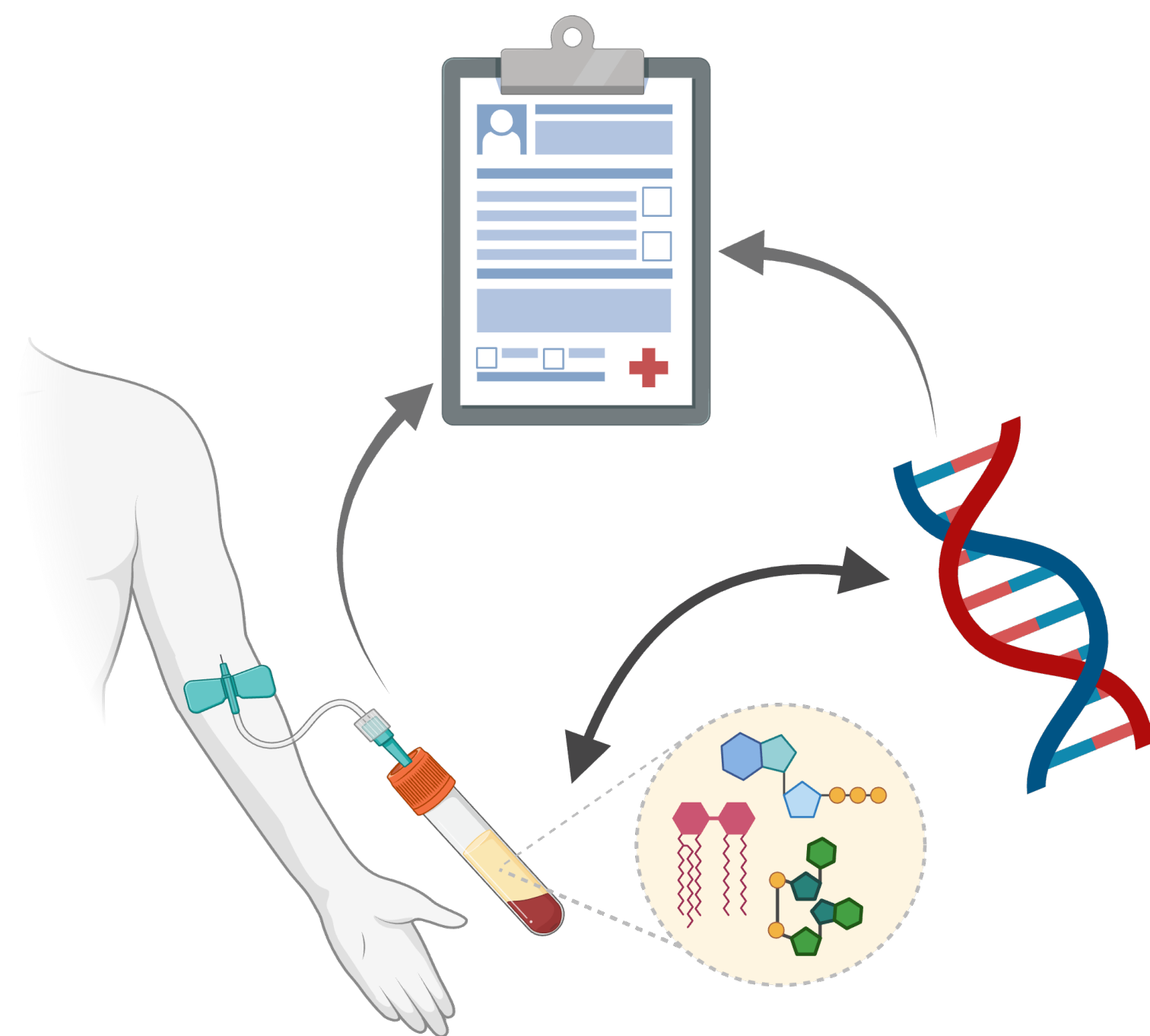
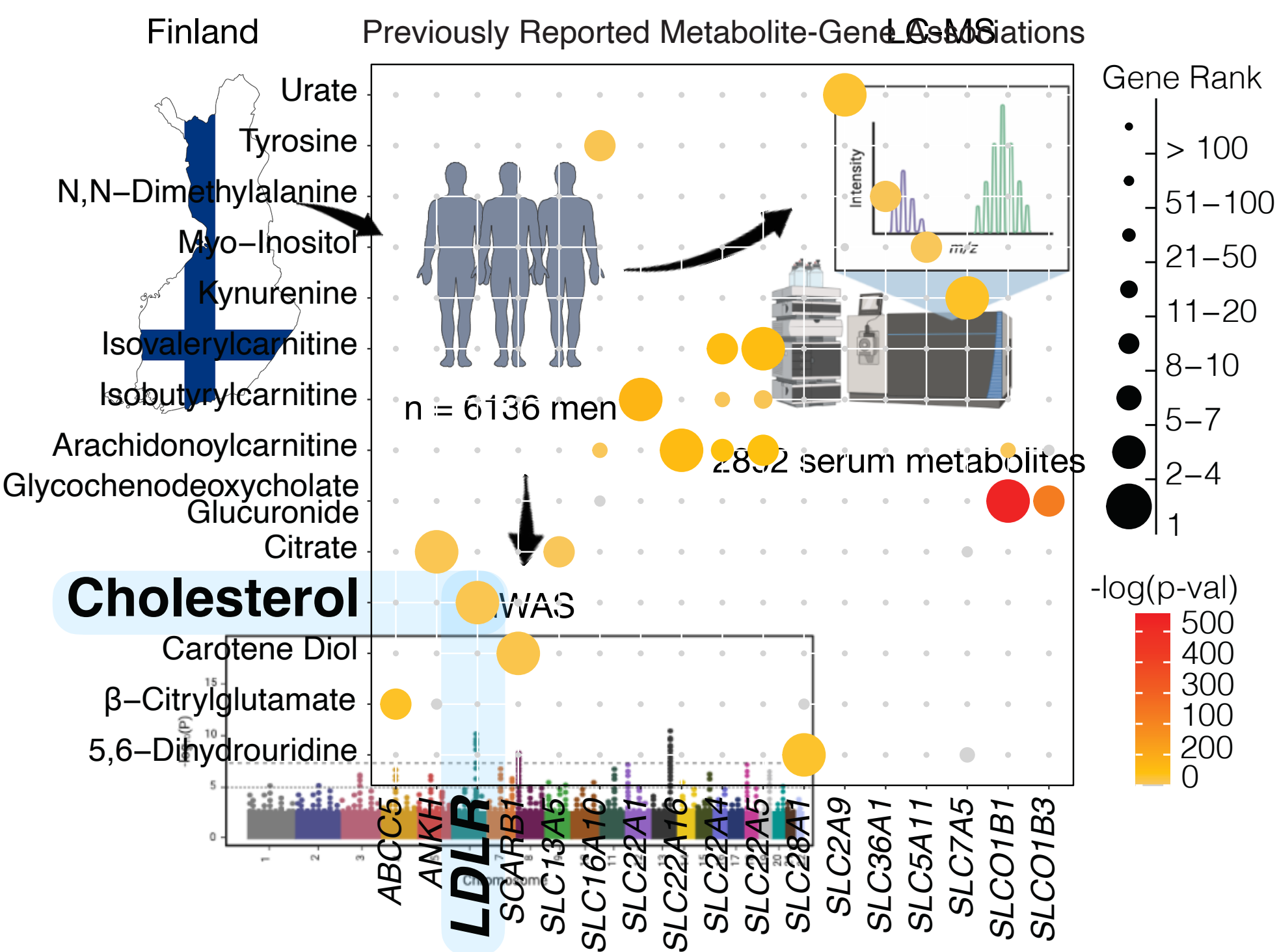
SLC Transporters (n=456)



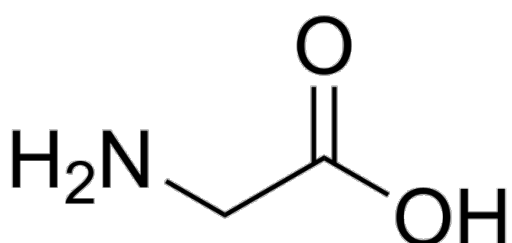
>50% of SLC transporters are associated with human disease

How can we systematically identify physiological substrates of metabolite transporters?

Human metabolite GWAS as a discovery platform to deorphanize metabolite transporters

