



Cellular Metabolism and Nutrient Transport

Timothy C. Kenny, PhD

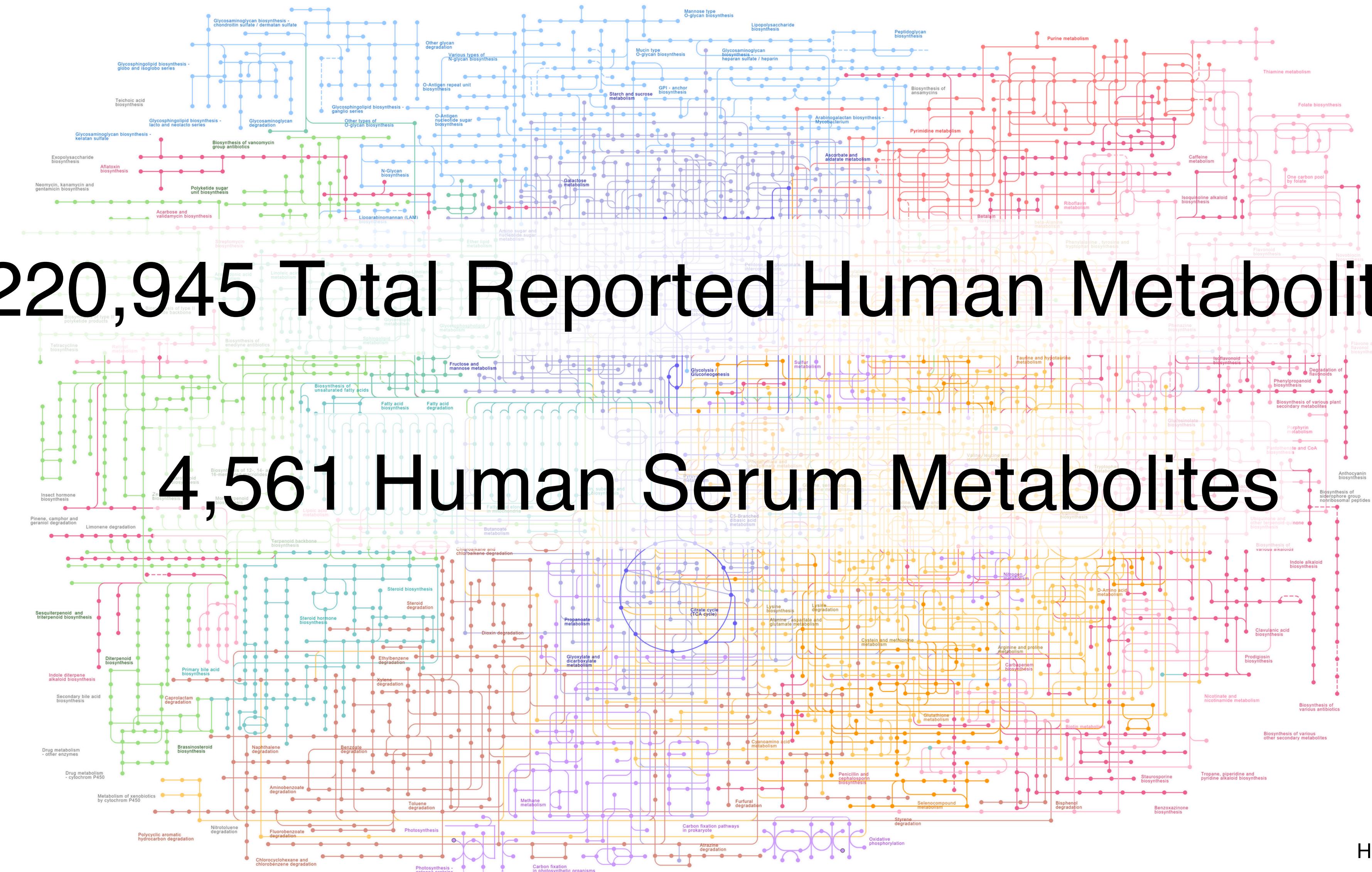
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Metabolism is the sum of all chemical reactions in a biological system

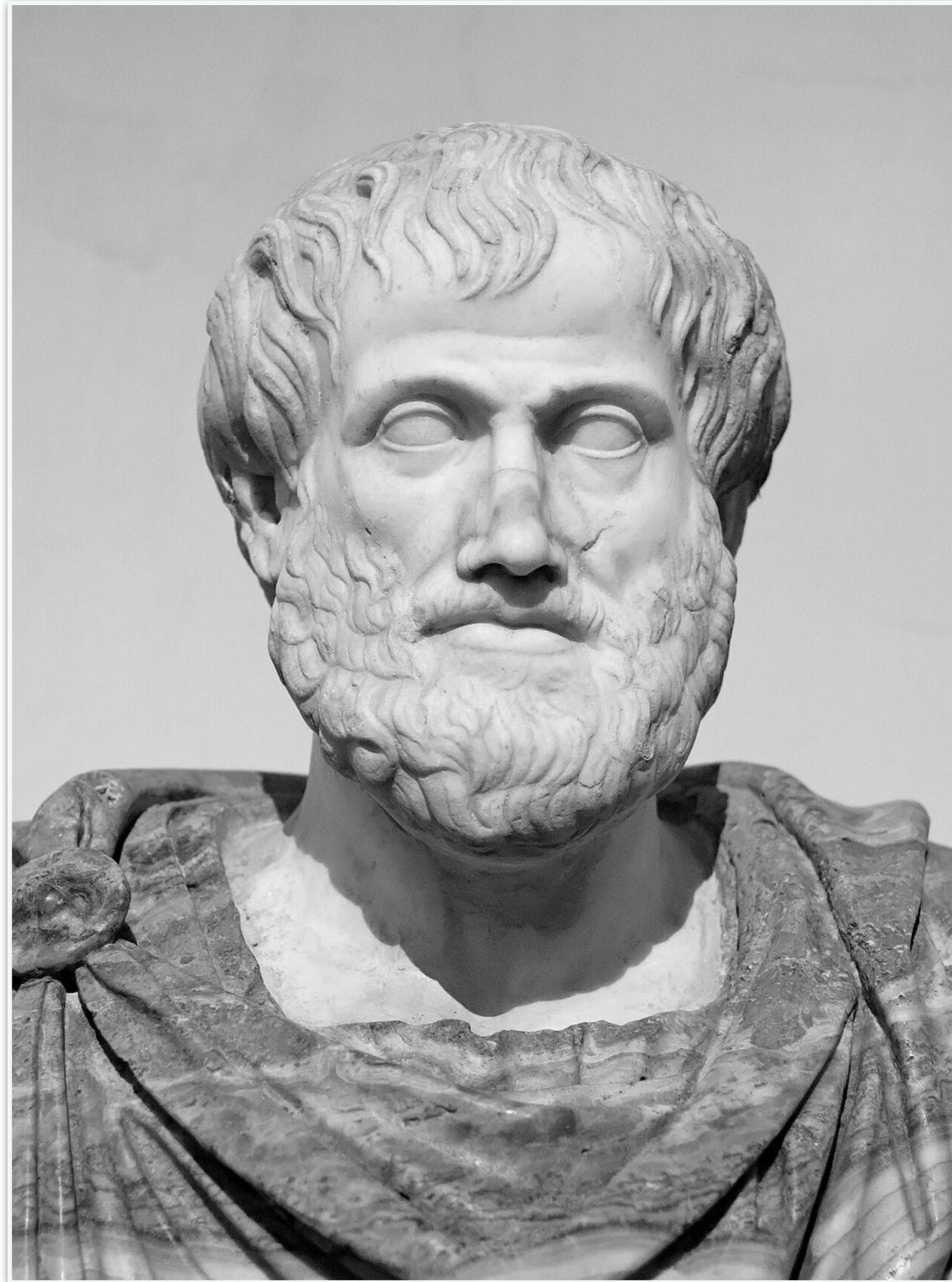
220,945 Total Reported Human Metabolites





How is metabolic homeostasis maintained?

