



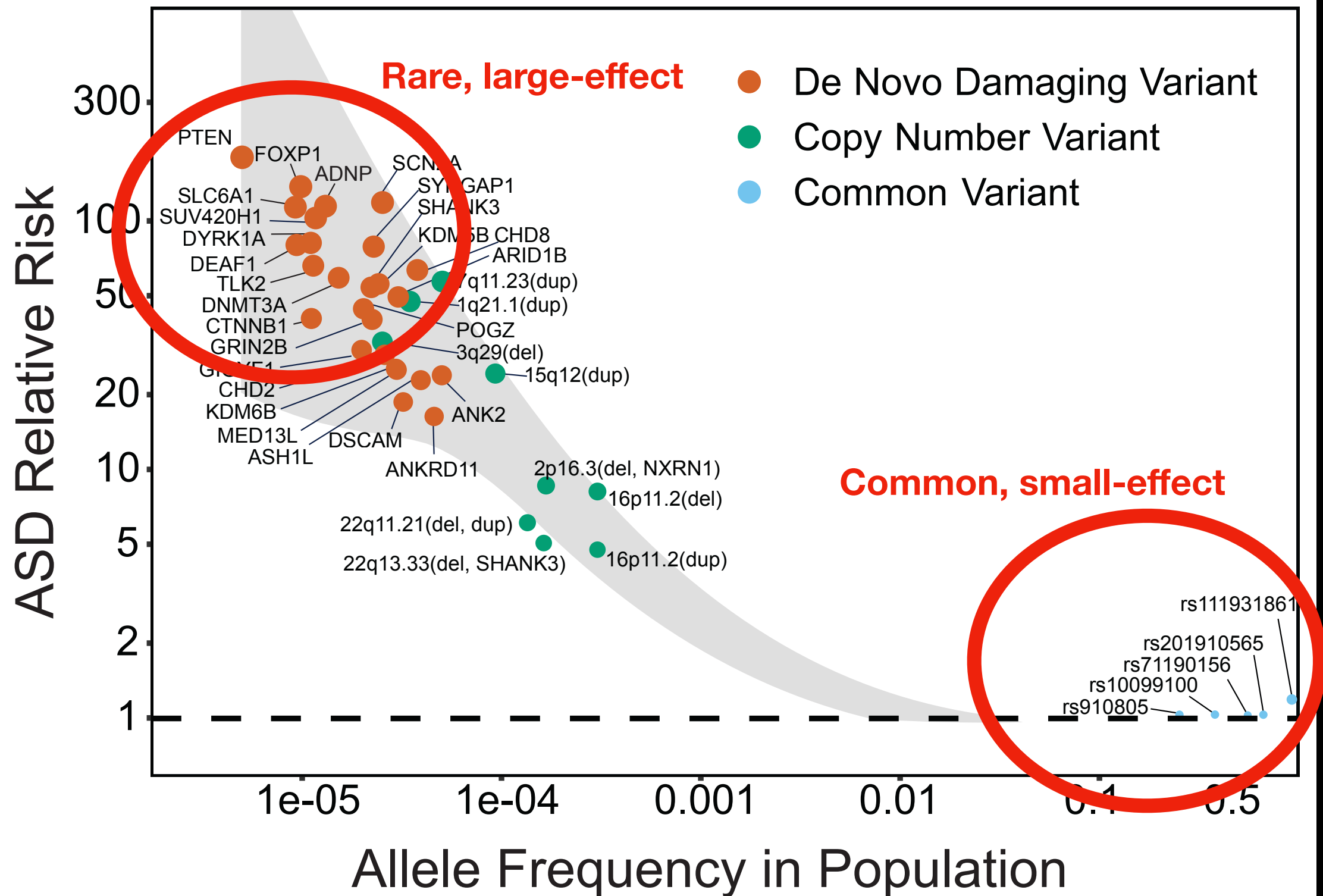
Using frogs to understand
complex psychiatric disorders