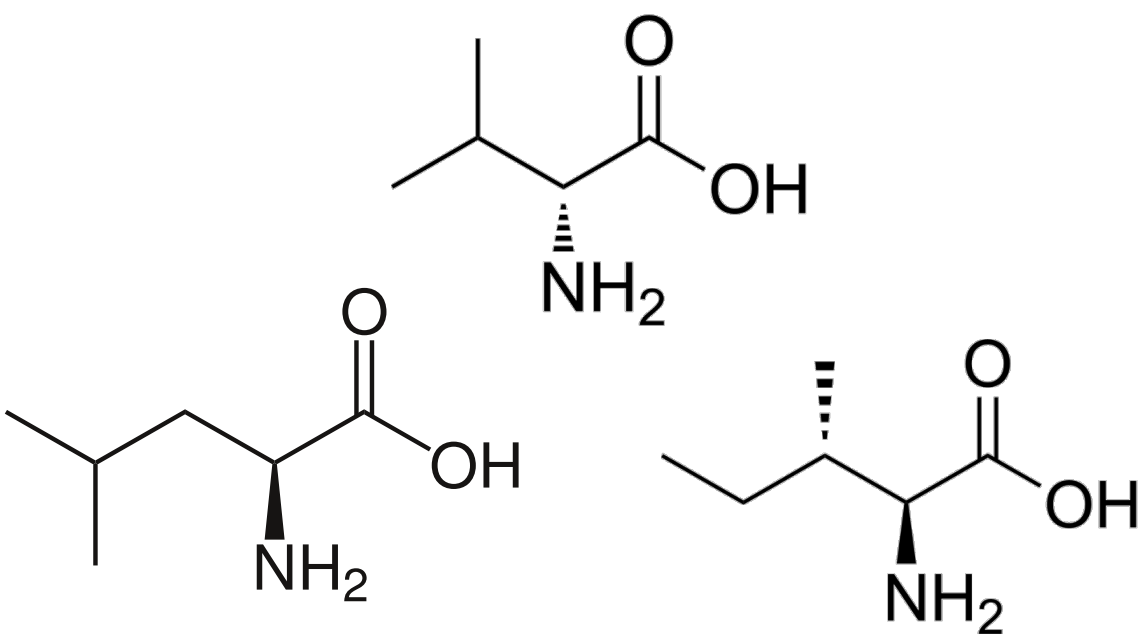


Glycine Encephalopathy



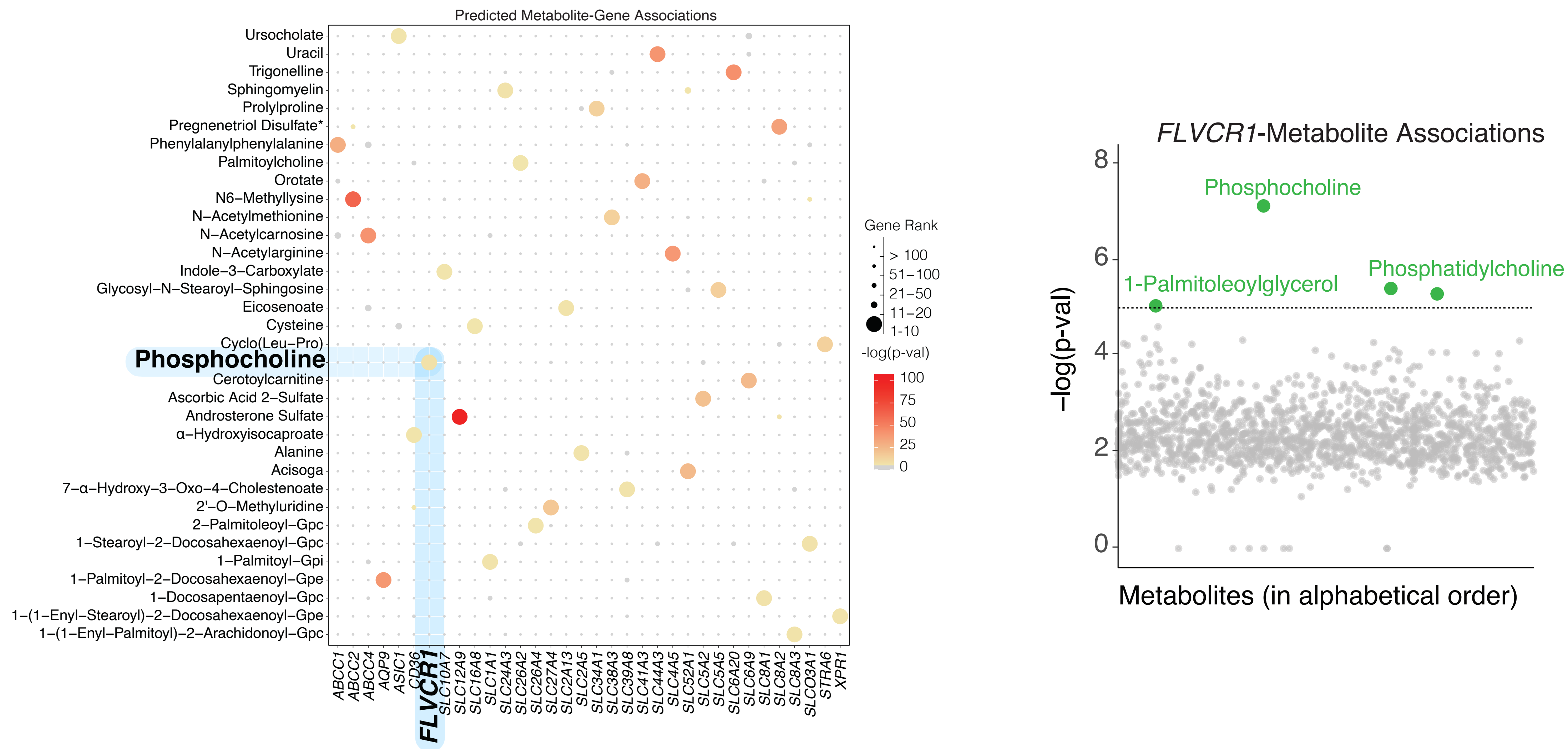
Glycine decarboxylase

Maple Syrup Urine Disease



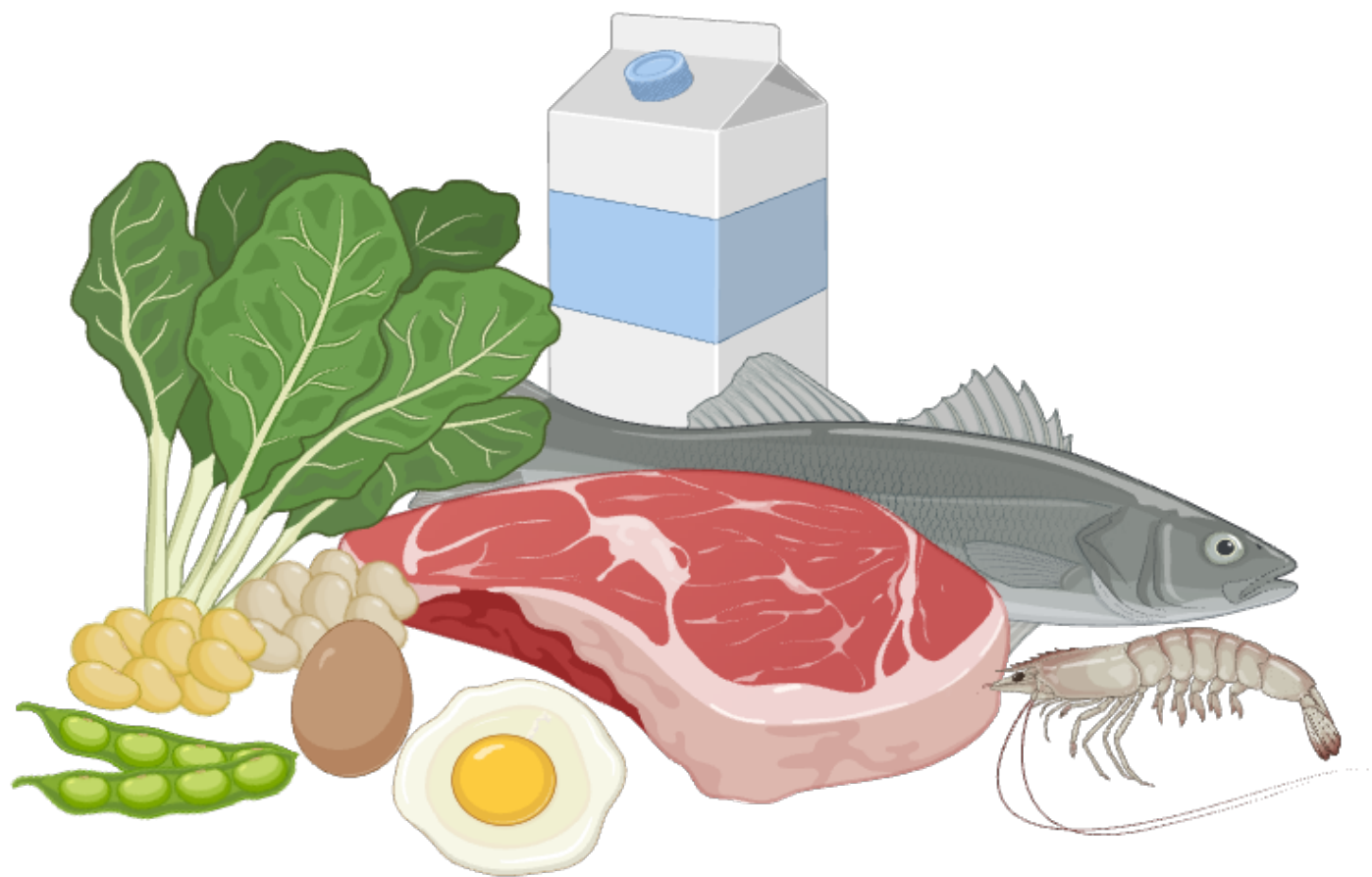
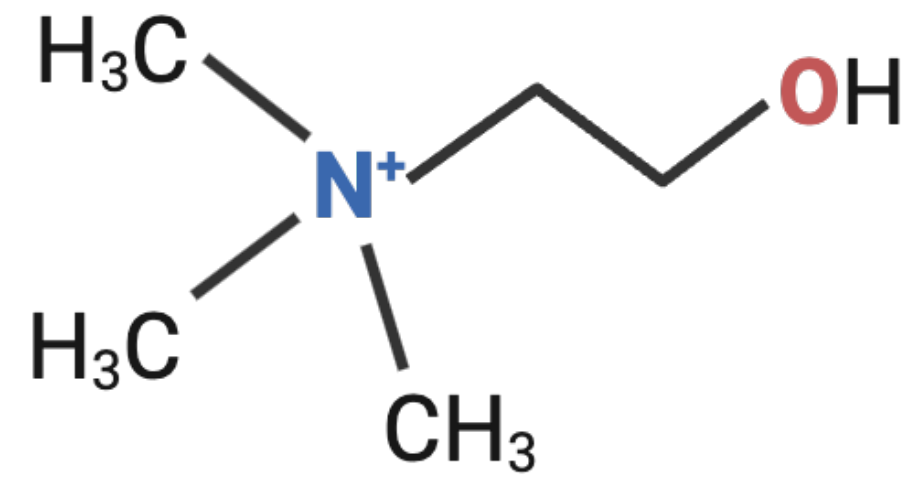
Branched chain ketoacid dehydrogenase kinase