*Food makes body
and heat*



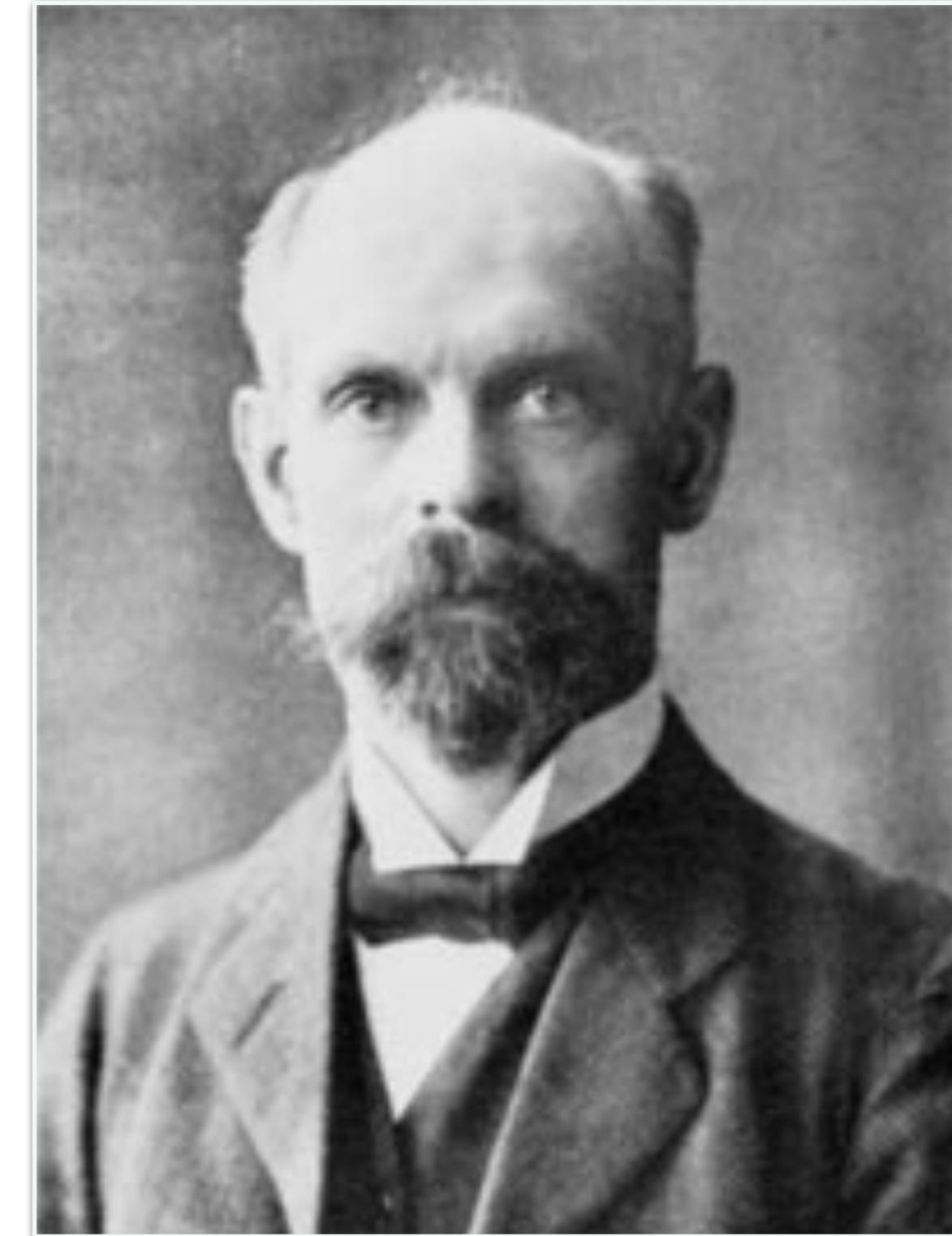
Aristotle
4th Century BCE

*Measurement of
consumption*



Sanctorius
17th Century AD

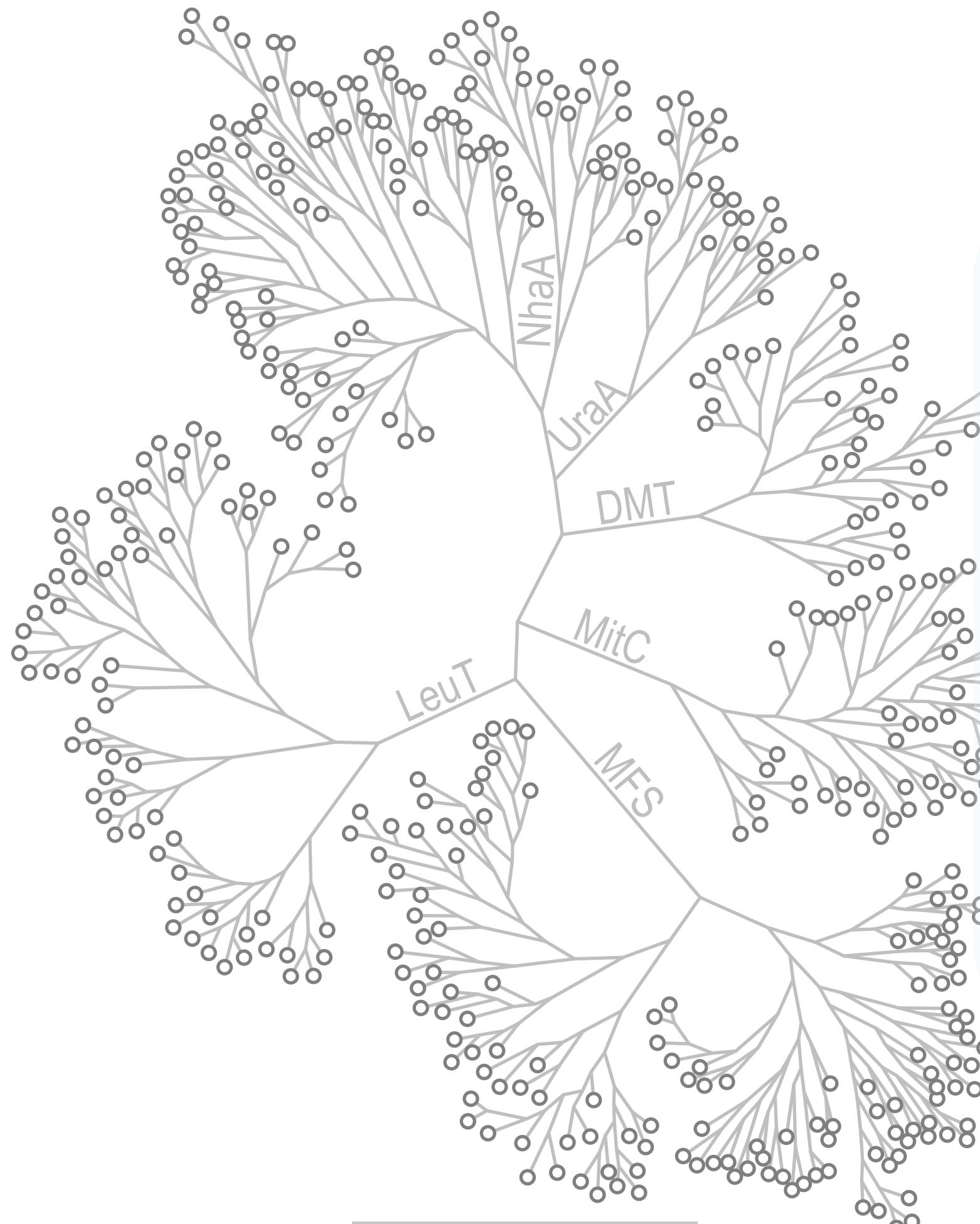
*Cellular metabolite
transport*



Ernest Overton
19th Century AD

Transporters are the gatekeepers of metabolism

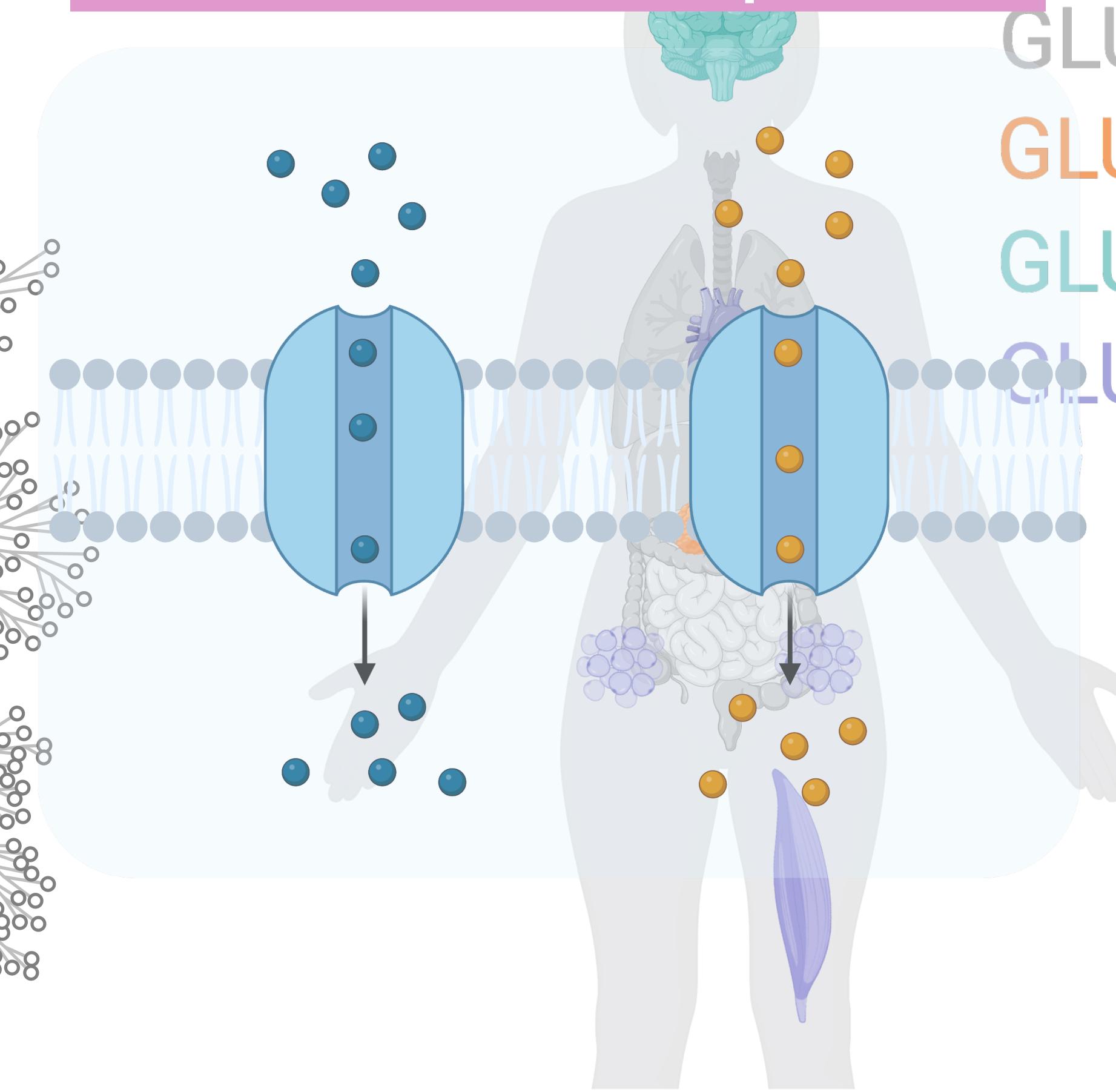
Solute Carrier (SLC) superfamily
of metabolic transporters



456 Genes

10% of the genome
encodes for transporters

Paralogs evolved to fine-tune
organismal metabolism



GLUT1/SLC2A1

GLUT2/SLC2A2

GLUT3/SLC2A3

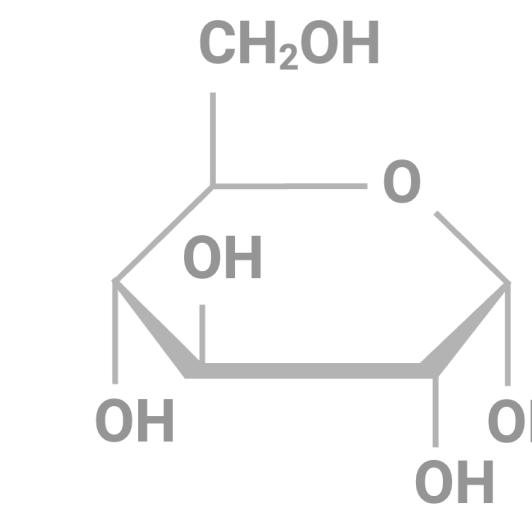
GLUT4/SLC2A4

Ubiquitous expression,
Lower affinity

Pancreatic Beta cells,
Low affinity

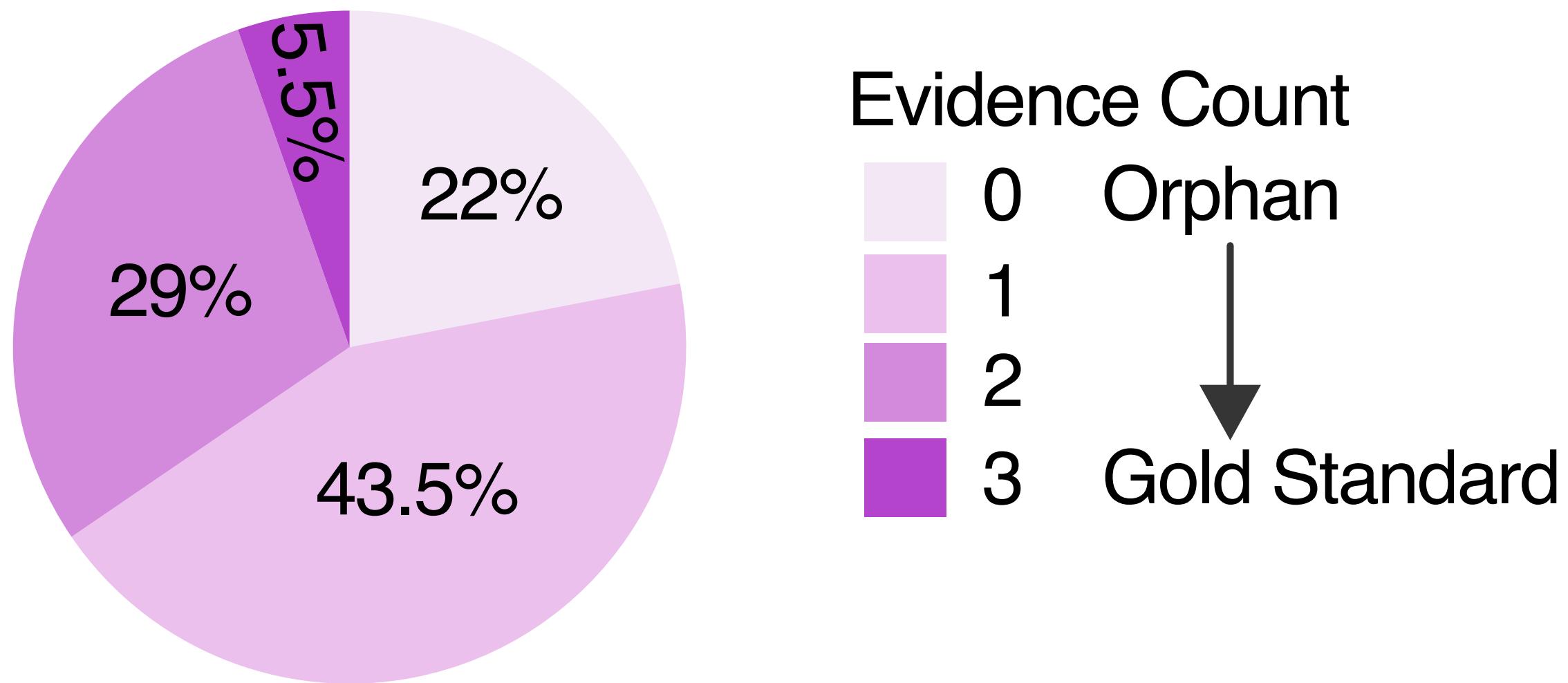
Neuronal expression,
High affinity

Adipose tissue and
muscle, High affinity



SLC transporters are implicated in disease but poorly understood

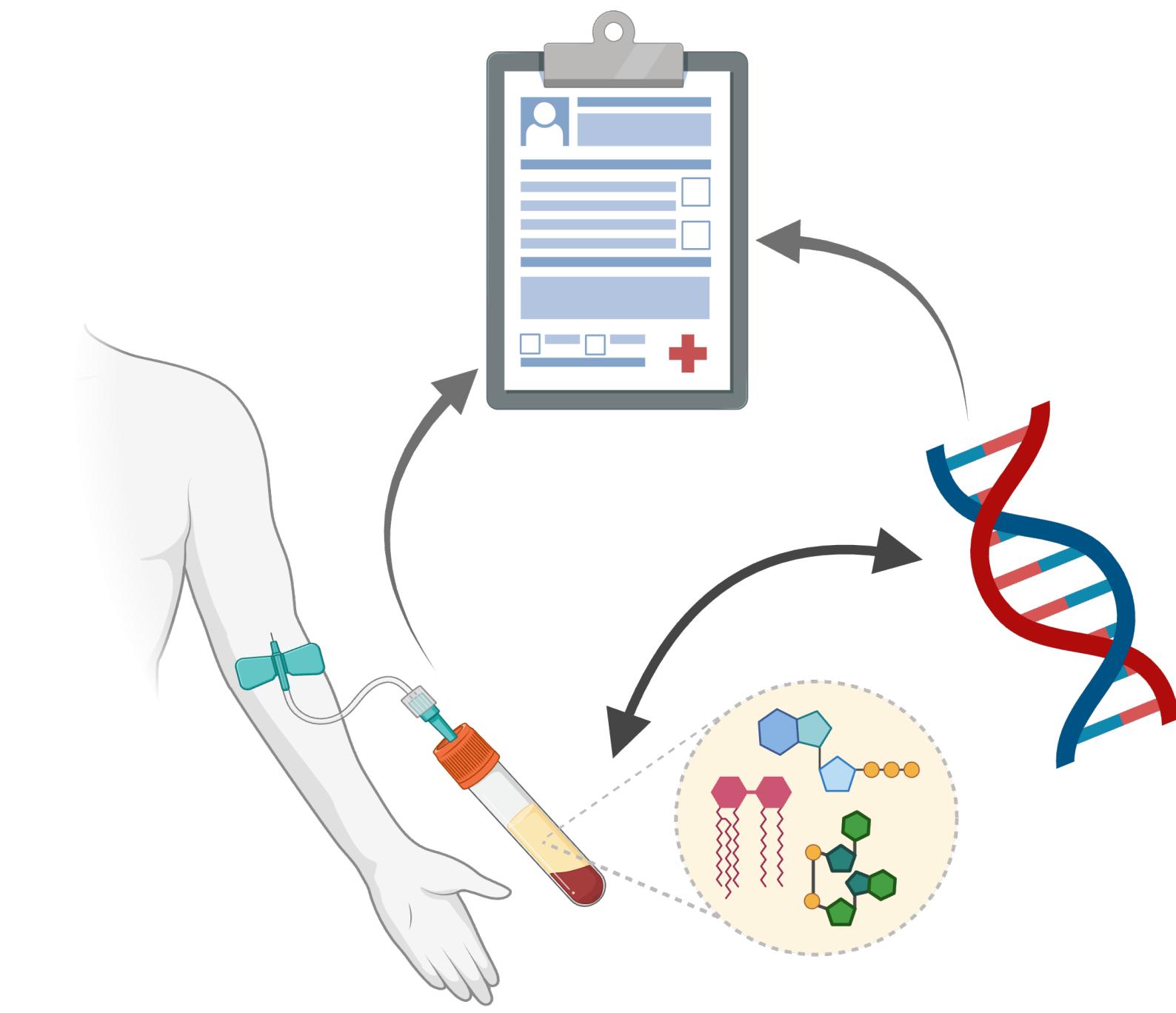
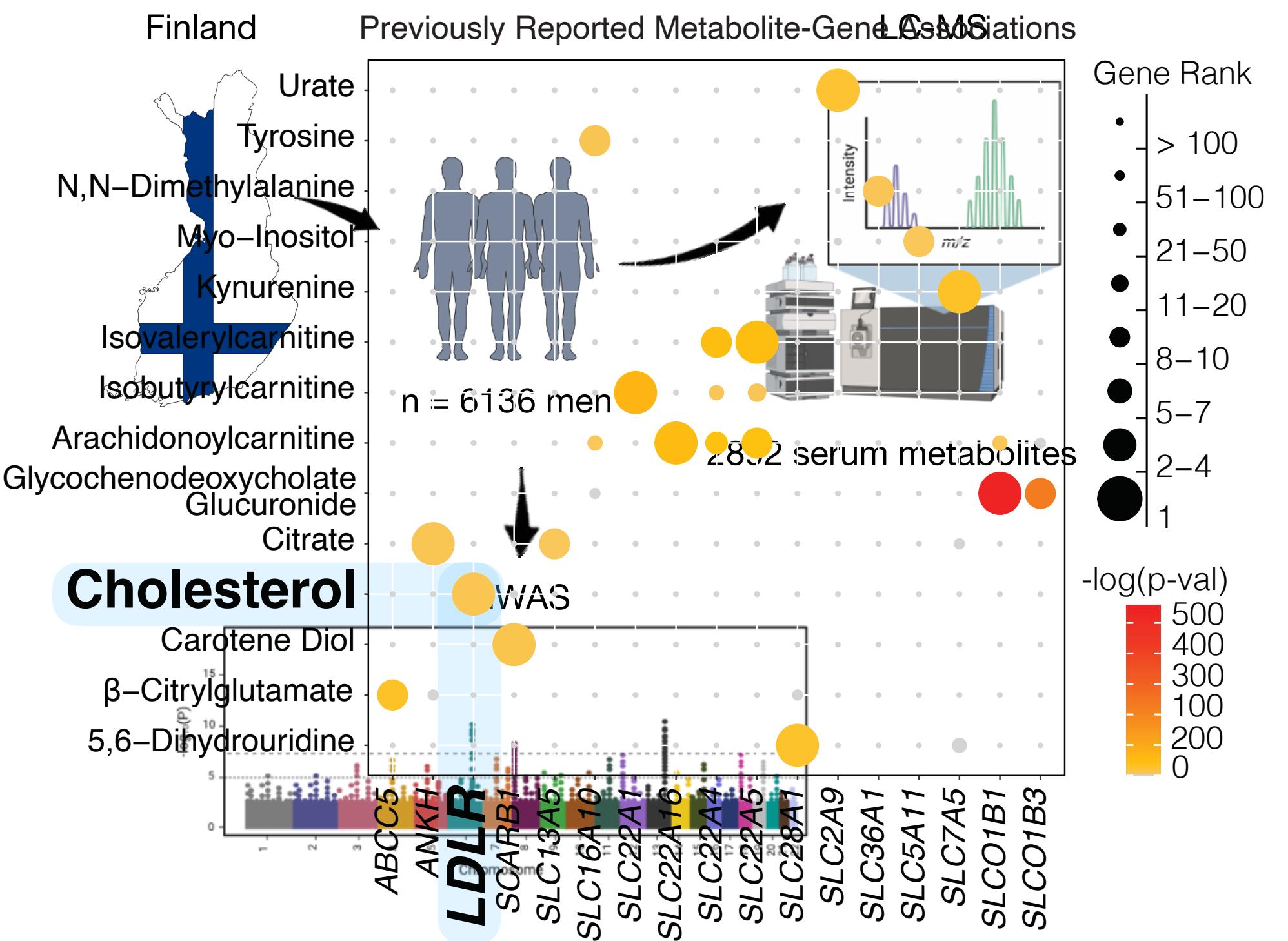
SLC Transporters (n=456)