Helen Willsey, PhD
UCSF

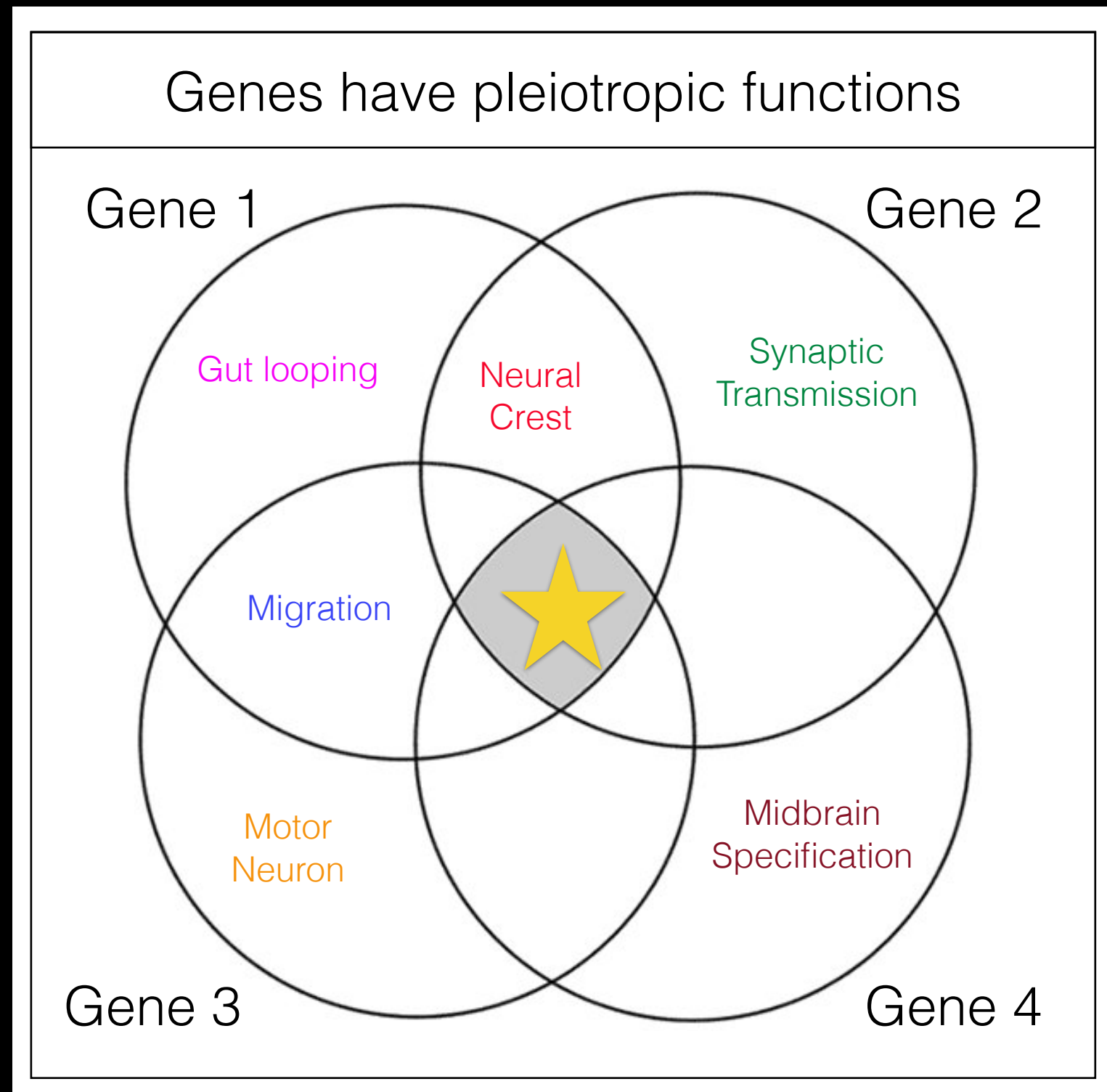
What are the relevant brain regions, timepoints, or processes for a psychiatric disorder?