FLVCR1/SLC49A1 is genetically associated with choline metabolites

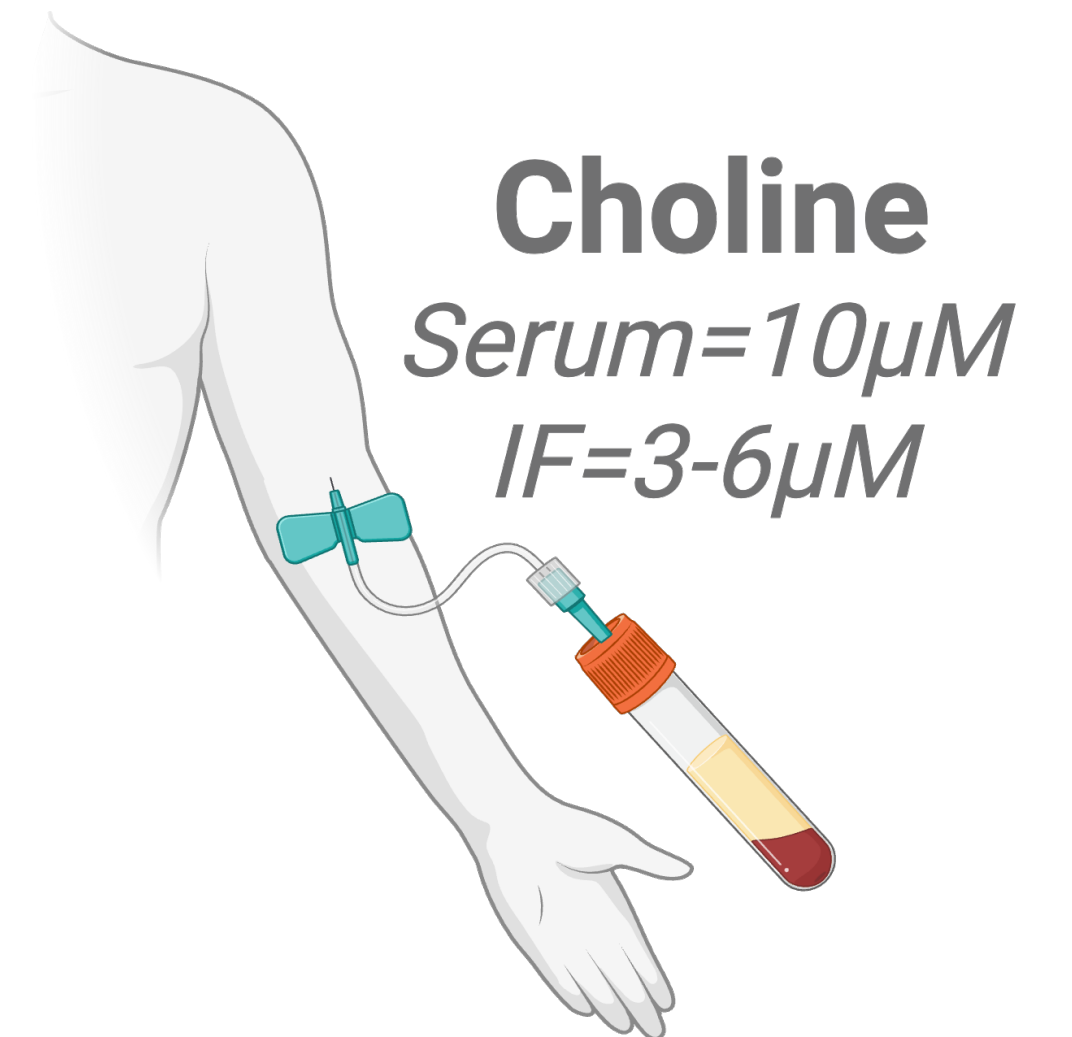


Choline metabolism

Choline



Choline must be obtained from the diet



Choline in physiology and human nutrition

*Choline reverses
fatty liver disease*



Frederick Banting & Charles Best
1930s

*Choline is essential
human nutrient*



Steven Zeisel
1970s

*Choline dietary
recommendations*

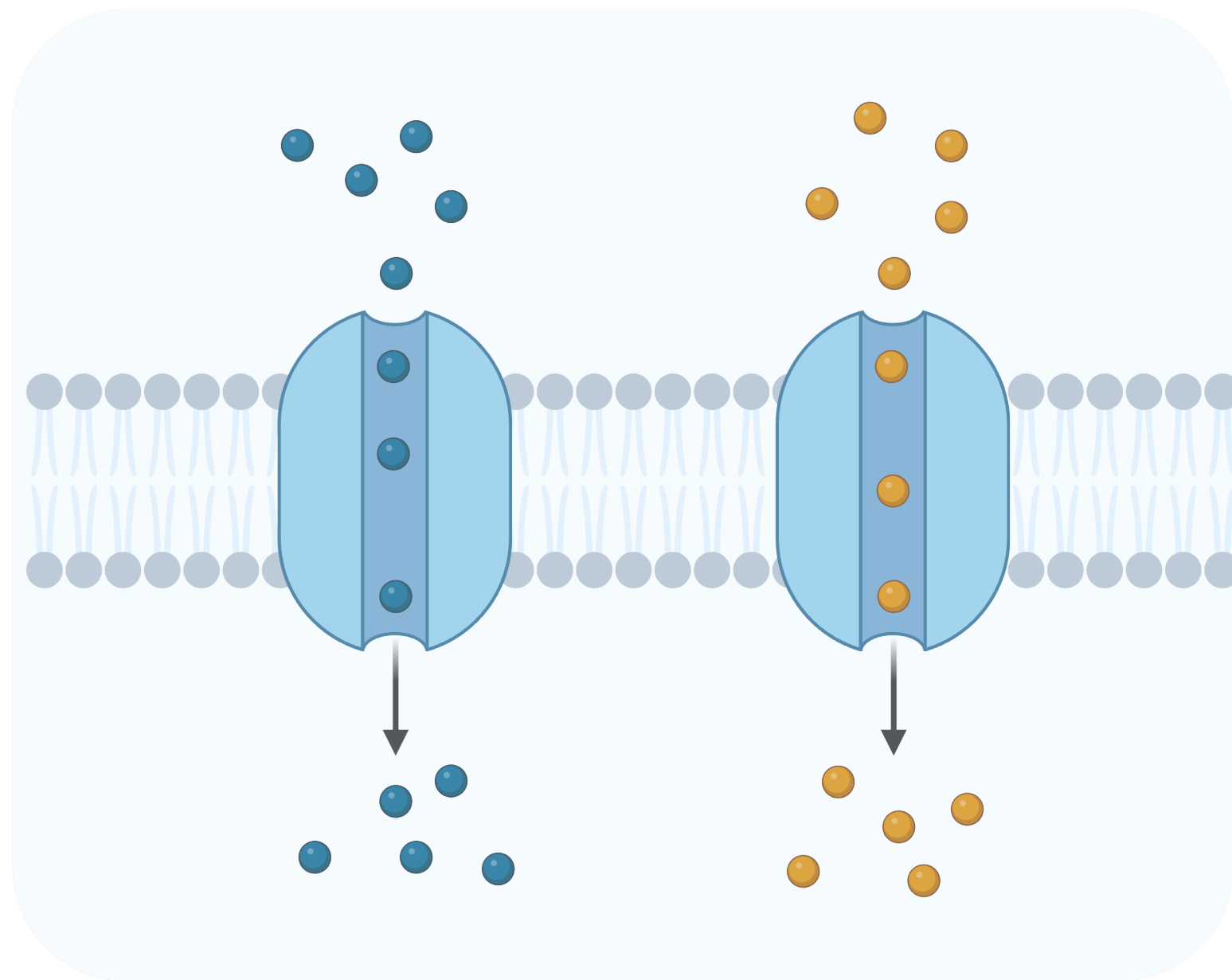


♀ 425 mg/day*
♂ 550 mg/day

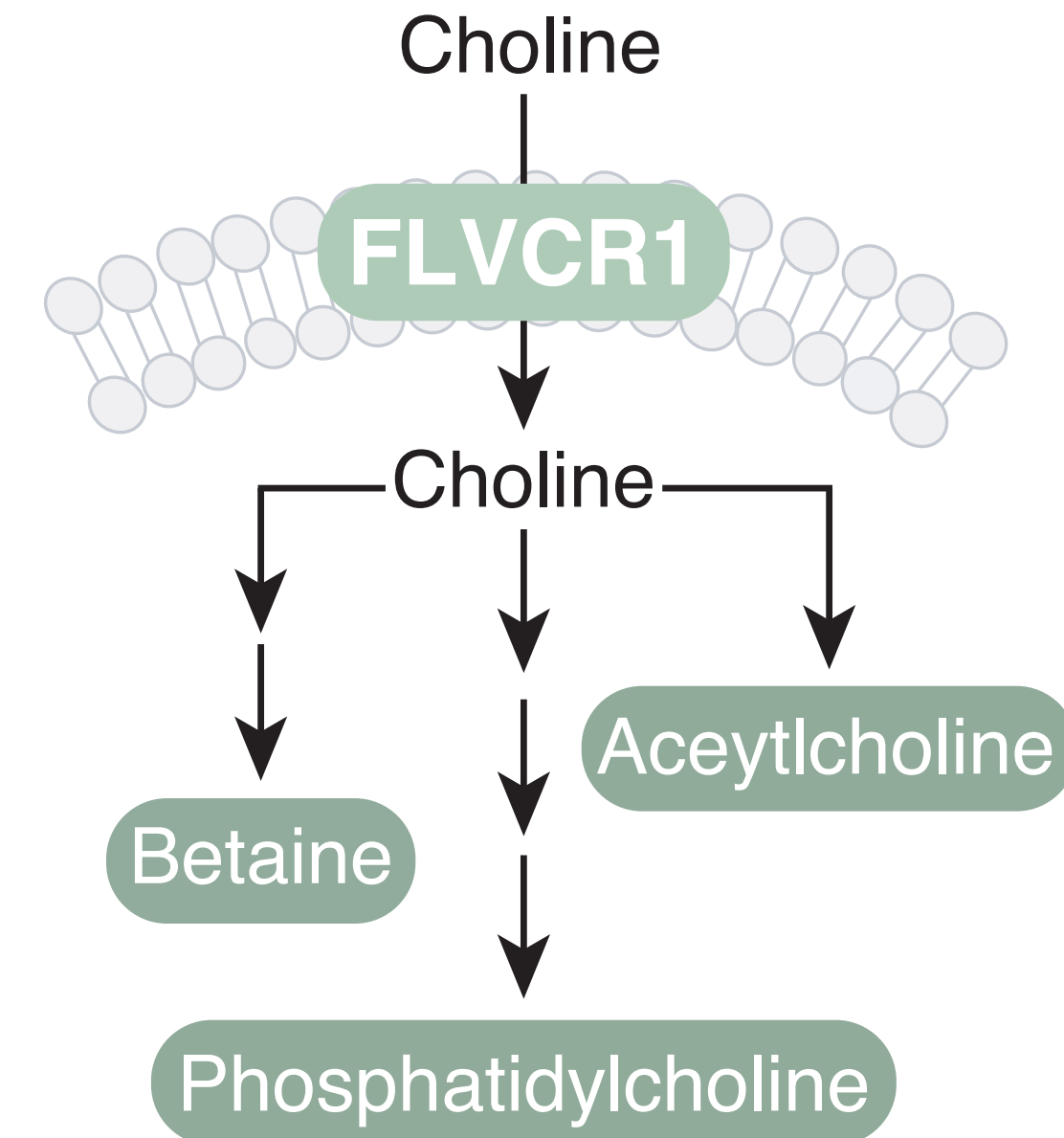
Institute of Medicine
1998

Choline transport

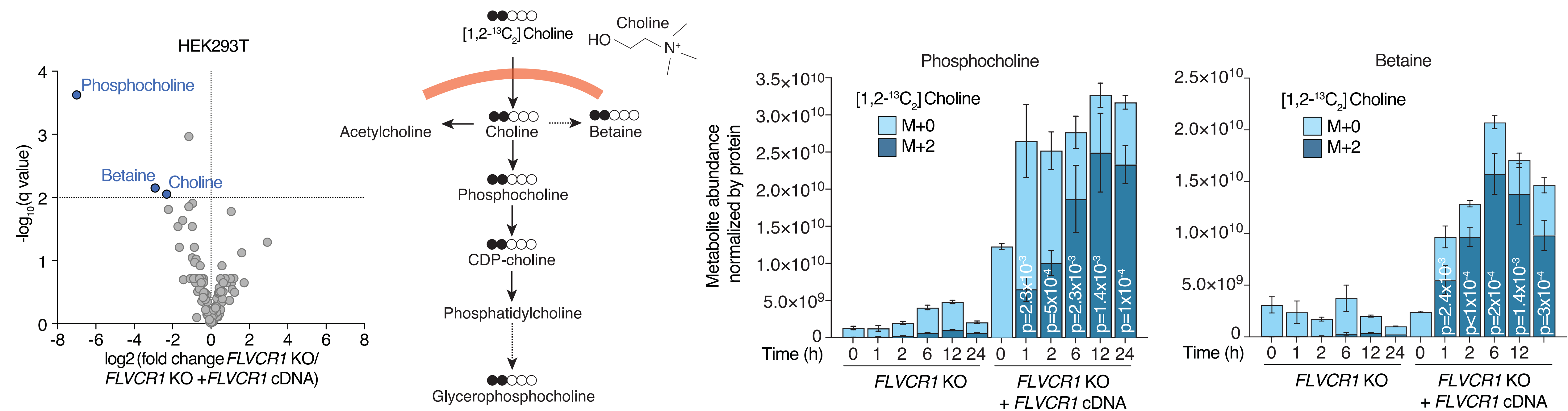
Choline must be transported into the cell