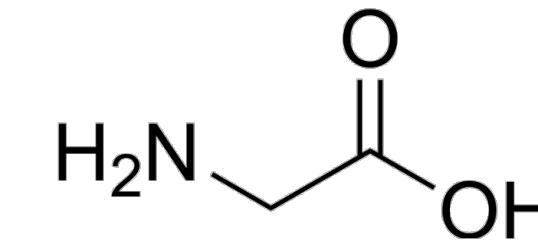
>50% of SLC transporters
are associated with
human disease

How can we systematically identify physiological substrates of metabolite transporters?

Human metabolite GWAS as a discovery platform to deorphanize metabolite transporters

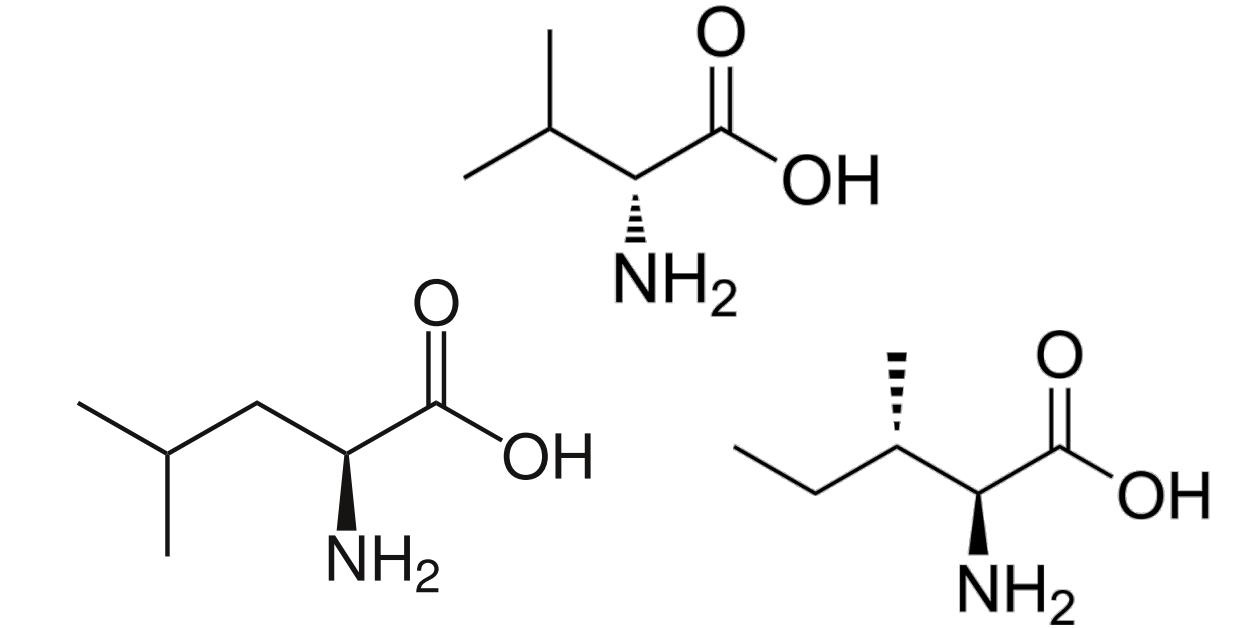


Glycine Encephalopathy



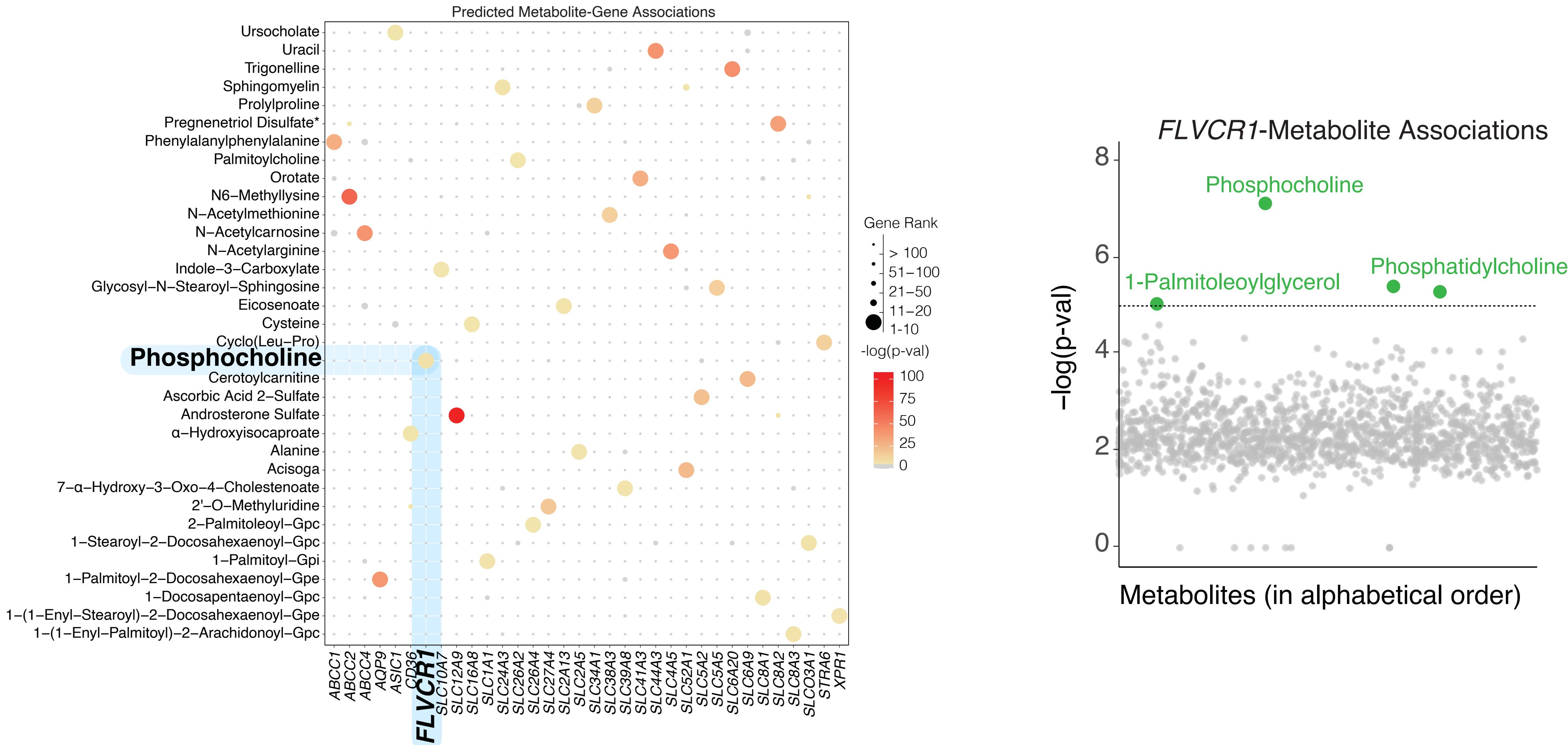
Glycine decarboxylase

Maple Syrup Urine Disease



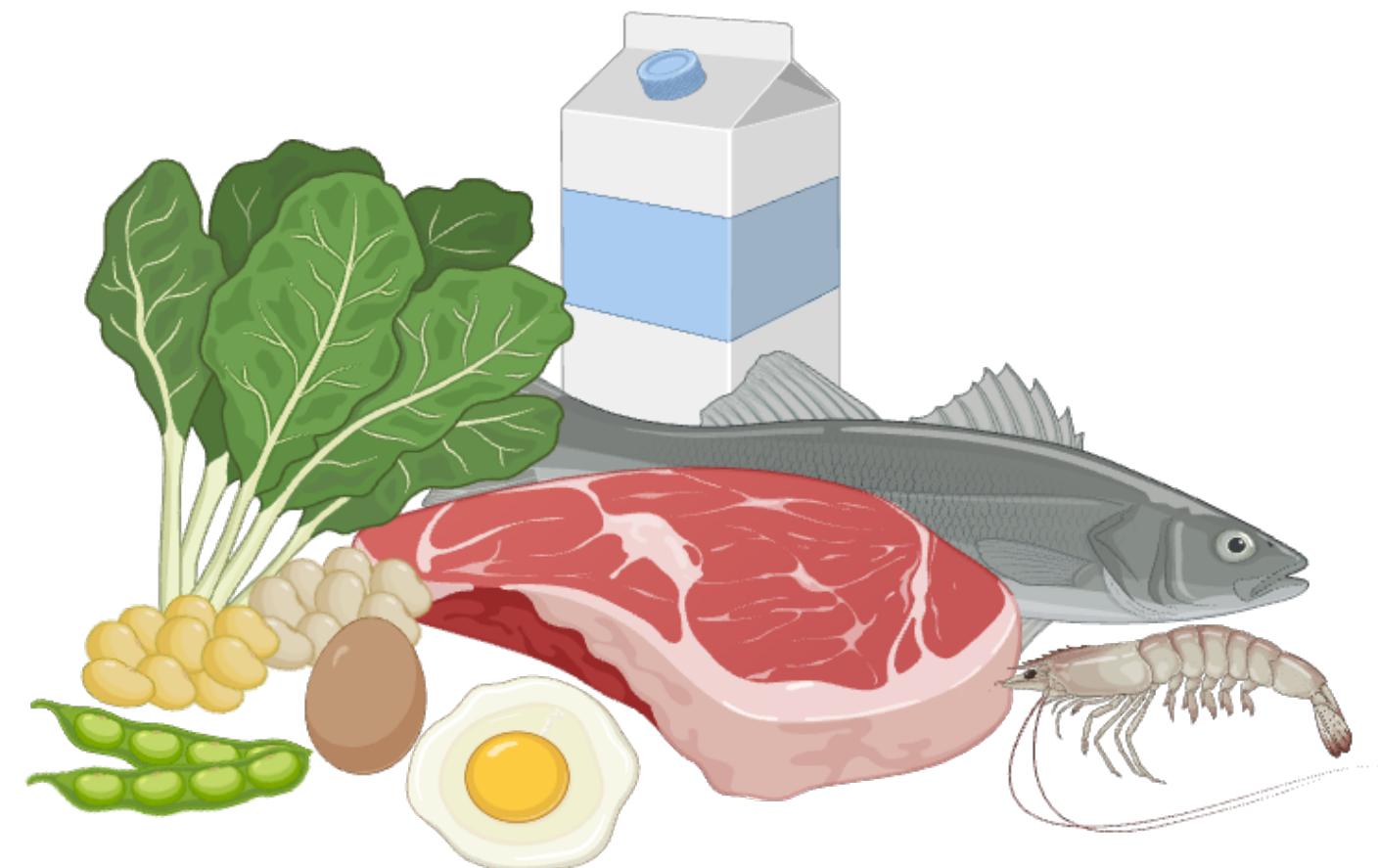
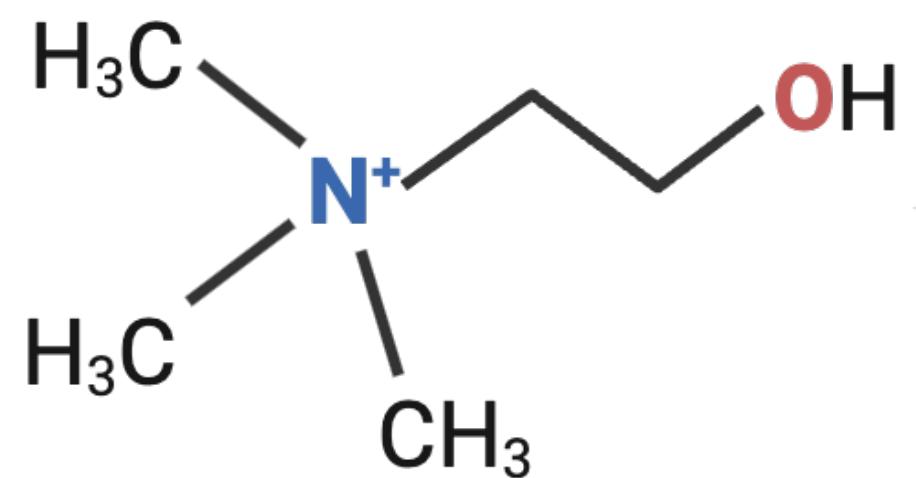
Branched chain ketoacid dehydrogenase kinase