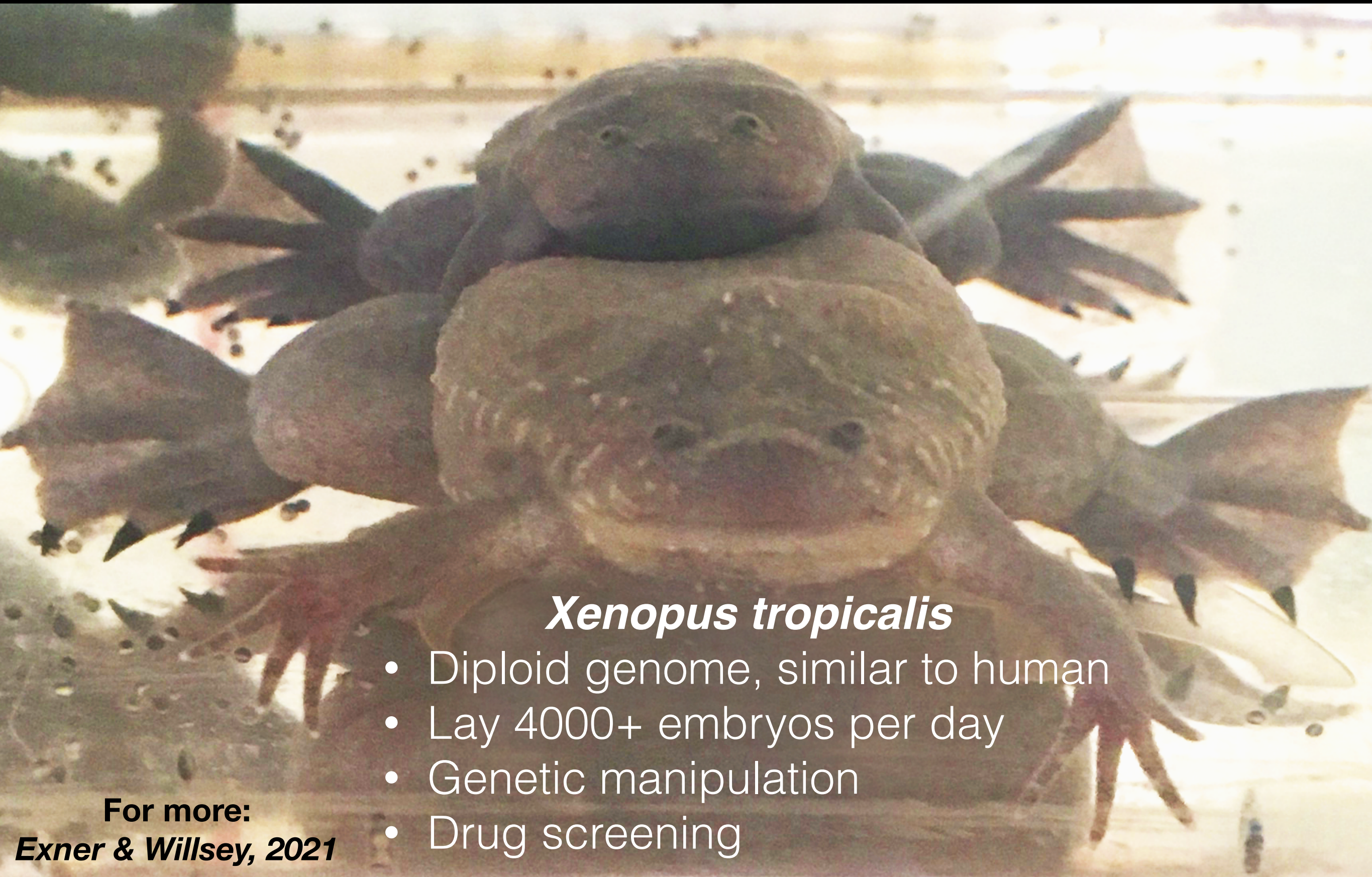
Human genetics provides starting point



Many genes involved, each has multiple functions (pleiotropic)