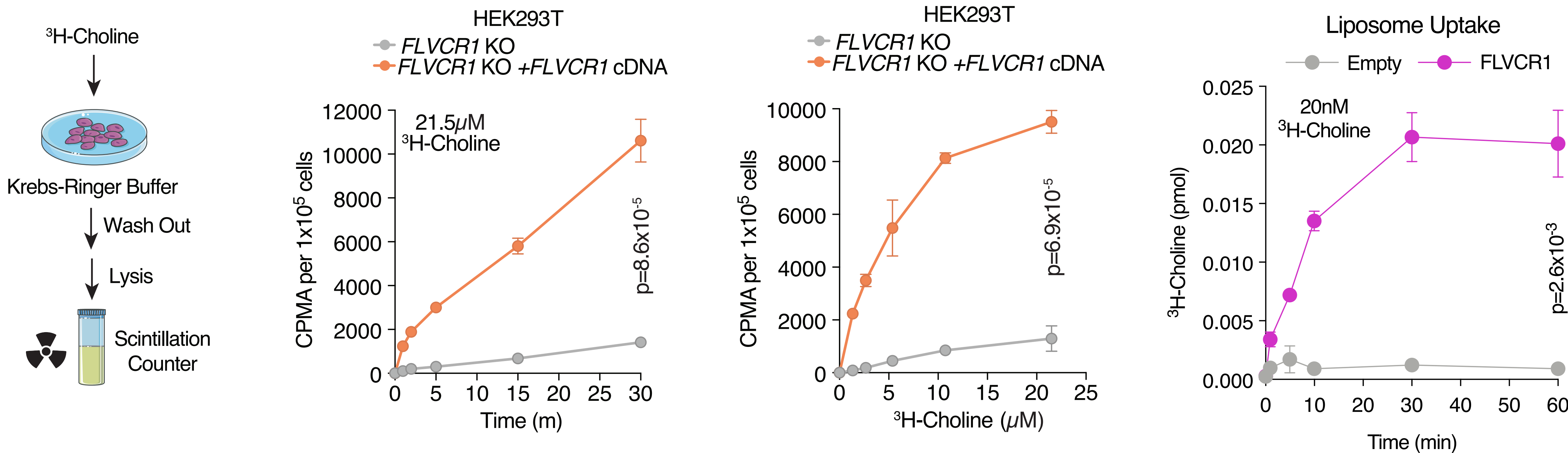
Is FLVCR1 a high affinity choline transporter?



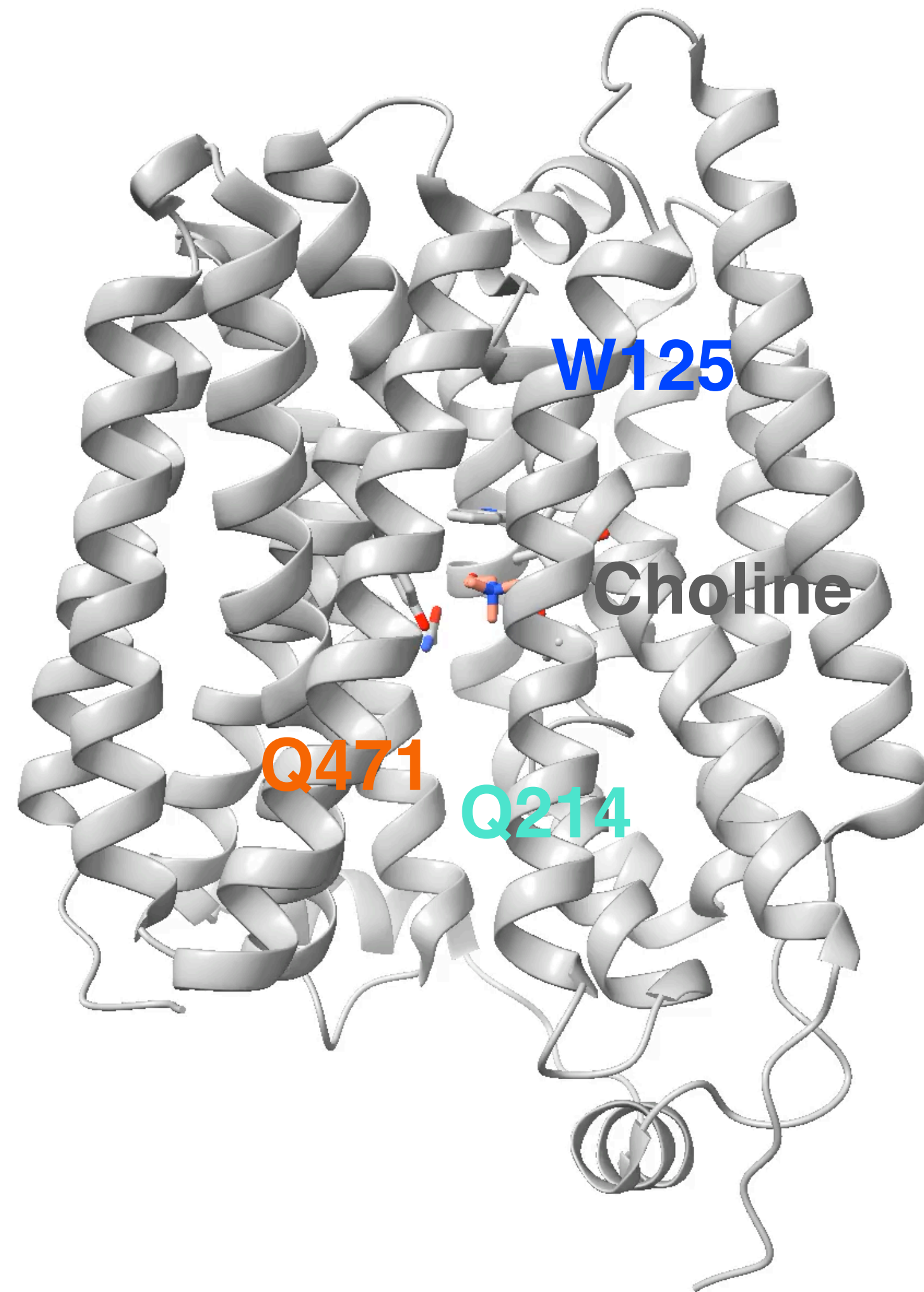
FLVCR1 is required for choline metabolism in cells



FLVCR1 is a high affinity choline transporter



Structural basis of choline transport by FLVCR1

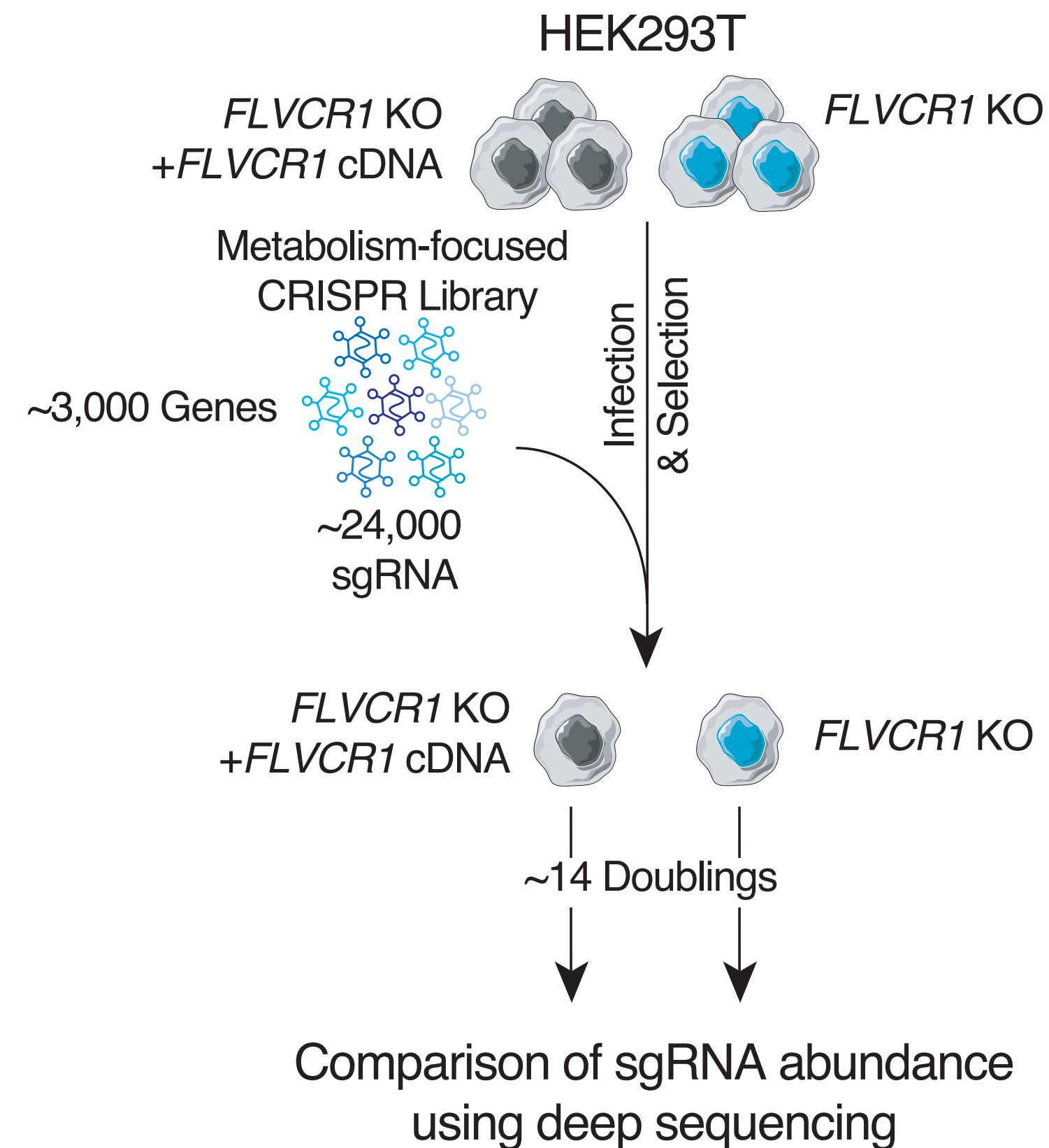
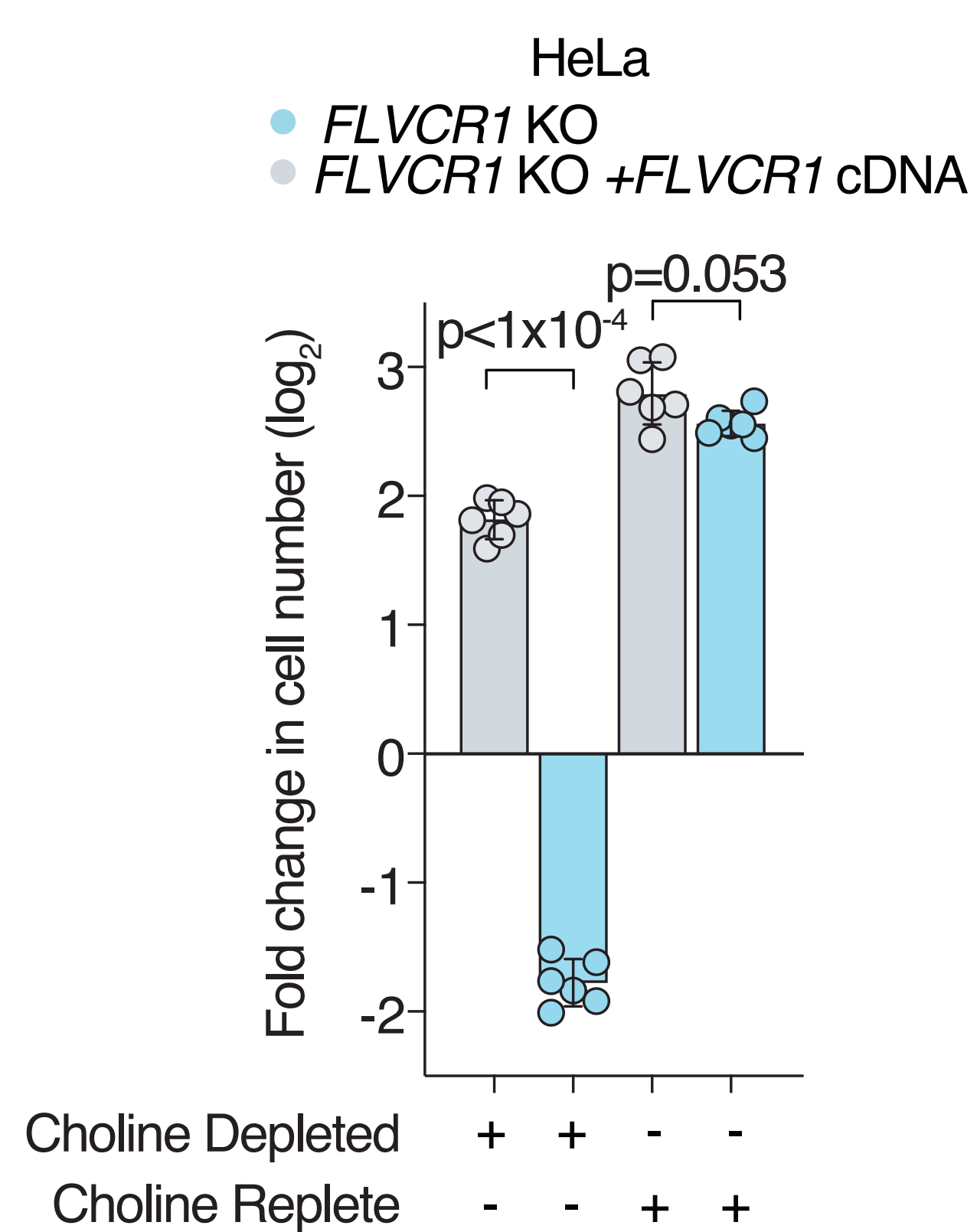