FLVCR1/SLC49A1 is genetically associated with choline metabolites

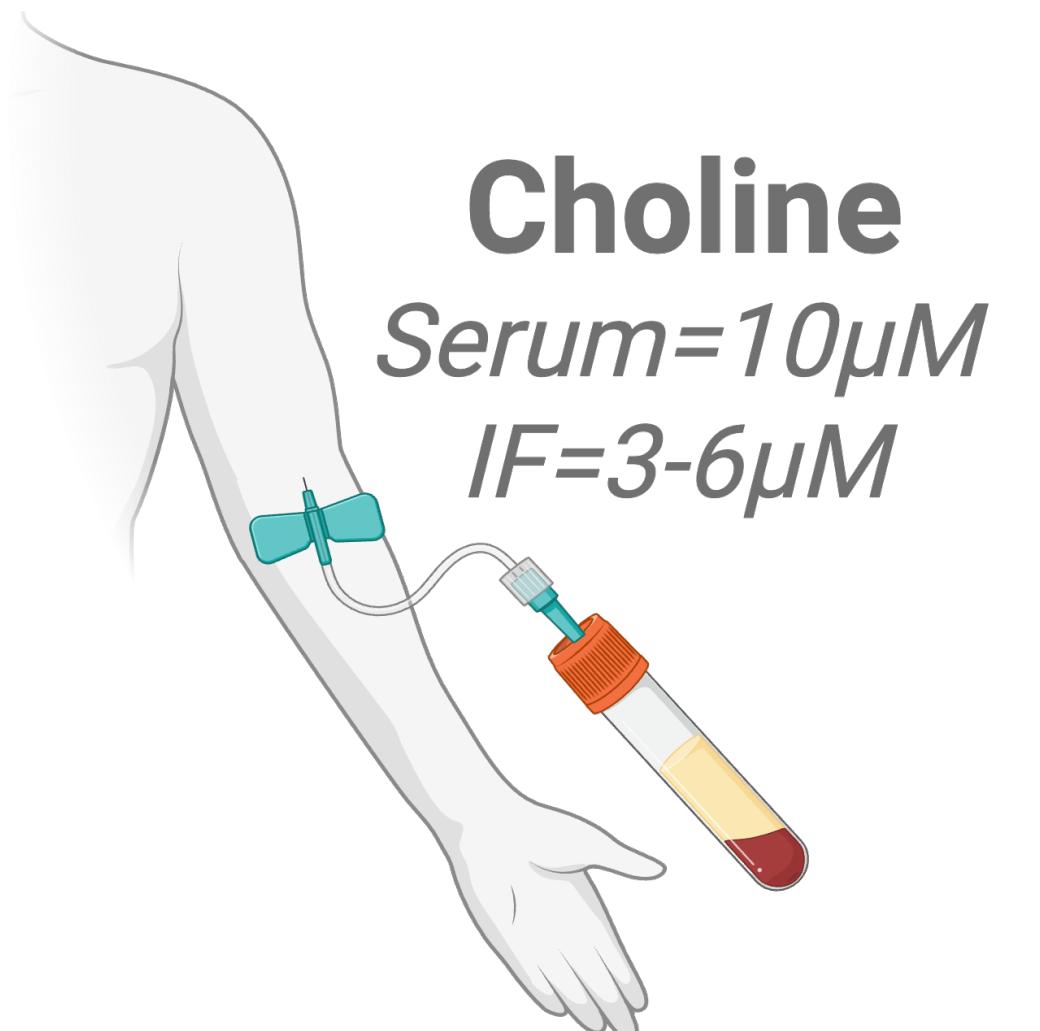


Choline metabolism

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

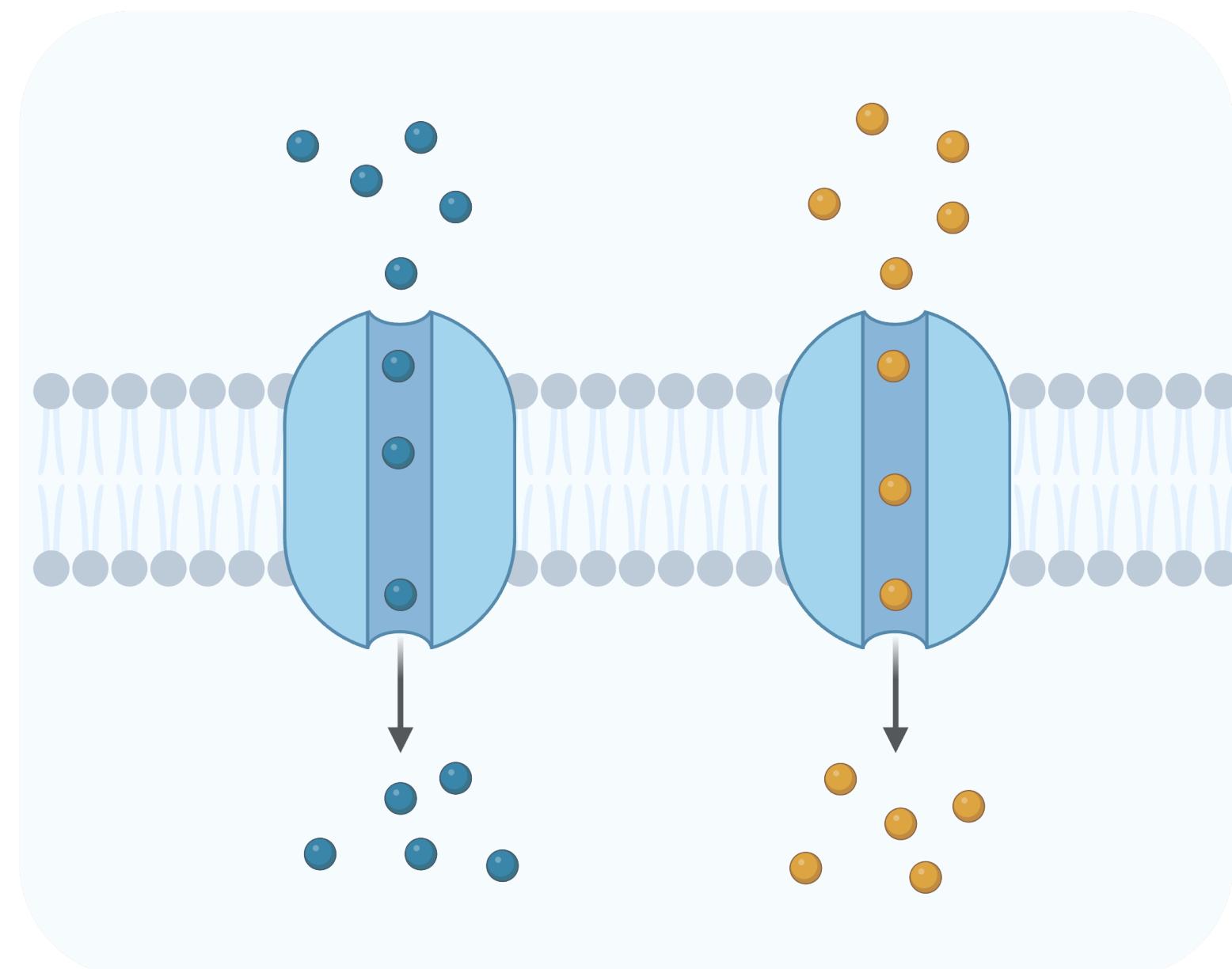


♀ 425 mg/day*
♂ 550 mg/day

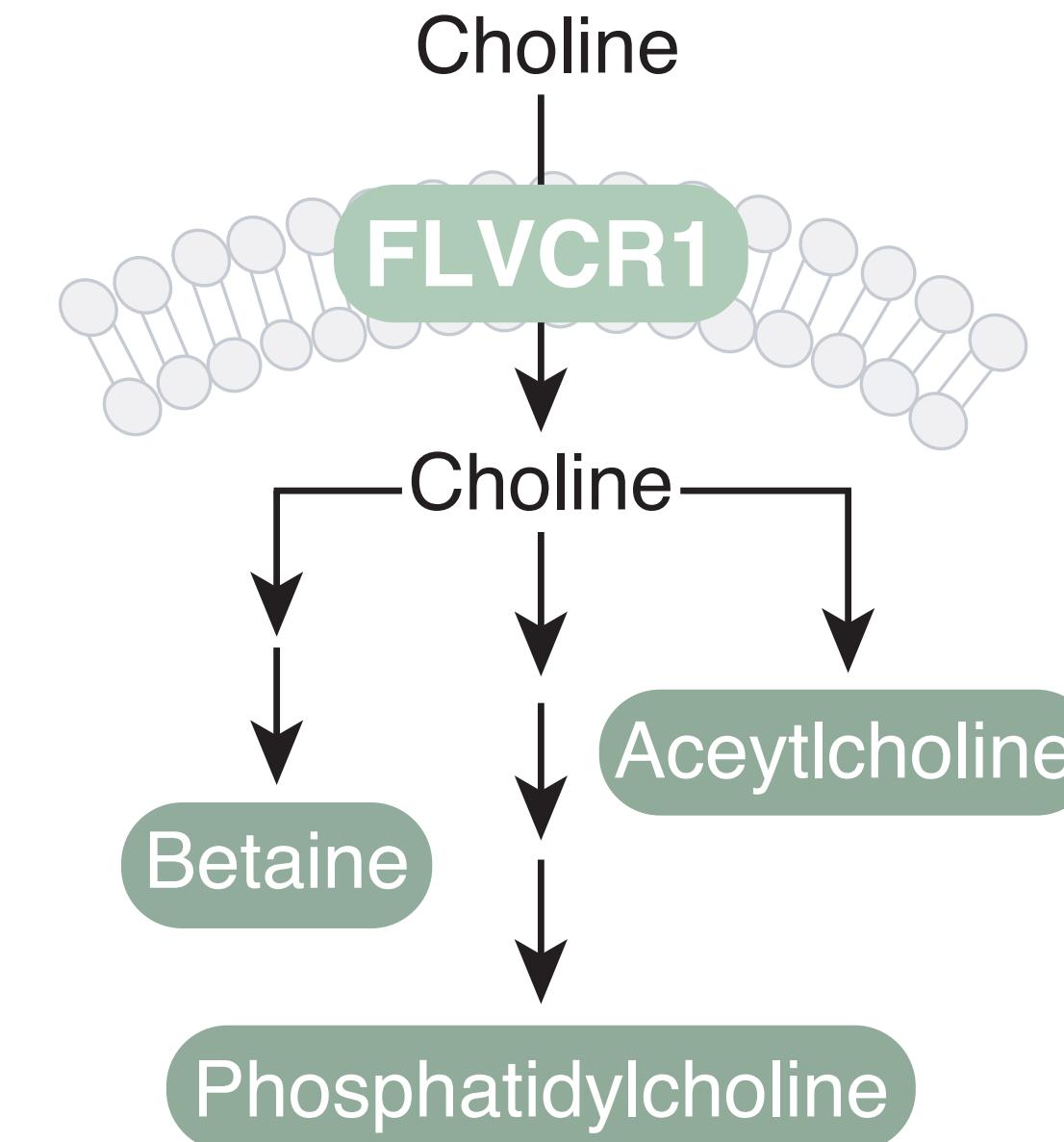
Institute of Medicine
1998

Choline transport

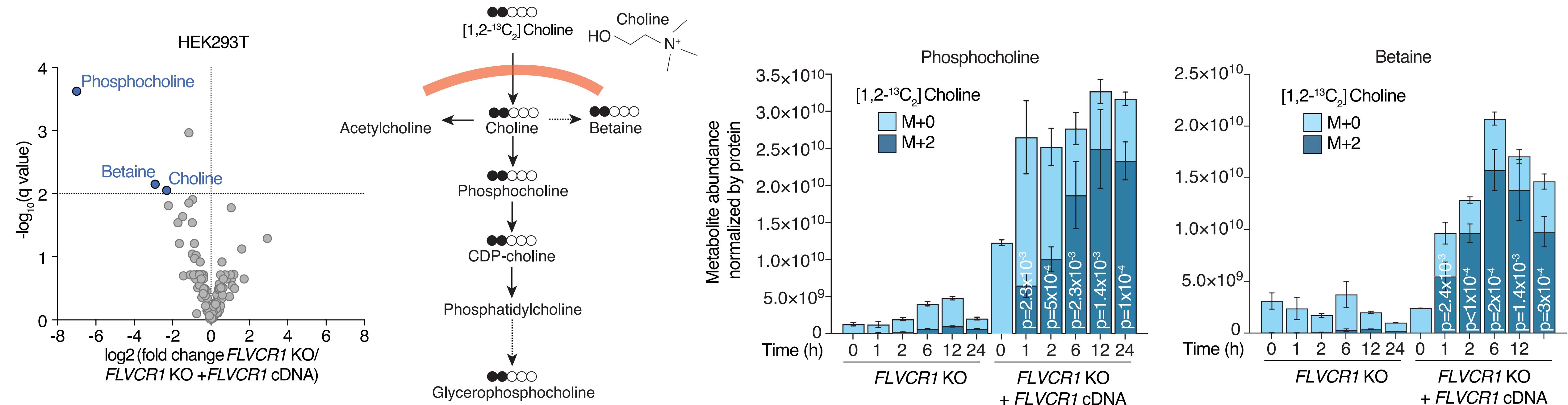
Choline must be transported into the cell