Frogs are a higher-throughput, cost-effective genetic model



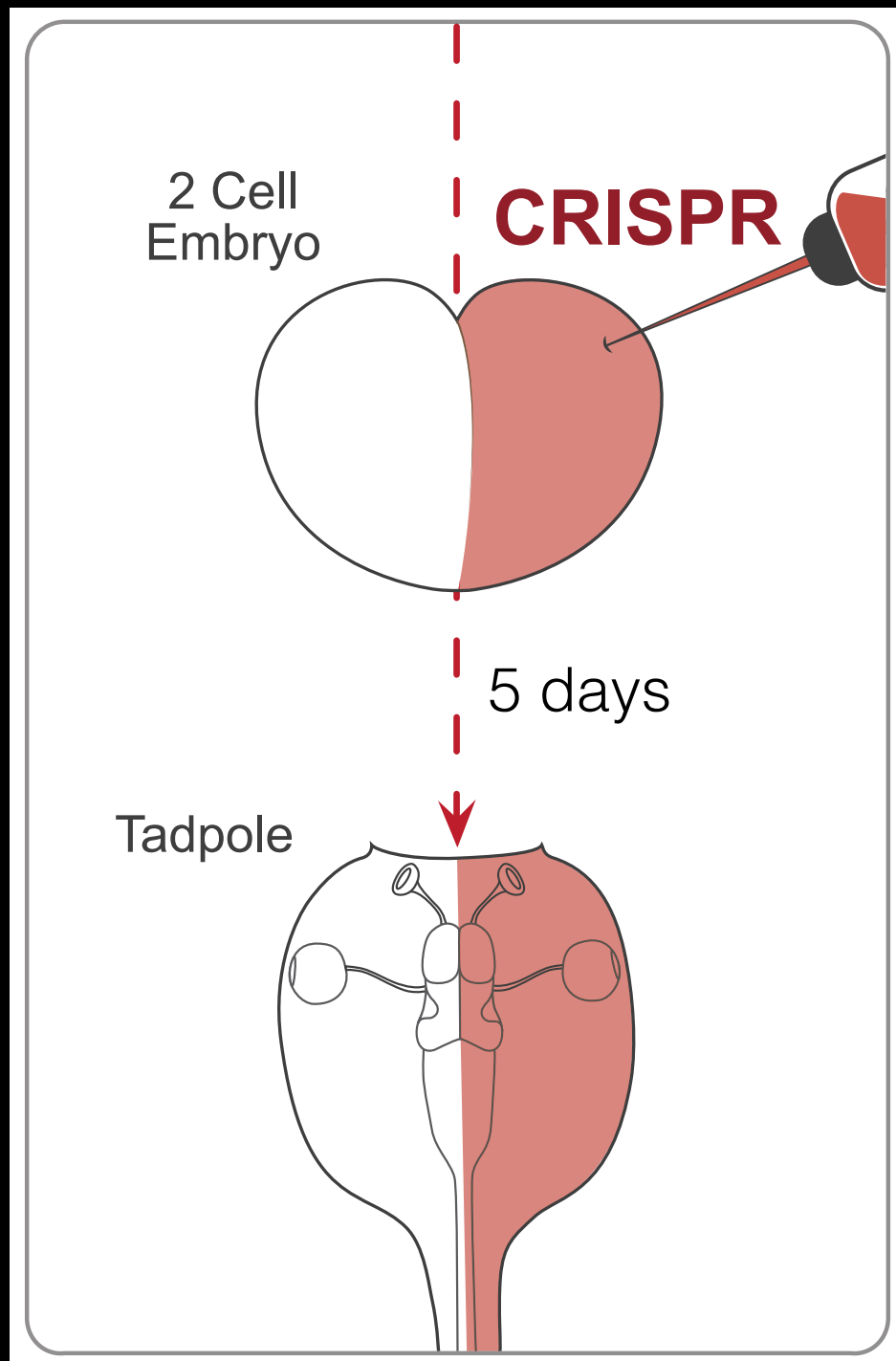
Xenopus tropicalis