Son, Kenny, Khan, Birsoy & Hite. *Nature* 2024

Cater and Mukherjee et al. *Nature* 2024

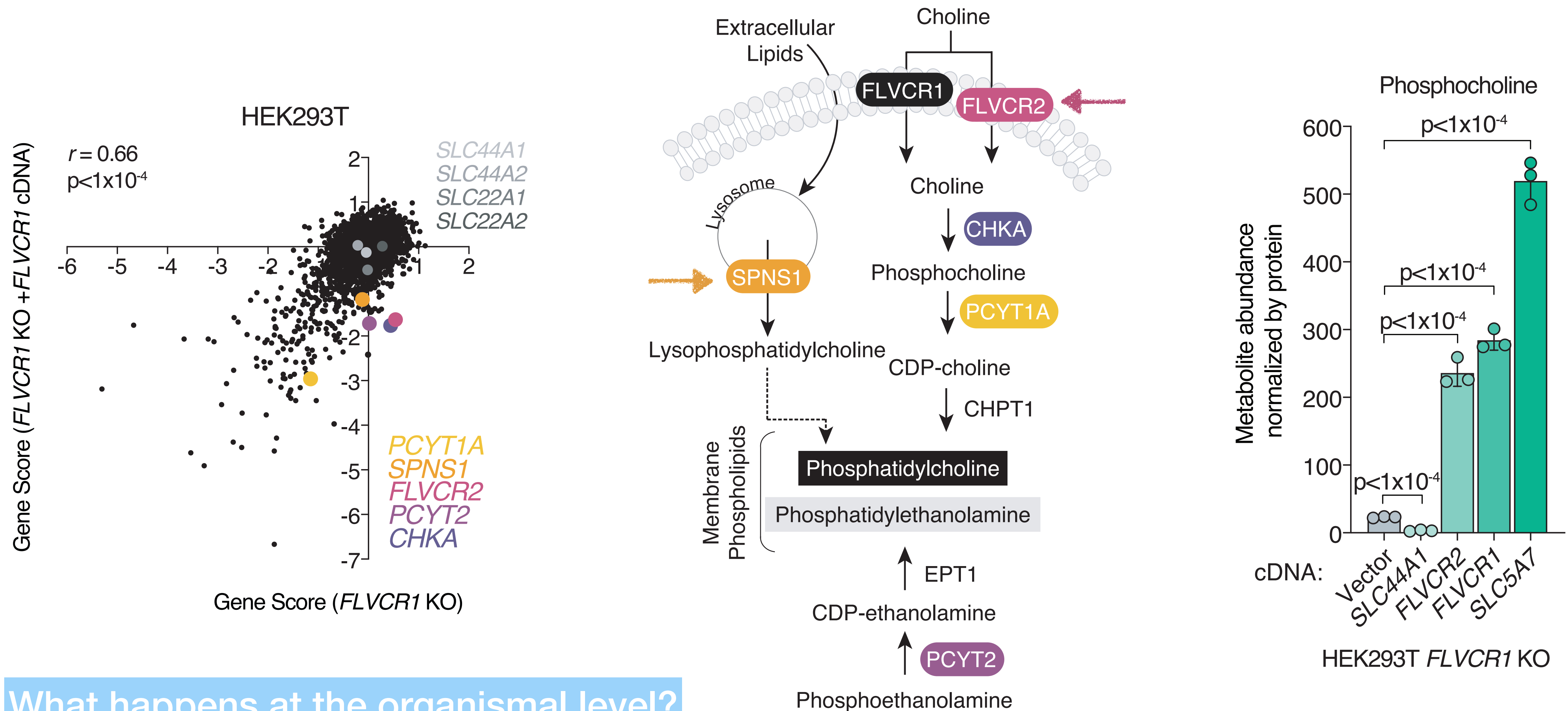
Ri, Weng, and Cabezudo et al. *Nature* 2024

Cells without FLVCR1 can proliferate normally in standard media conditions



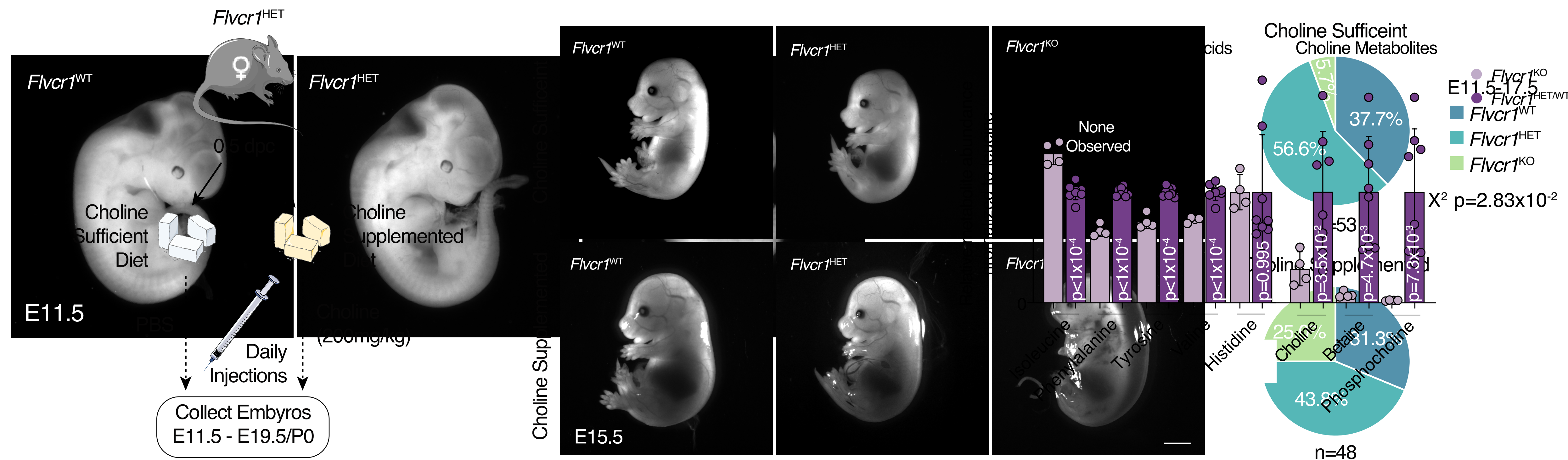
How do cells sustain choline metabolism to proliferate without FLVCR1?

Choline salvage and alternative transport enable proliferation in the absence of FLVCR1



What happens at the organismal level?