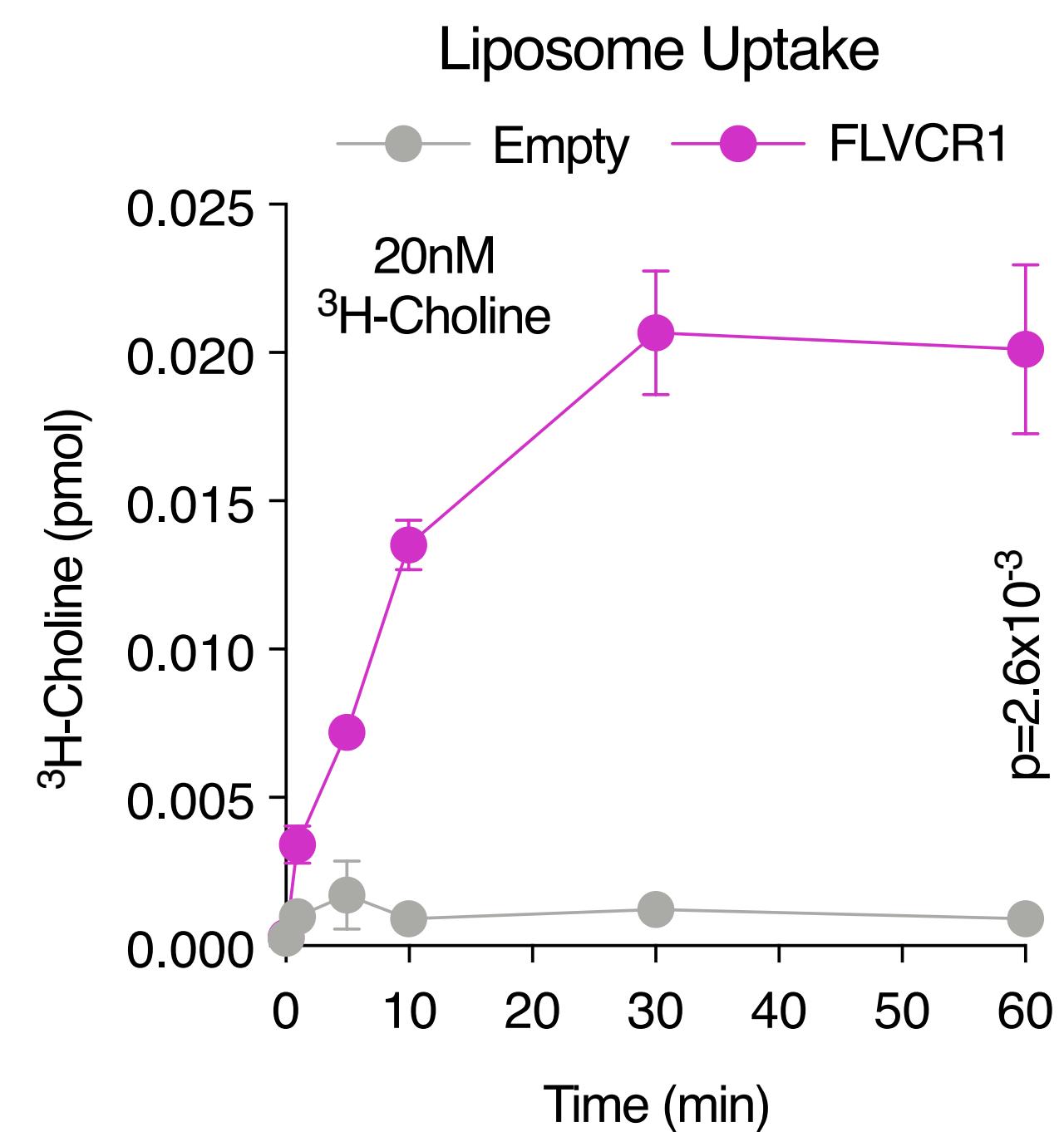
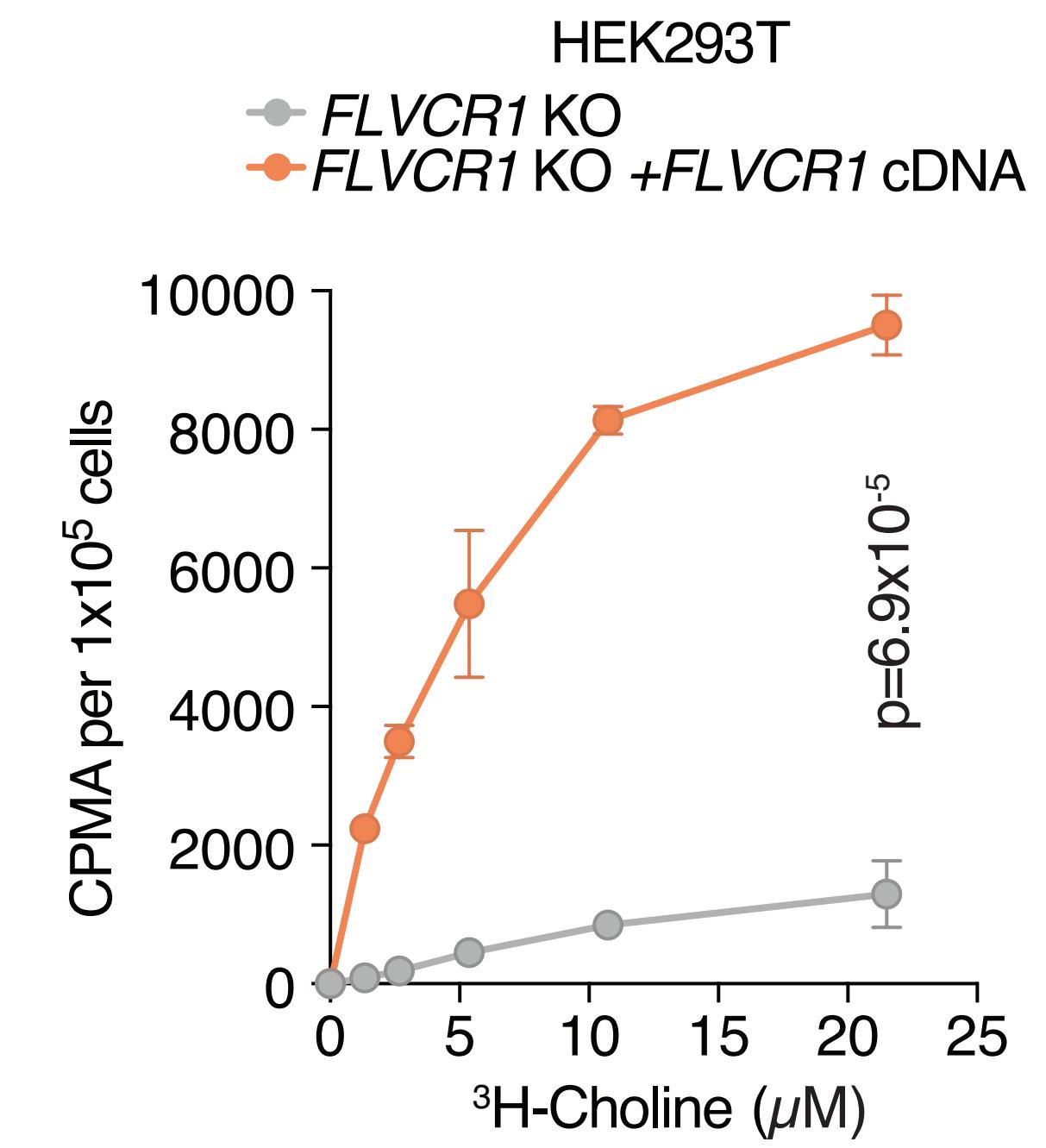
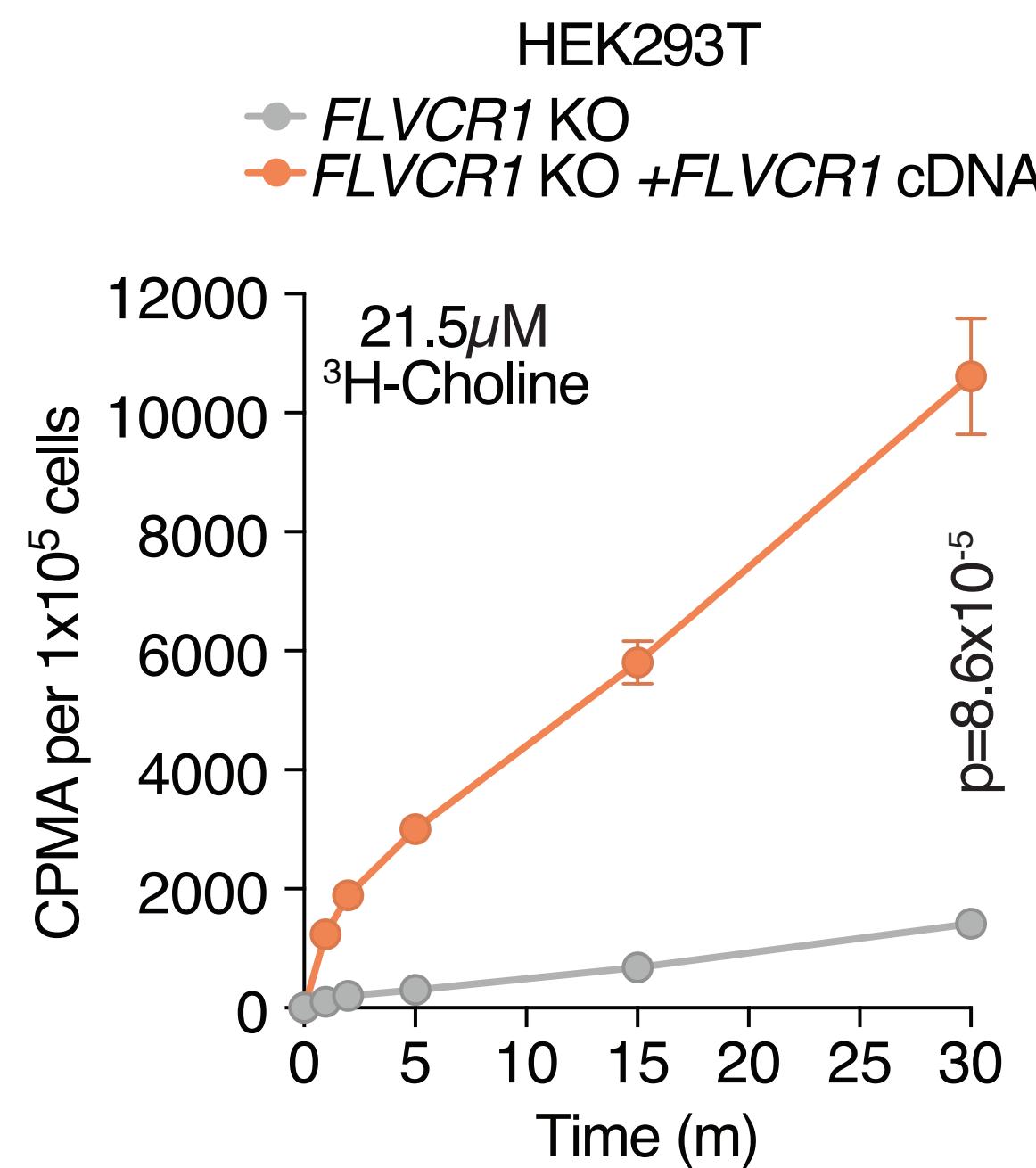
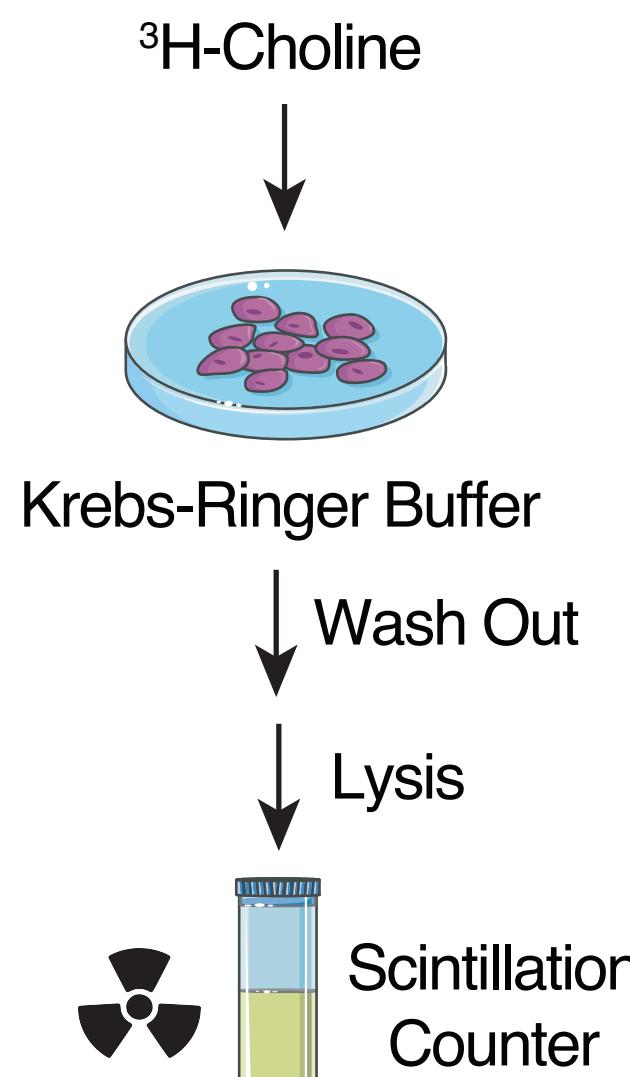
Is FLVCR1 a high affinity choline transporter?