- Diploid genome, similar to human
- Lay 4000+ embryos per day
- Genetic manipulation
- Drug screening

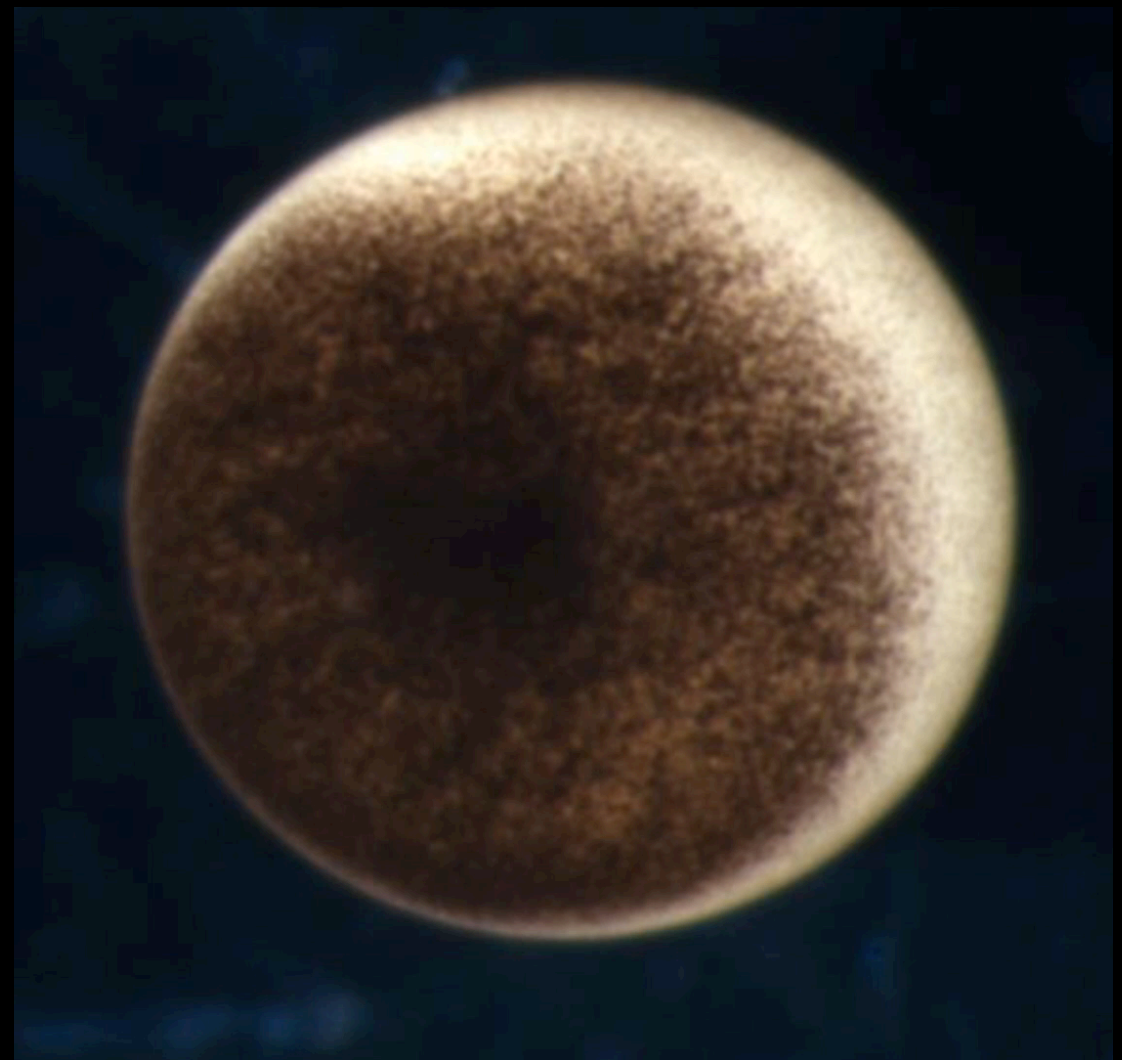
For more:

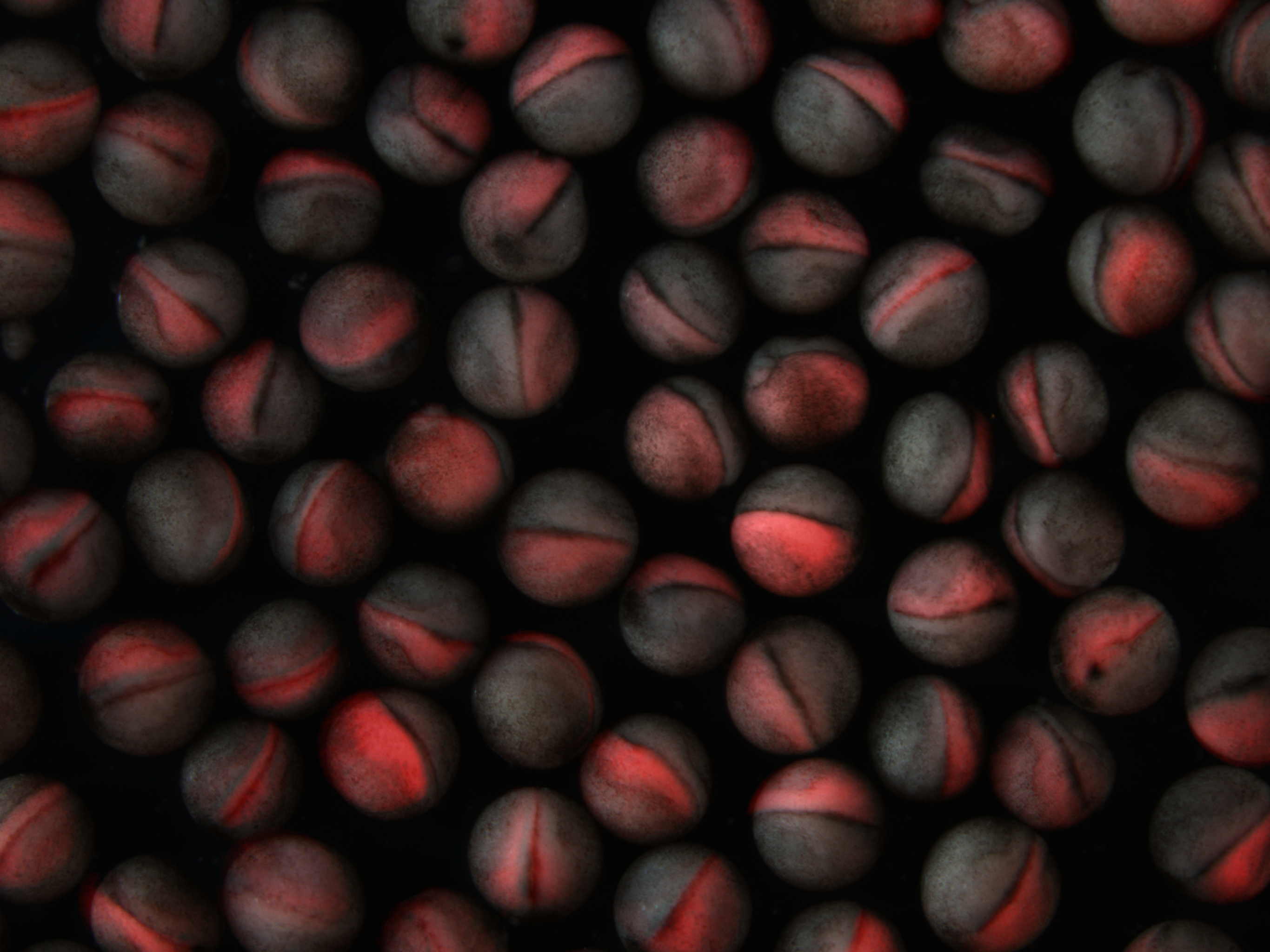
Exner & Willsey, 2021

We can make half-mutant tadpoles

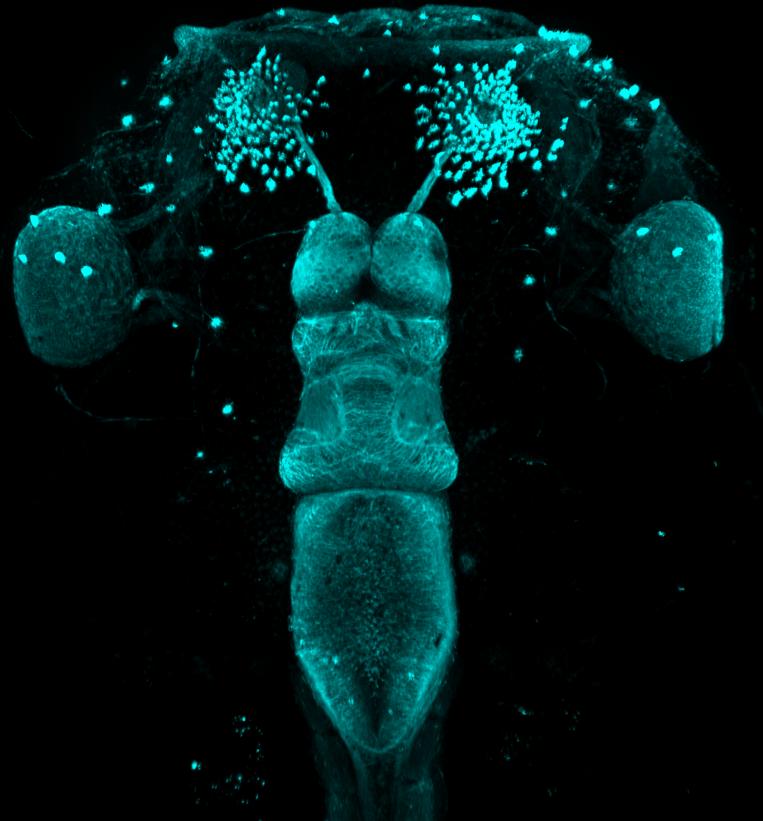