Choline transport via FLVCR1 is required for murine embryogenesis

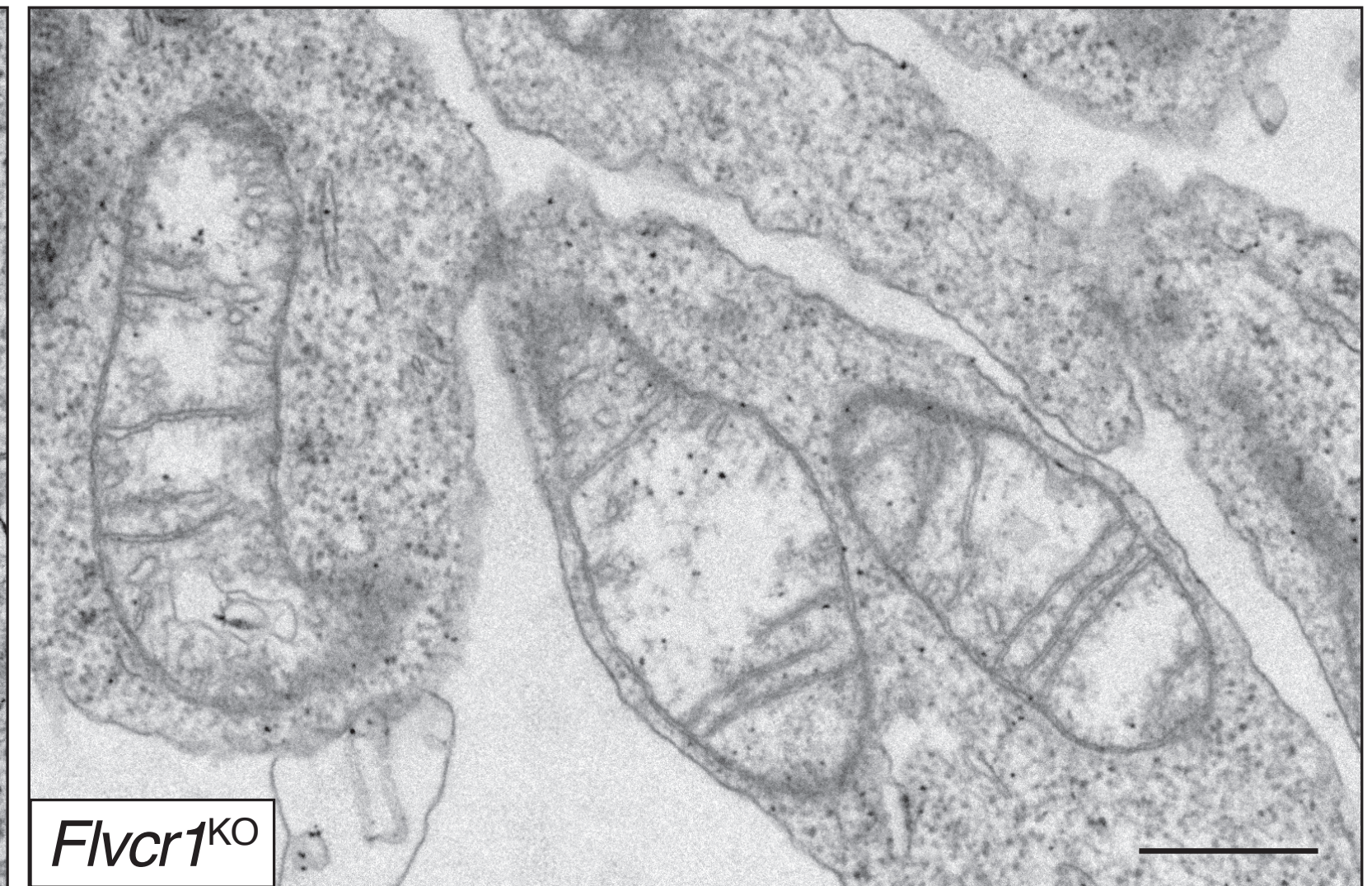
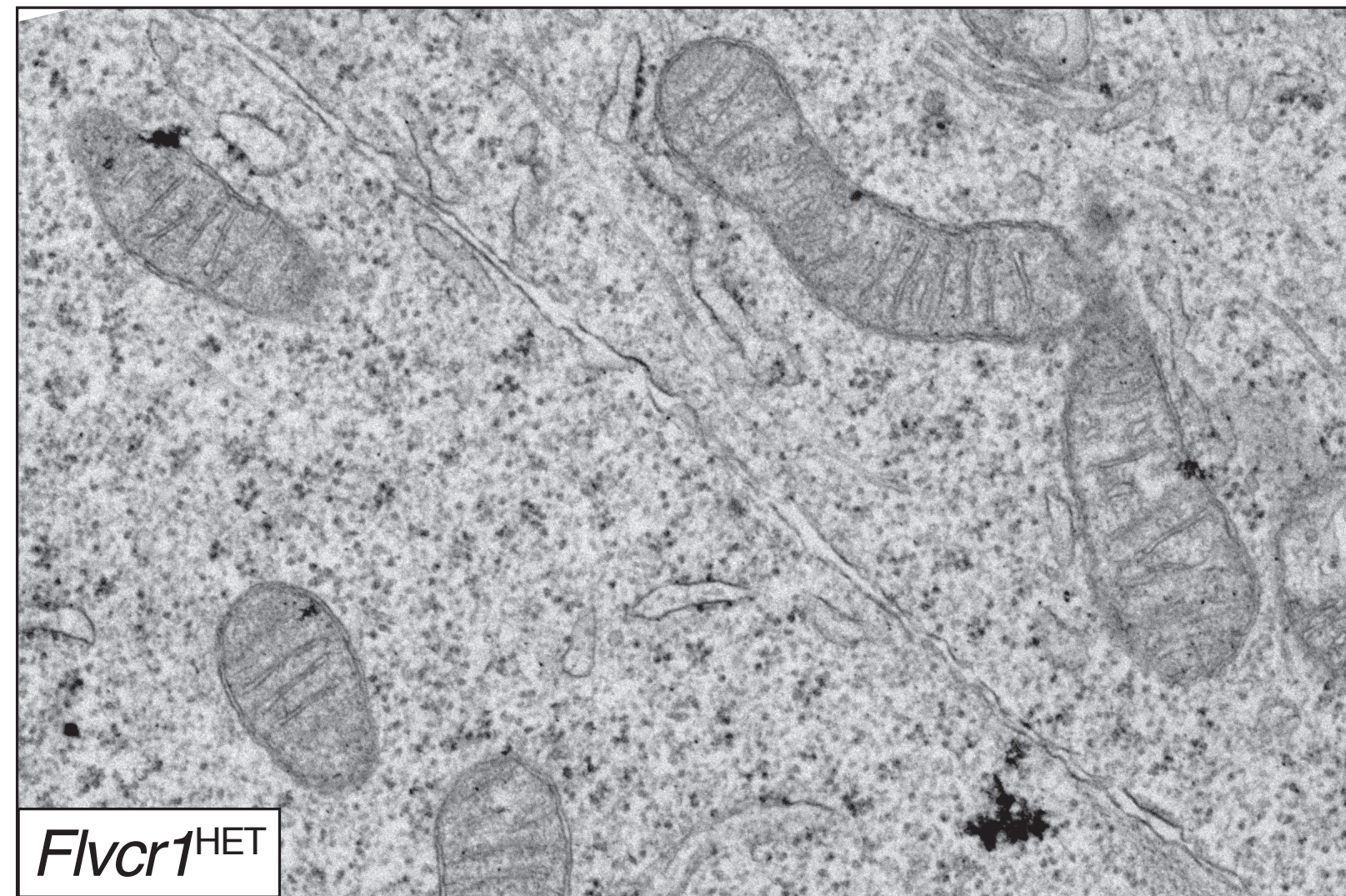


Why is FLVCR1 loss embryonically lethal?