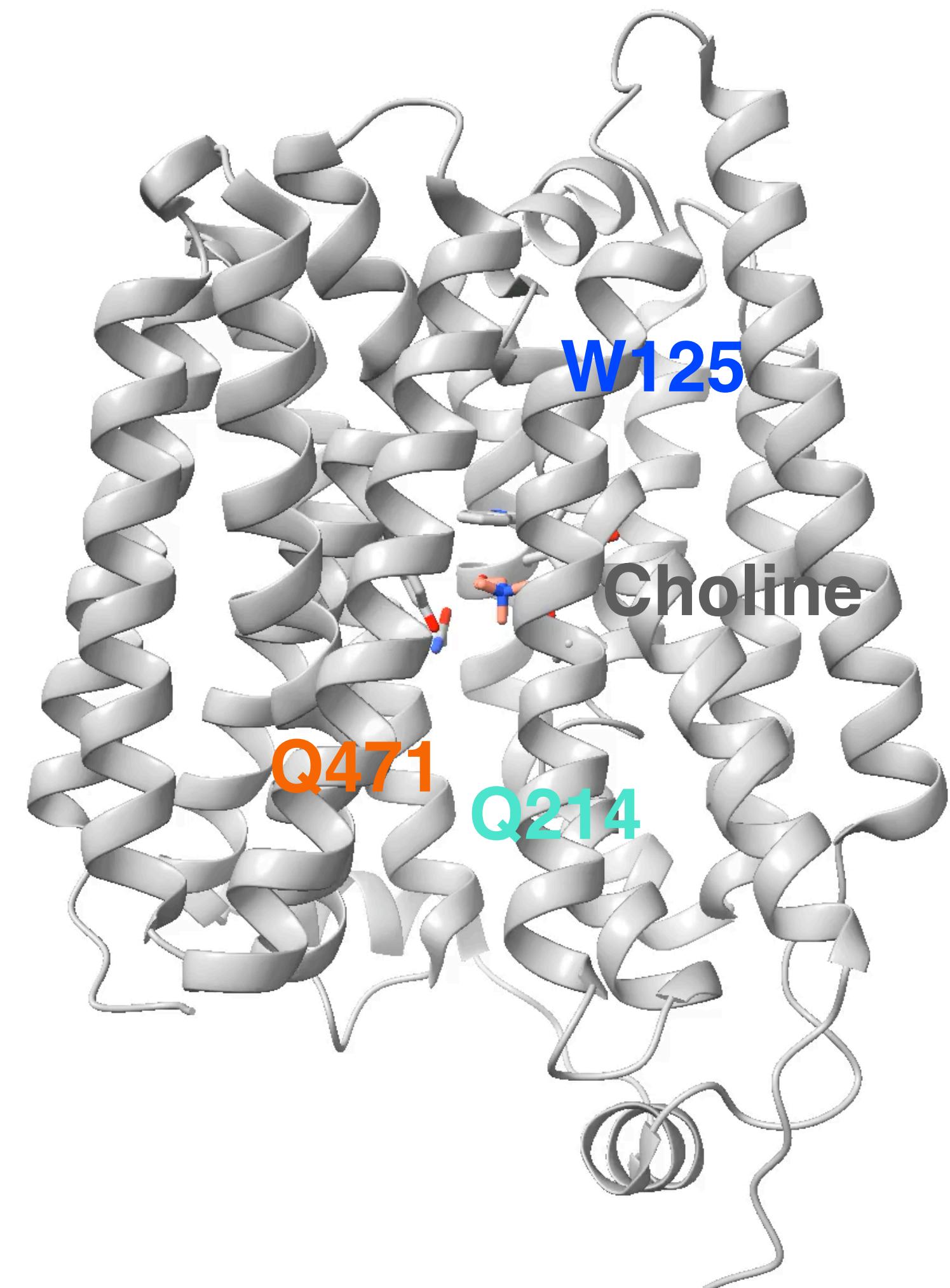
FLVCR1 is required for choline metabolism in cells



FLVCR1 is a high affinity choline transporter



Structural basis of choline transport by FLVCR1

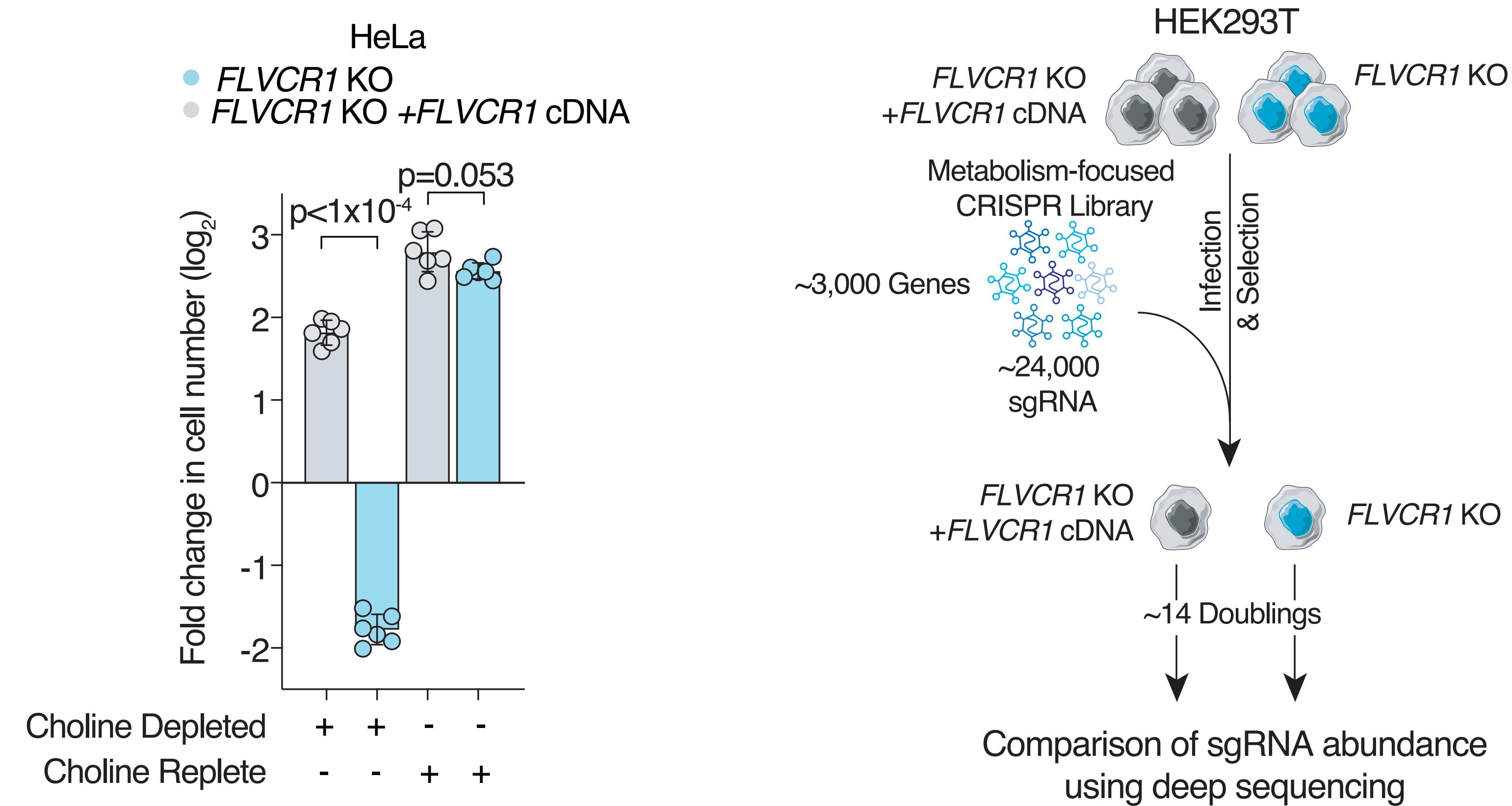


Son, Kenny, Khan, Birsoy & Hite. *Nature* 2024

Cater and Mukherjee et al. *Nature* 2024

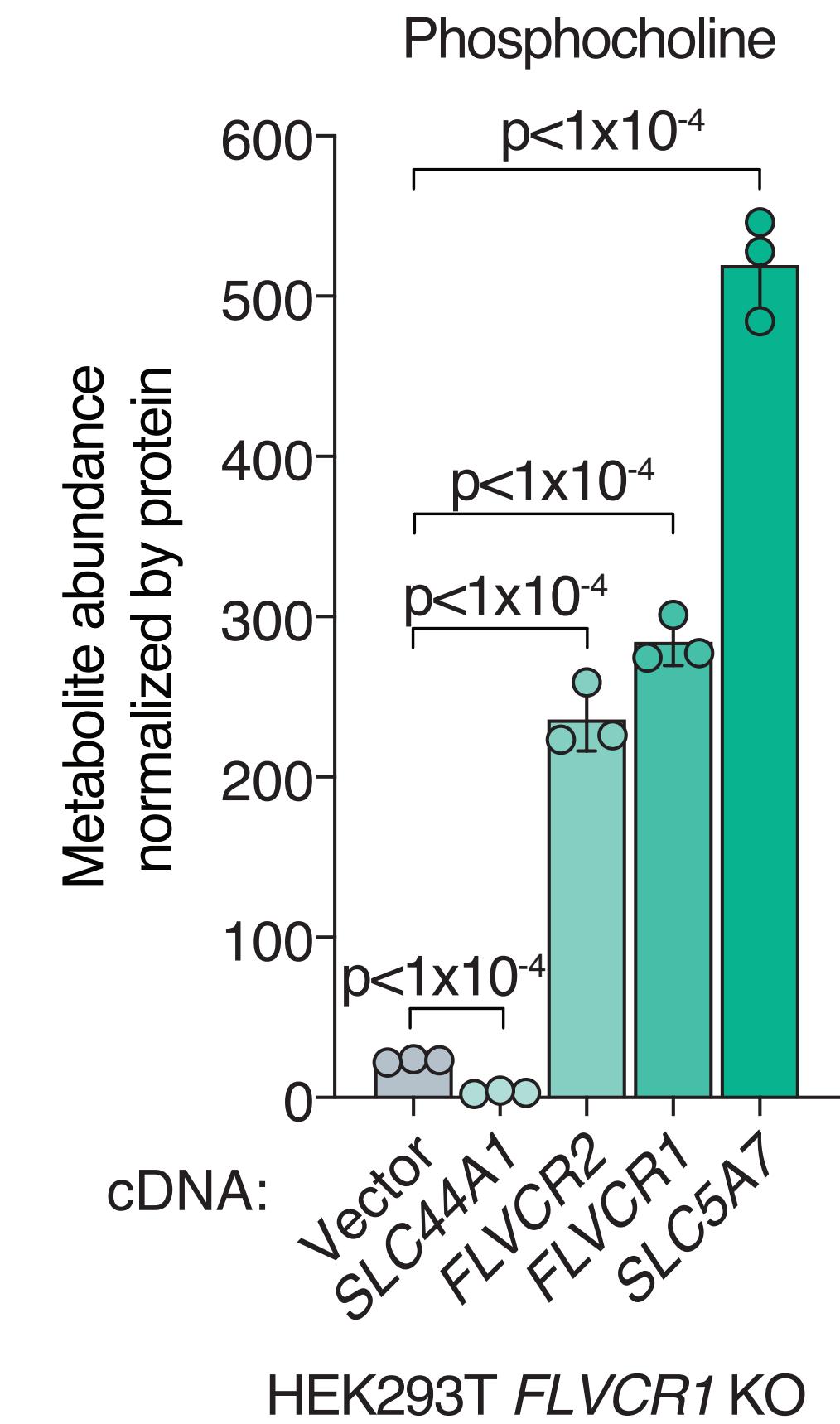
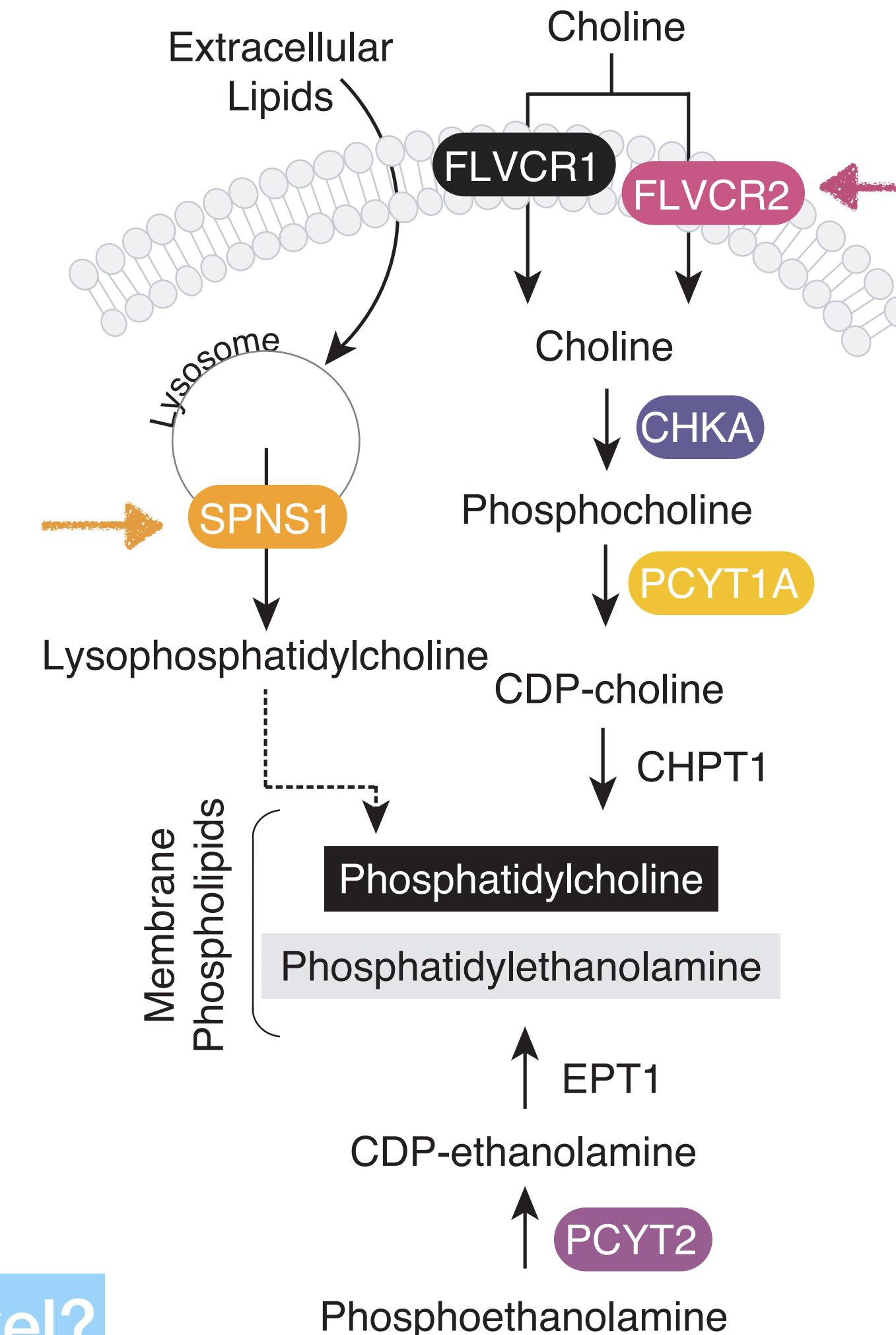
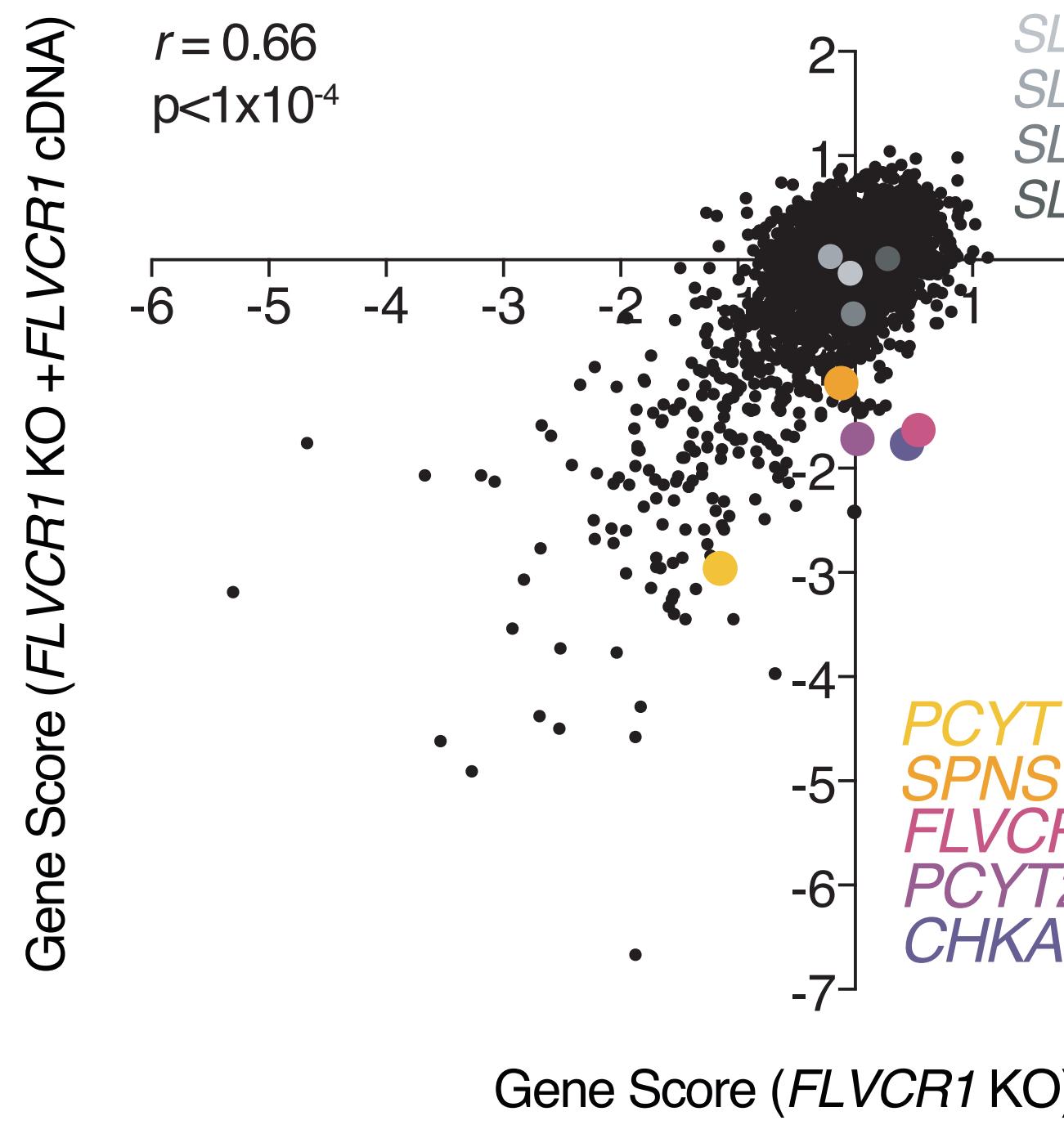
Ri, Weng, and Cabezudo et al. *Nature* 2024