\$25 per gene





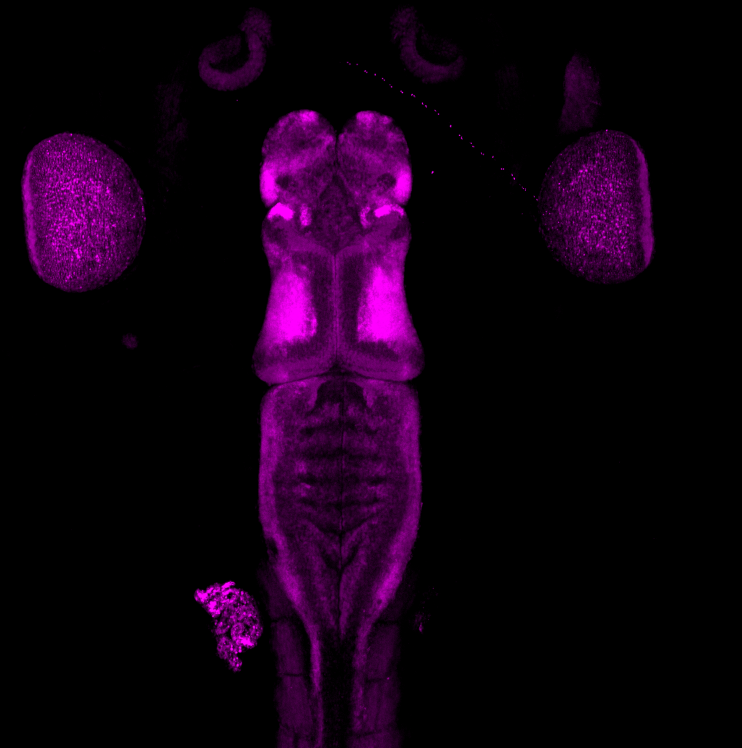
All Neurons



Progenitors



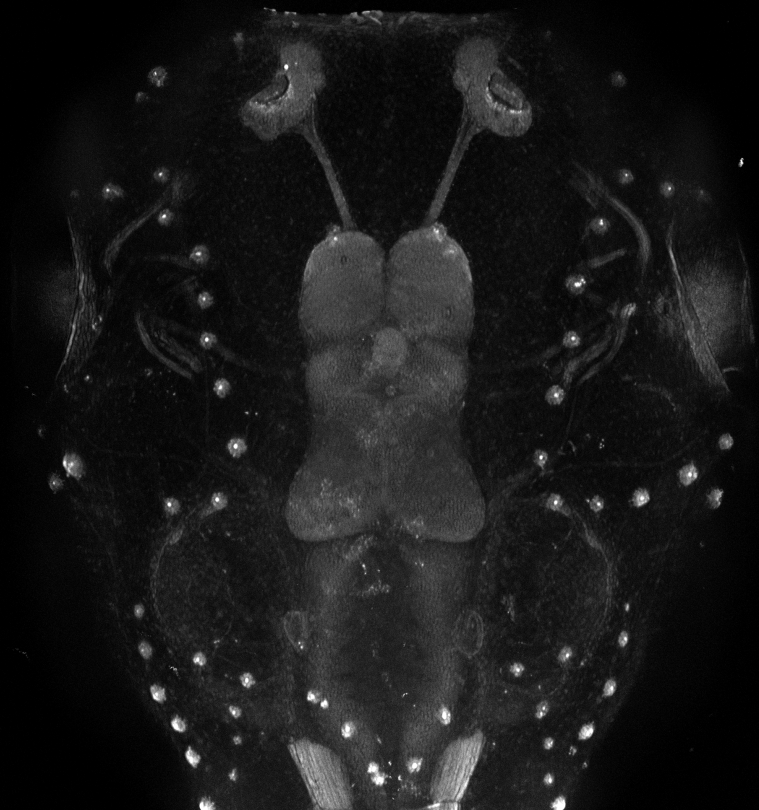