Embryos lacking FLVCR1 have severe mitochondrial dysfunction



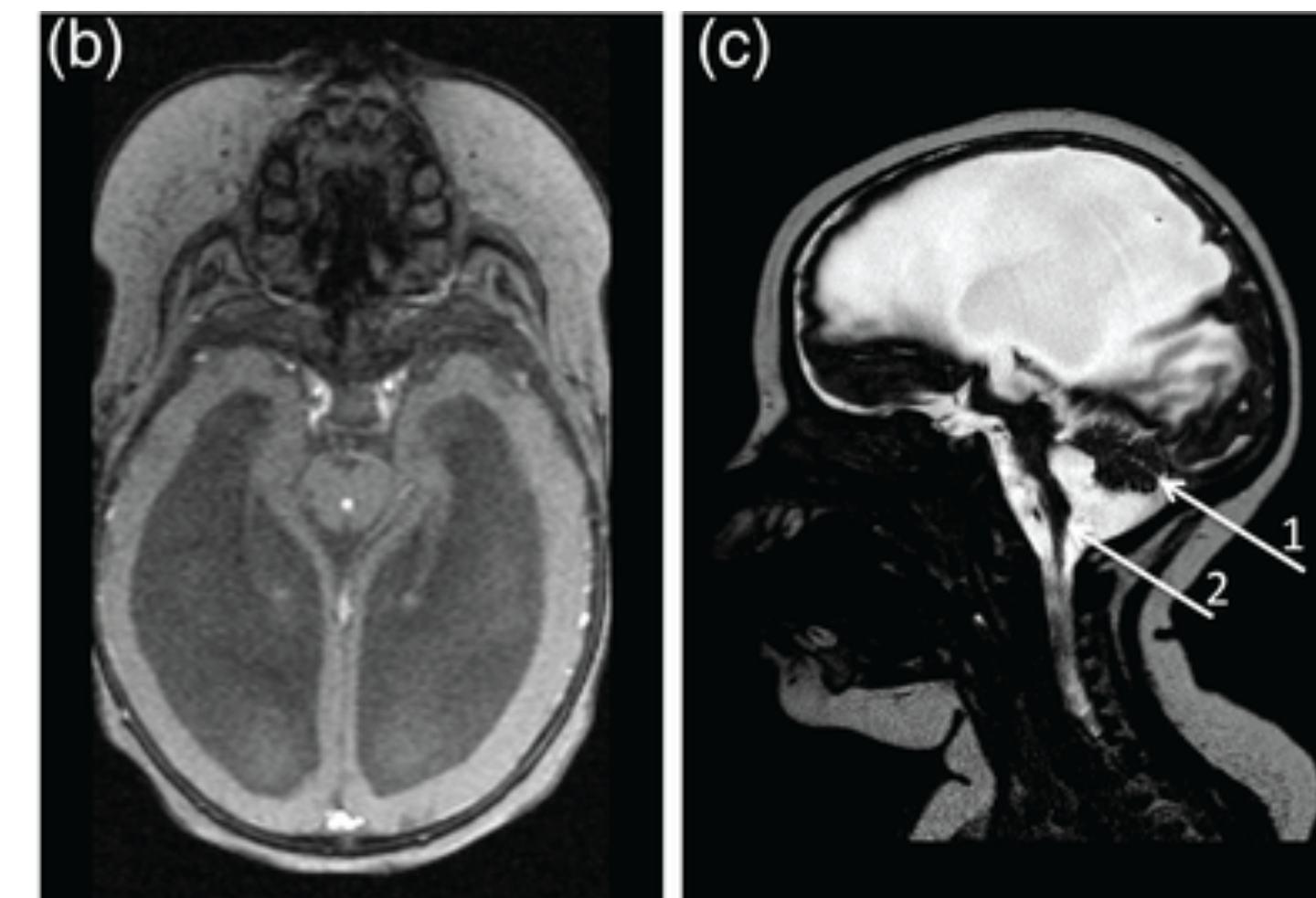
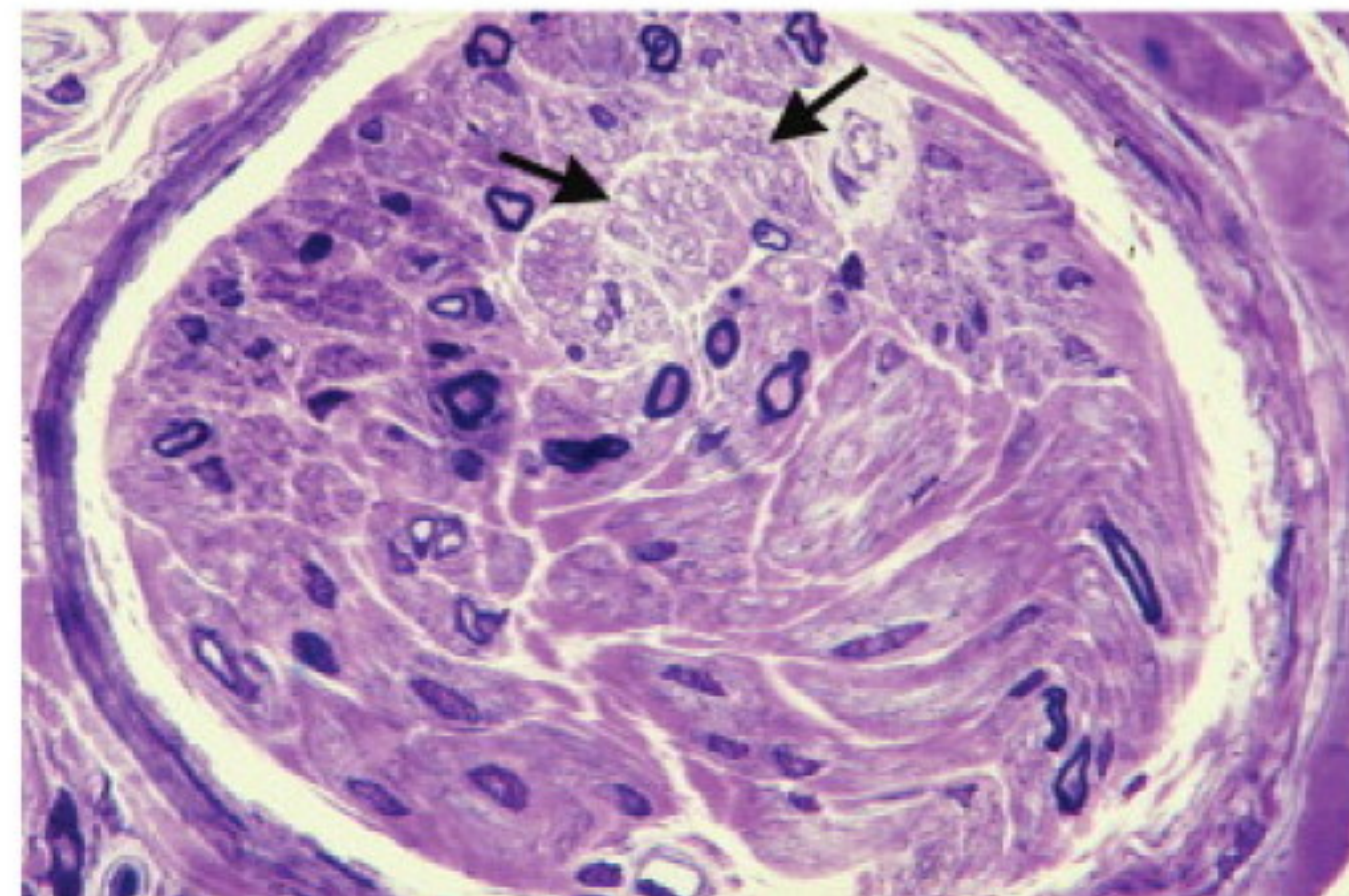
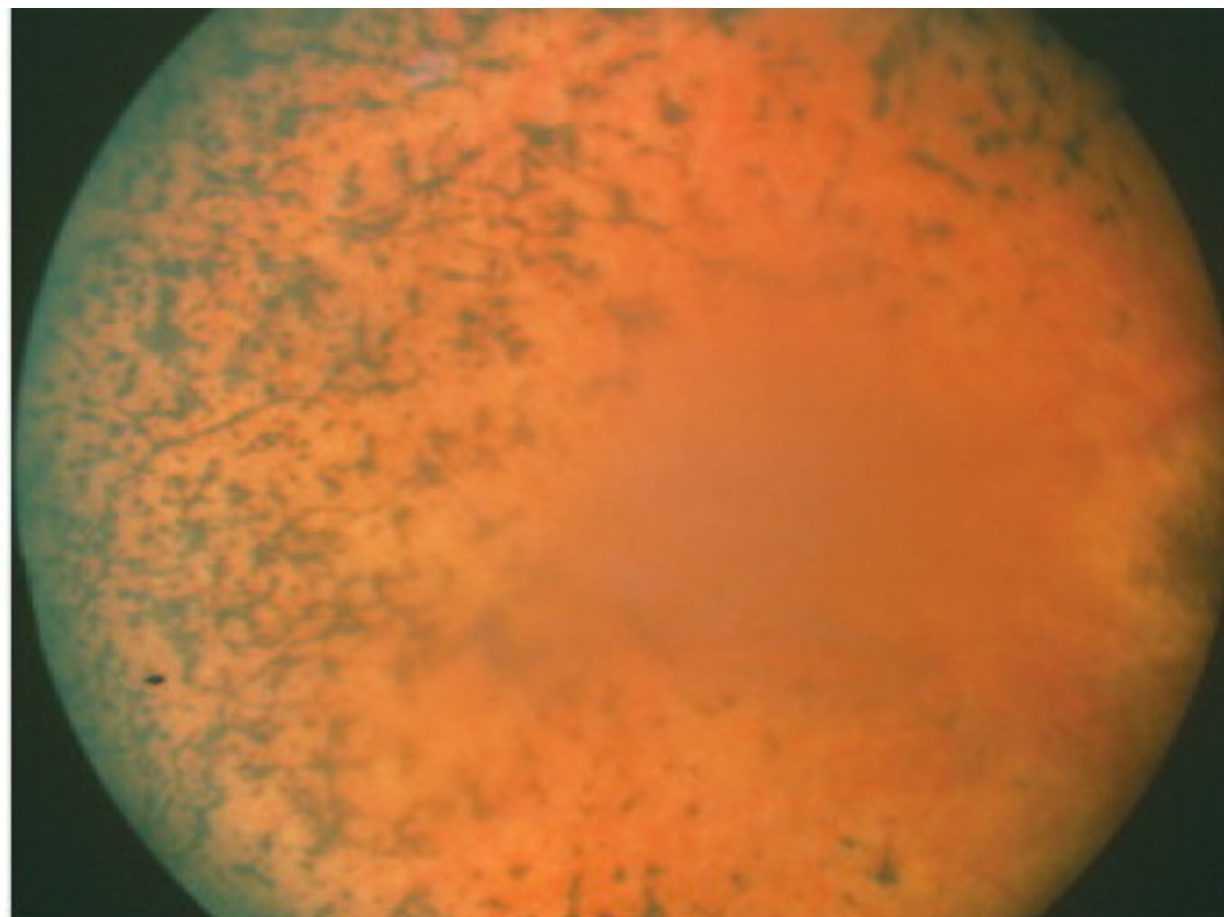
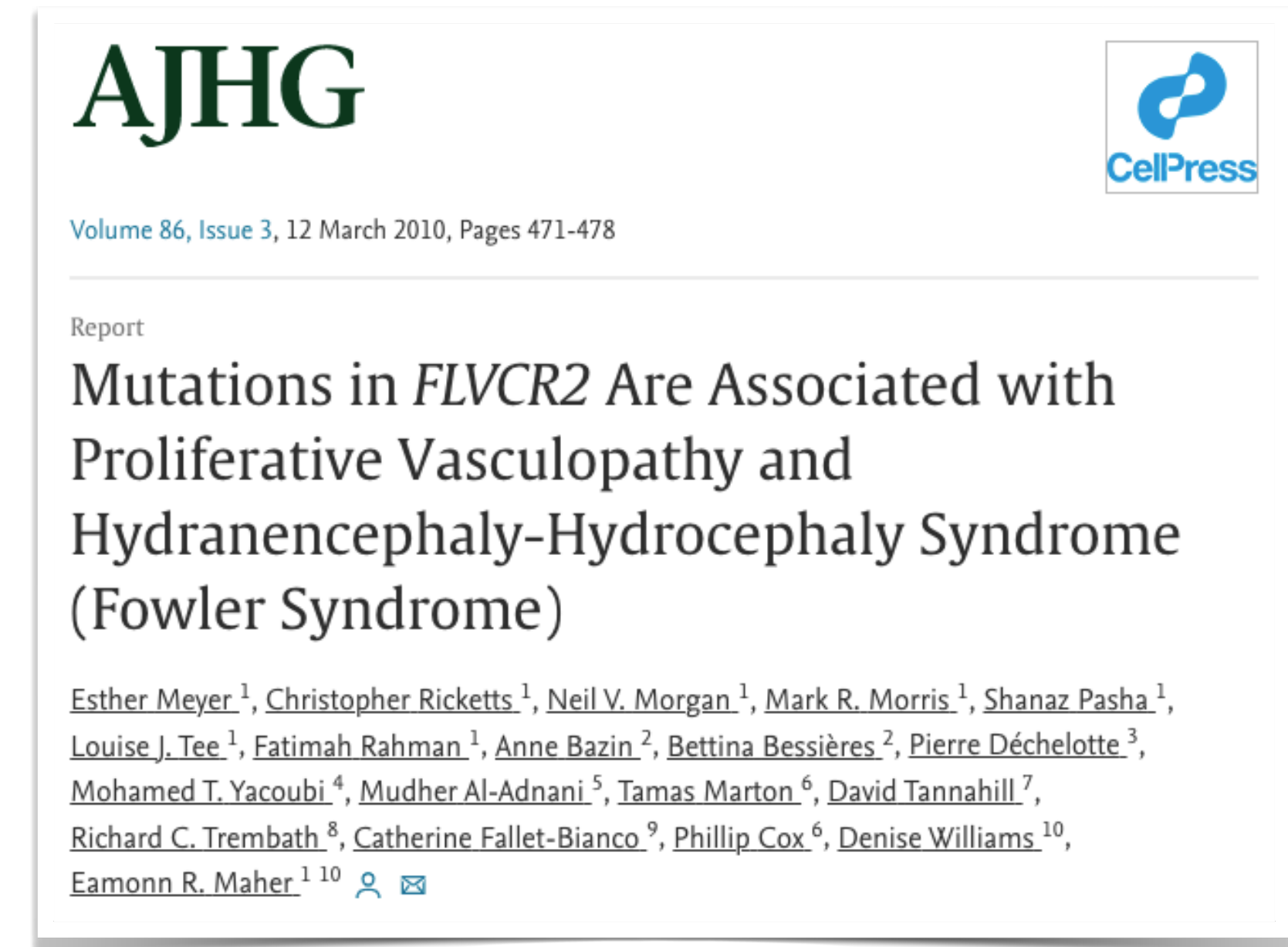
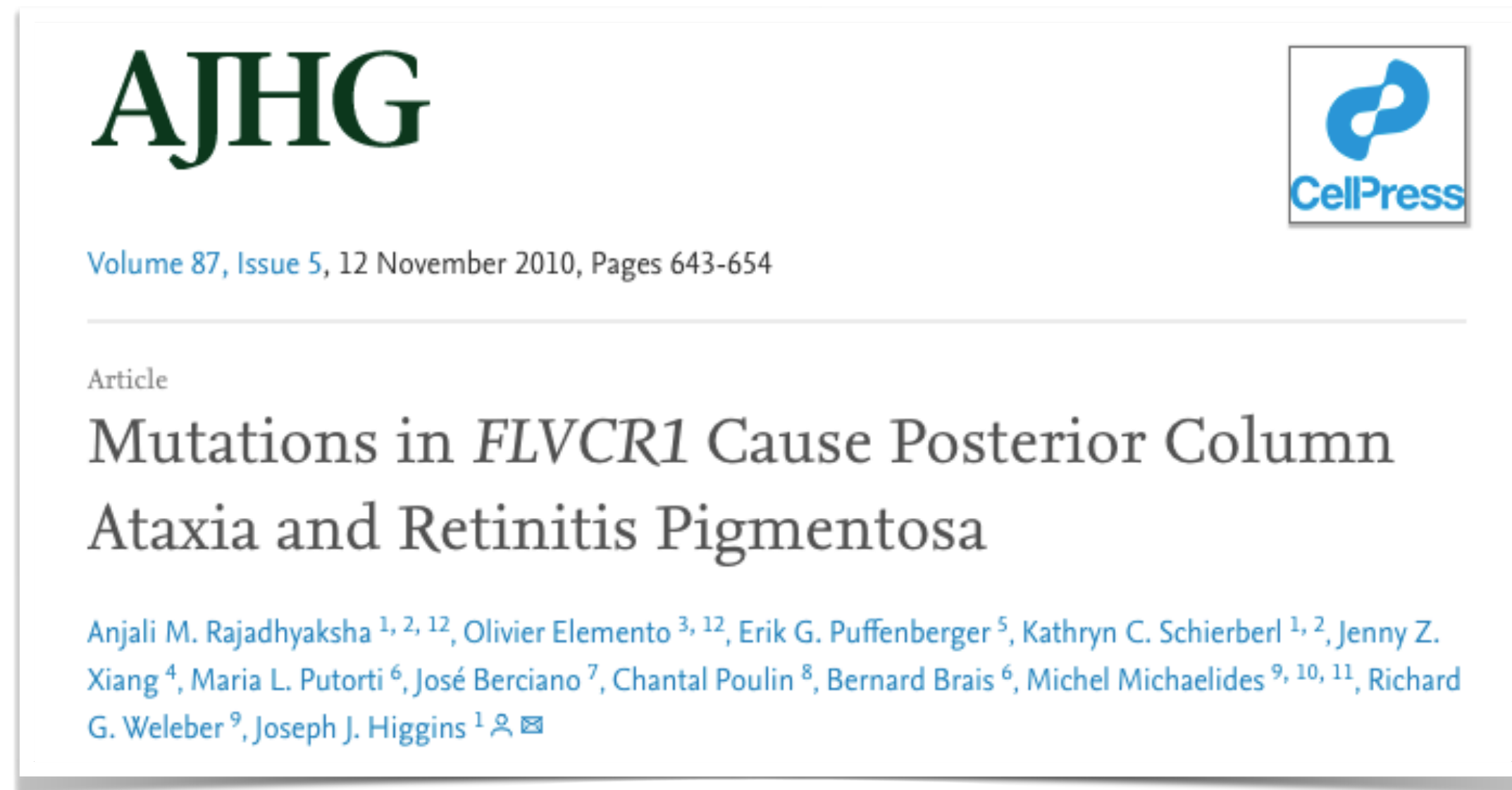
Brain