Cells without FLVCR1 can proliferate normally in standard media conditions



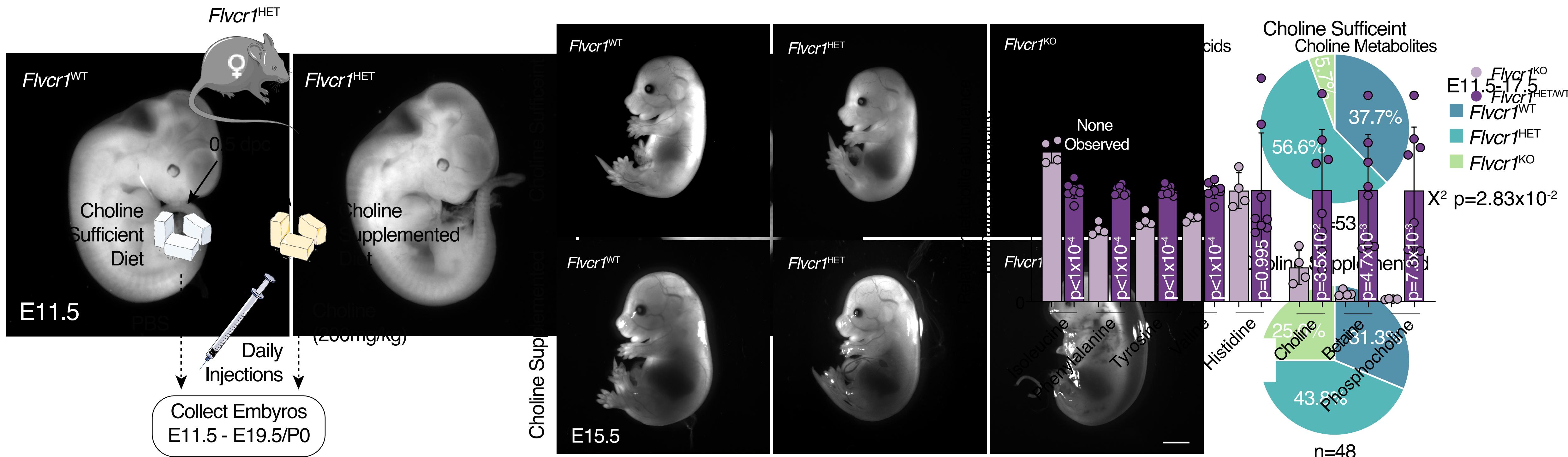
How do cells sustain choline metabolism to proliferate without FLVCR1?

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



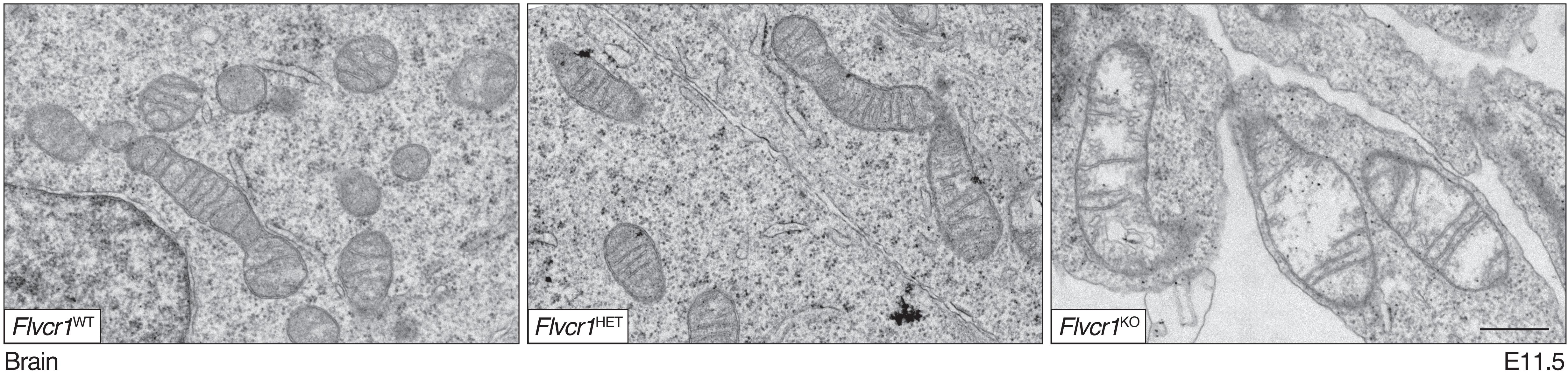
What happens at the organismal level?

Choline transport via FLVCR1 is required for murine embryogenesis



Why is FLVCR1 loss embryonically lethal?

Embryos lacking FLVCR1 have severe mitochondrial dysfunction



What about in humans?

FLVCR1/2 is implicated in human disease

AJHG

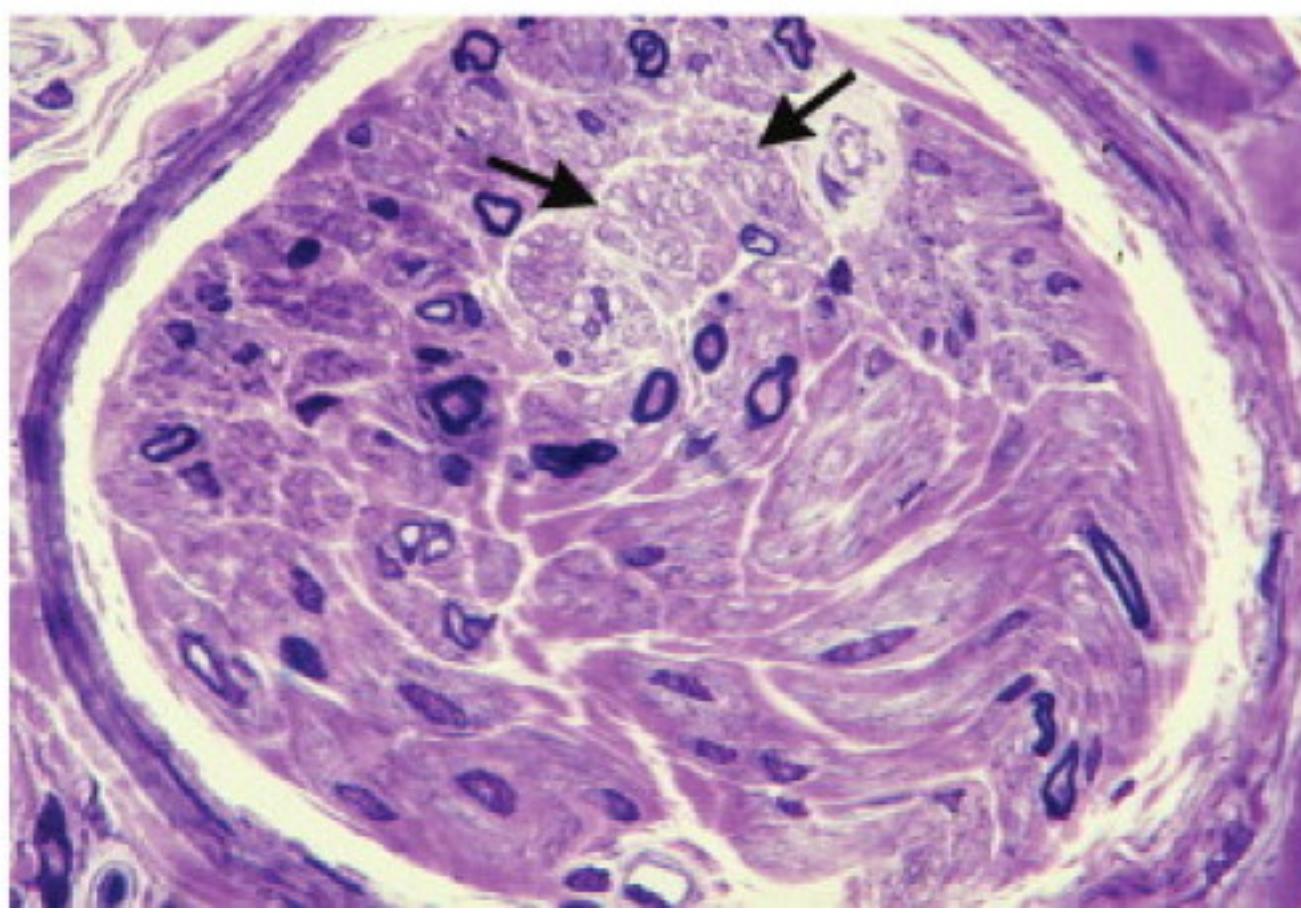
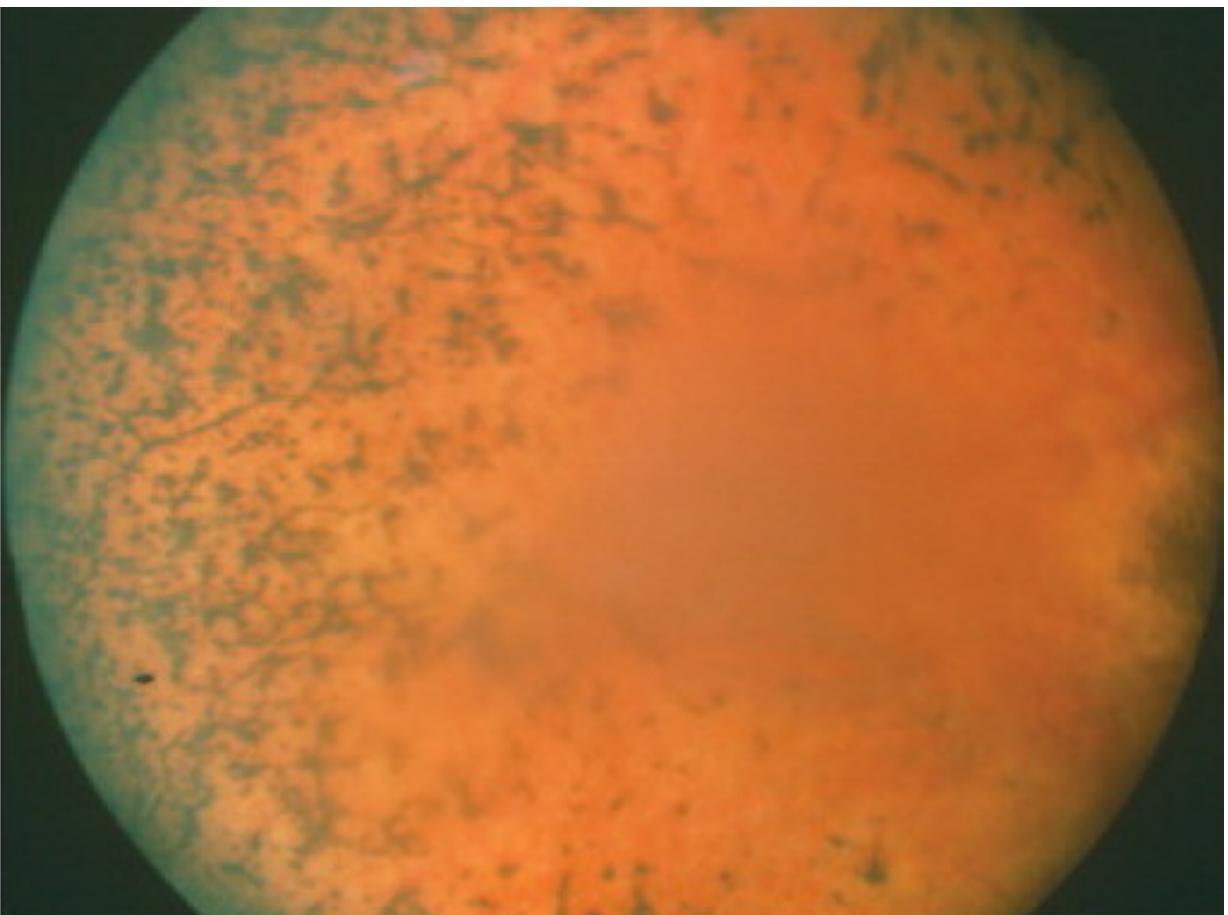


Volume 87, Issue 5, 12 November 2010, Pages 643-654

Article

Mutations in *FLVCR1* Cause Posterior Column Ataxia and Retinitis Pigmentosa

Anjali M. Rajadhyaksha ^{1, 2, 12}, Olivier Elemento ^{3, 12}, Erik G. Puffenberger ⁵, Kathryn C. Schierberl ^{1, 2}, Jenny Z. Xiang ⁴, Maria L. Putorti ⁶, José Berciano ⁷, Chantal Poulin ⁸, Bernard Brais ⁶, Michel Michaelides ^{9, 10, 11}, Richard G. Weleber ⁹, Joseph J. Higgins ¹



AJHG

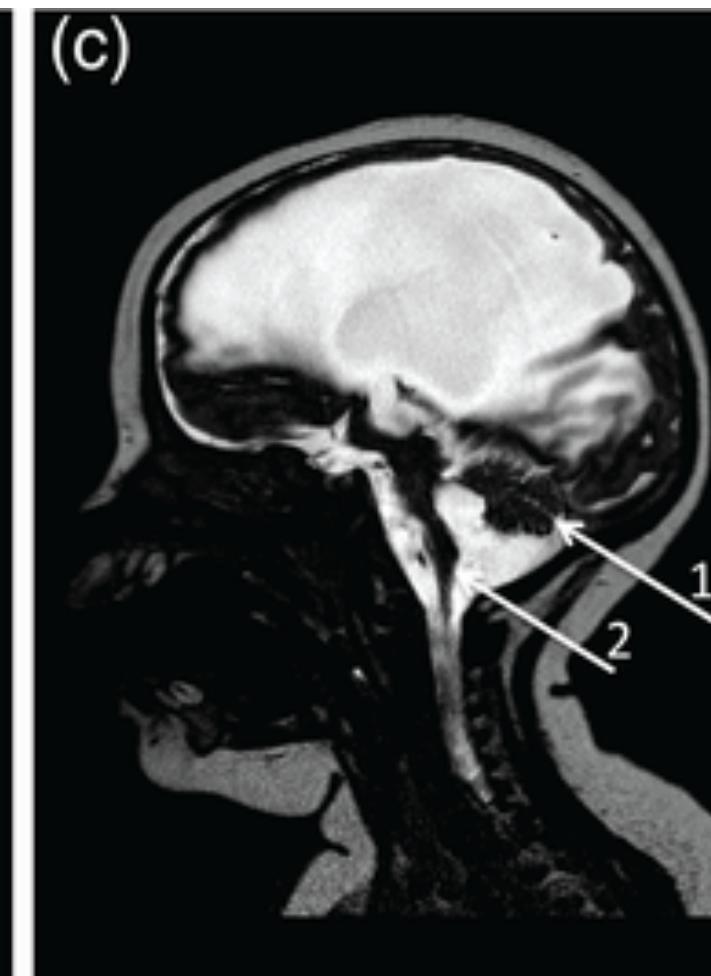
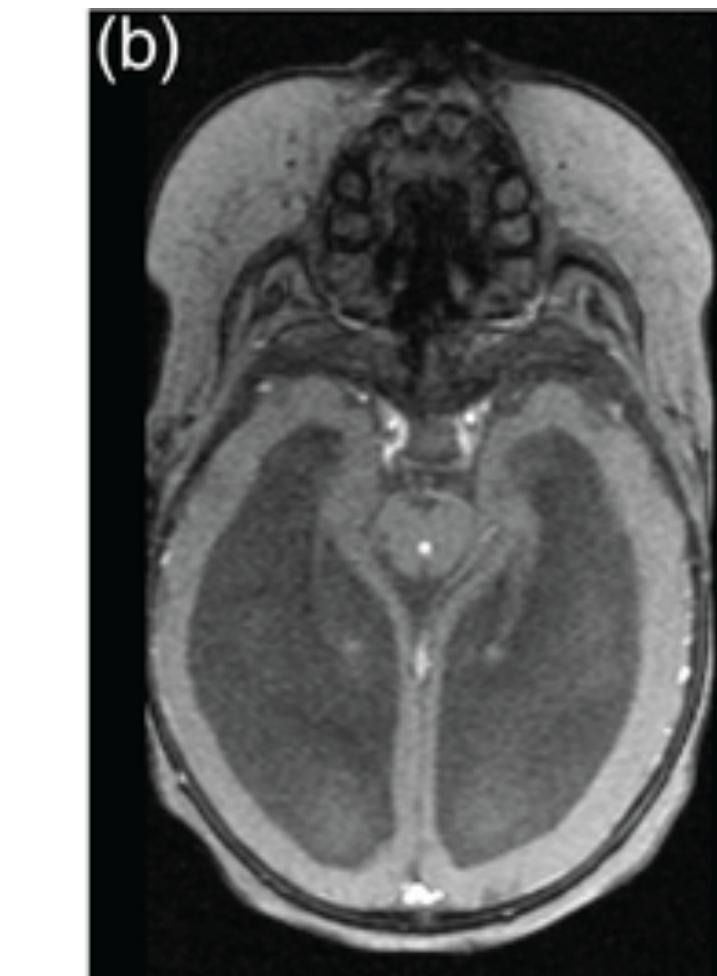


Volume 86, Issue 3, 12 March 2010, Pages 471-478

Report

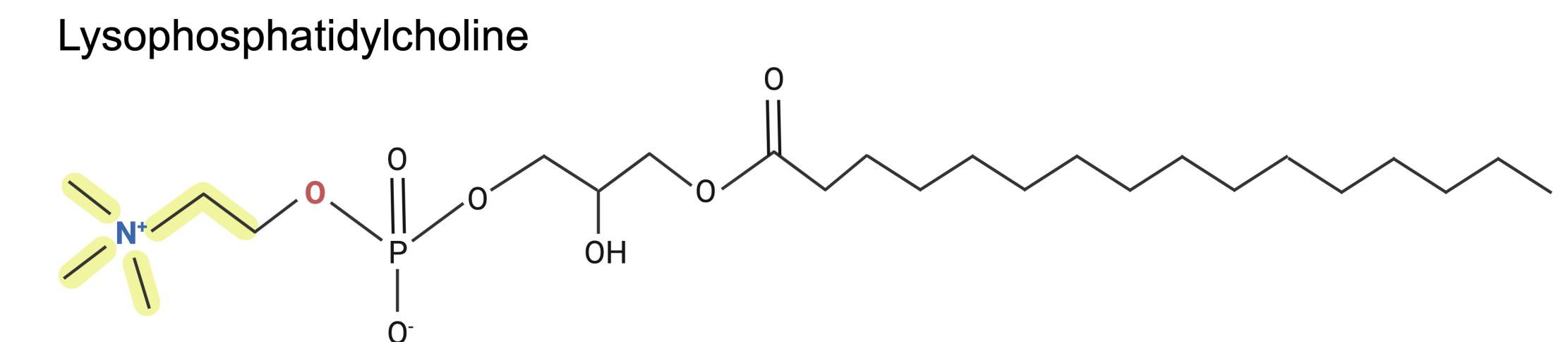
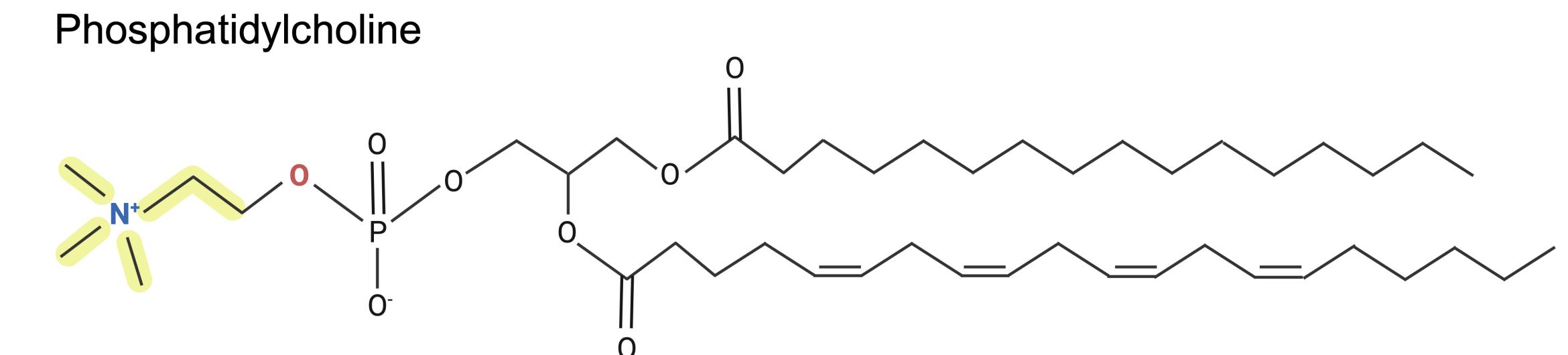
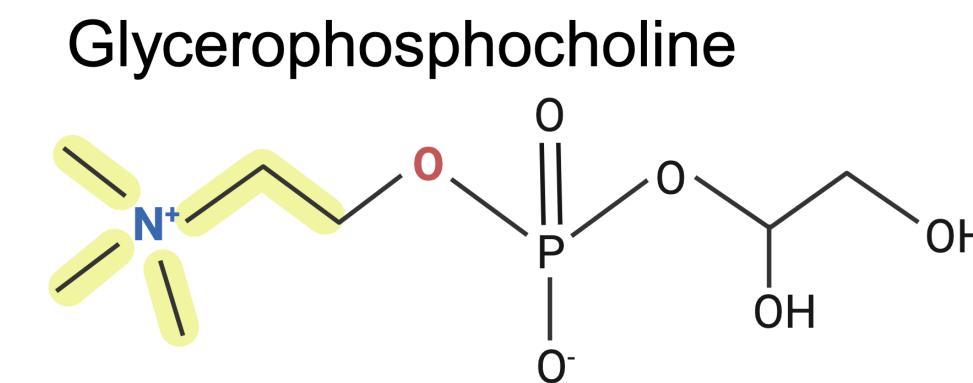
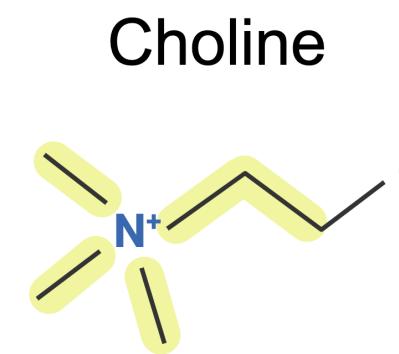
Mutations in *FLVCR2* Are Associated with Proliferative Vasculopathy and Hydranencephaly-Hydrocephaly Syndrome (Fowler Syndrome)

Esther Meyer ¹, Christopher Ricketts ¹, Neil V. Morgan ¹, Mark R. Morris ¹, Shanaz Pasha ¹, Louise J. Tee ¹, Fatimah Rahman ¹, Anne Bazin ², Bettina Bessières ², Pierre Déchelotte ³, Mohamed T. Yacoubi ⁴, Mudher Al-Adnani ⁵, Tamas Marton ⁶, David Tannahill ⁷, Richard C. Trembath ⁸, Catherine Fallet-Bianco ⁹, Phillip Cox ⁶, Denise Williams ¹⁰, Eamonn R. Maher ^{1, 10}

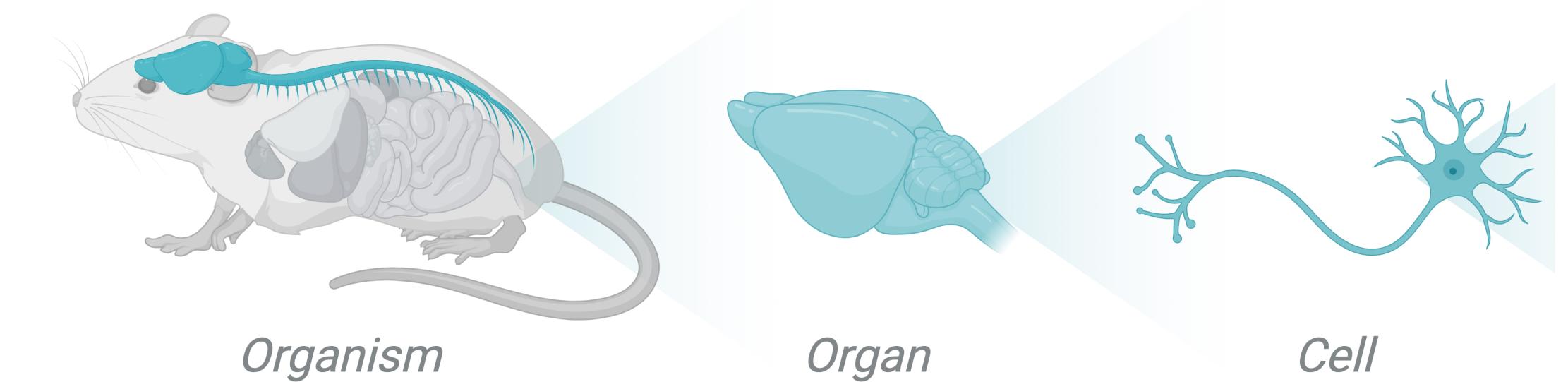


Deorphanization of nutrient transporters highlights potential therapies and new research avenues

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



Modulate nutrient transport to affect cellular metabolism in specific cell populations



Acknowledgments

Birsoy Lab

Kivanç Birsoy PhD

Gökhan Ünlü PhD

Hsi-Wen Yeh PhD

Yuyang Liu MS

Beste Uygar MS

Emilie Wang PhD MBA

Nicole DelGaudio MA

Mark Gad MS

Shanshan Liu PhD

Michelle Wilson BA

Artem Khan BS

Khando Wangdu BS

Michael Xiao BS

Fred Yen BS



Heintz Lab (RU)

Bianca Cotto PhD

Eric Schmidt PhD

Hite Lab (MSKCC)

Richard Hite PhD

Jecy Yeeun Son MS

Sung Lab (WCM)

Ching-Hwa Sung PhD

Jen-Zen (Alex) Chuang PhD

Friedman Lab (RU)

Zhaoyue Zhang PhD

Proteomics/Metabolomics

Resource Center

Hanan Alwaseem PhD

Søren Heissel PhD

Ece Kilic PhD

Electron Microscopy

Resource Center

Anurag Sharm PhD

Hilda Amalia Pasolli PhD



Funding

Merck Postdoctoral Fellowship

NIH NIDDK F32 DK127836

NIH NIDDK K99/R00 DK140517