E11.5

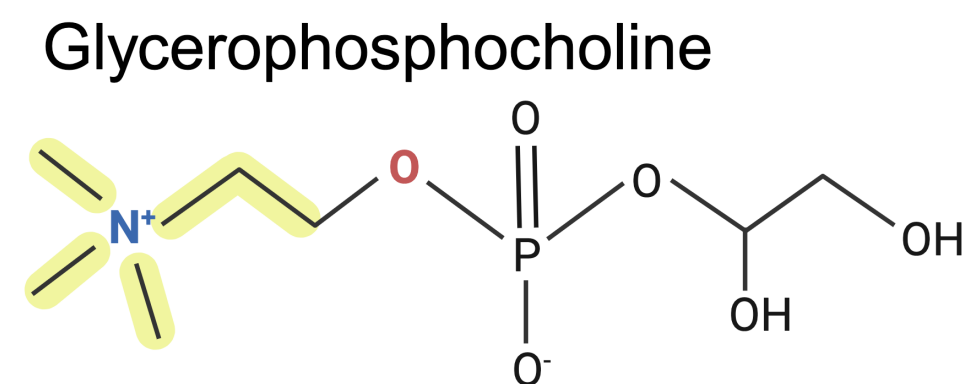
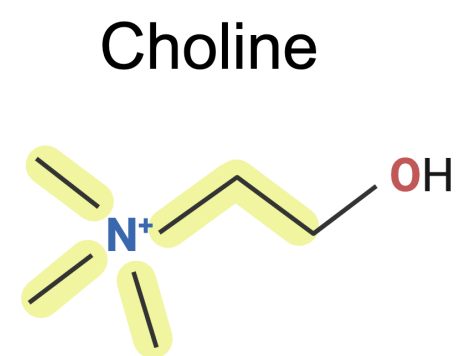
What about in humans?

FLVCR1/2 is implicated in human disease

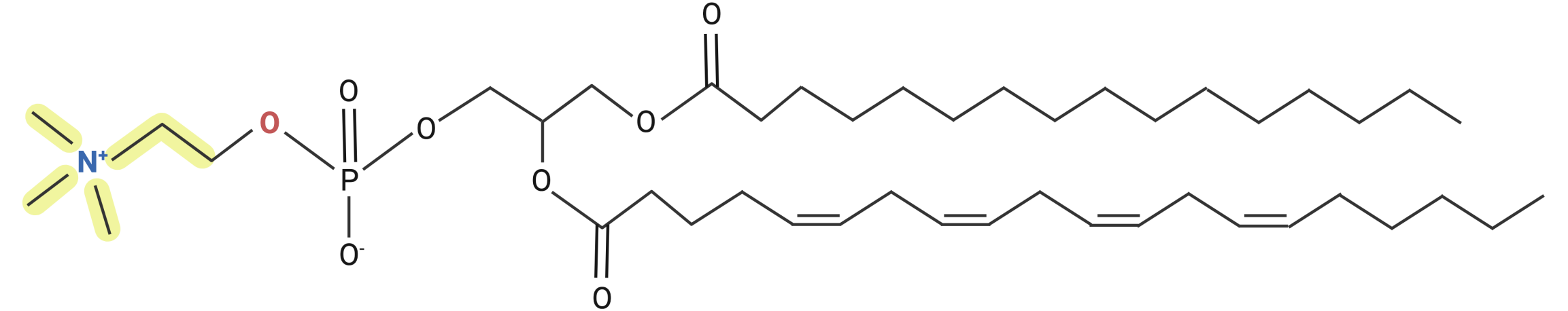


Deorphanization of nutrient transporters highlights potential therapies and new research avenues

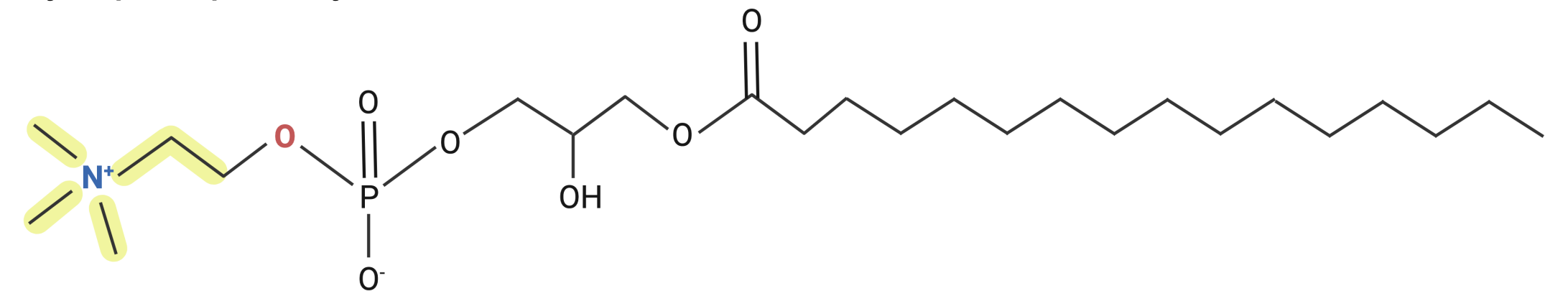
Patients with variants in FLVCR1/2 may benefit from dietary choline supplementation



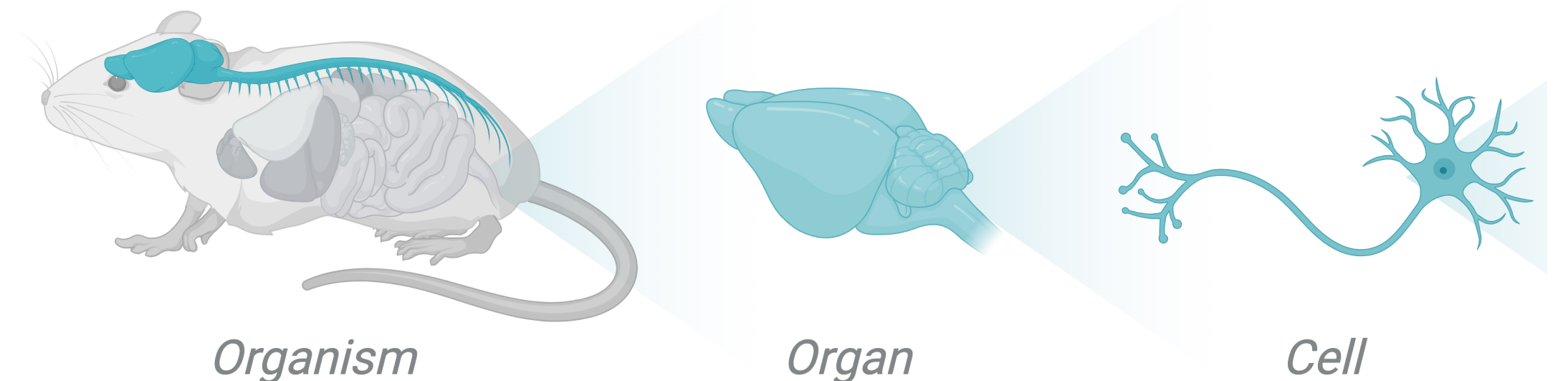
Phosphatidylcholine



Lysophosphatidylcholine



Modulate nutrient transport to affect cellular metabolism in specific cell populations



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