Excitatory Neurons



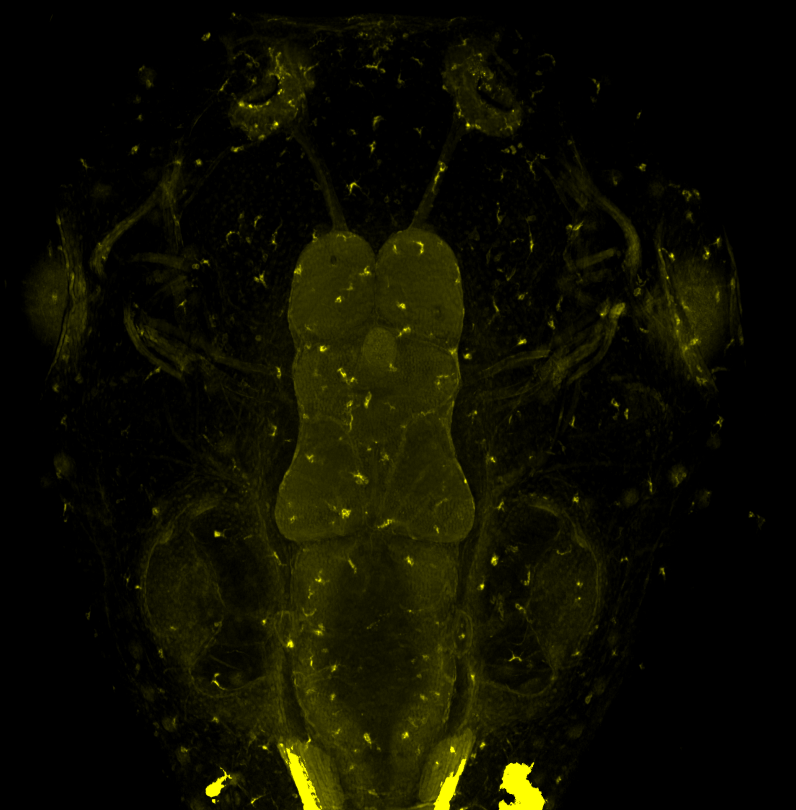
Inhibitory Neurons

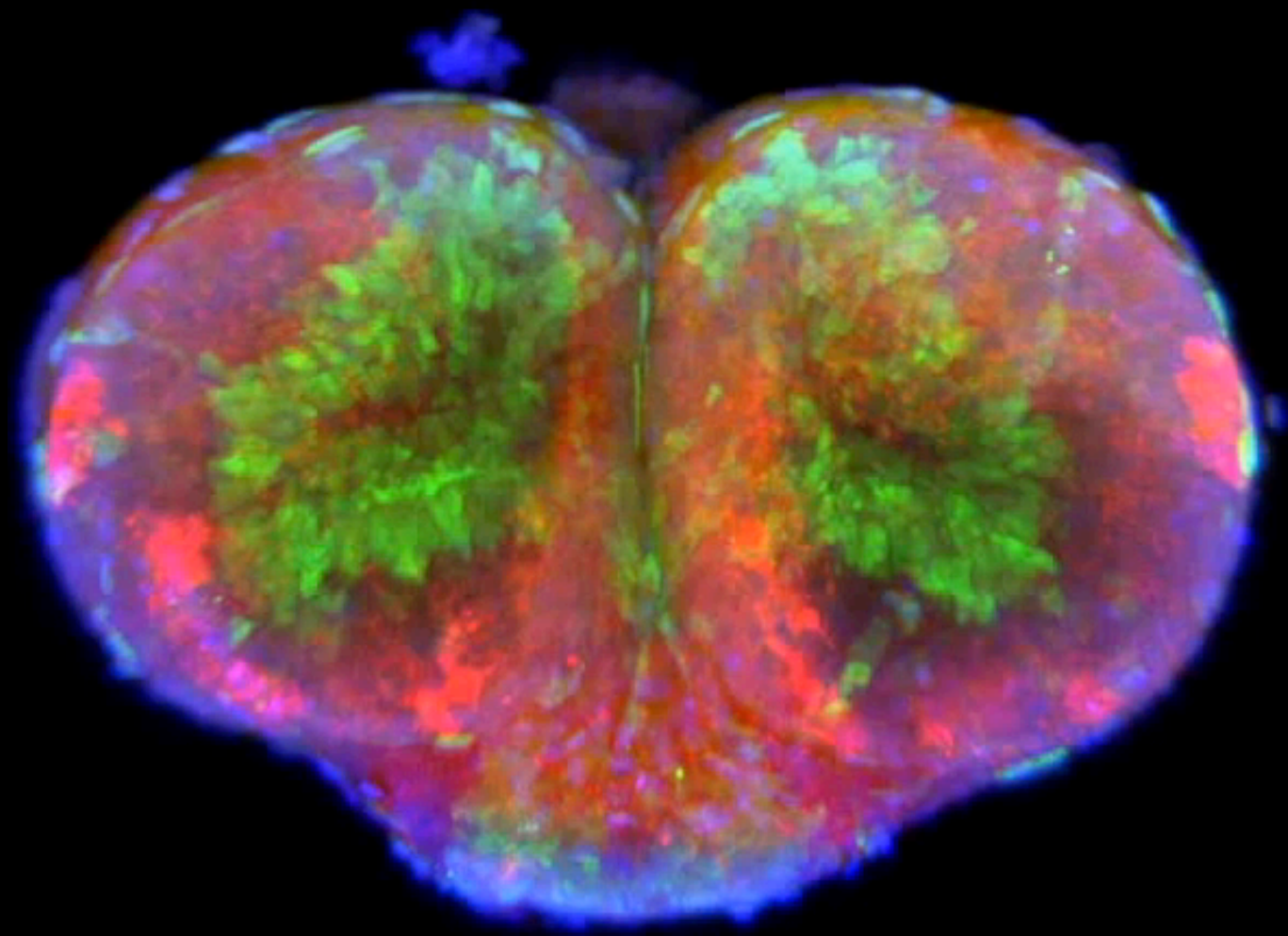
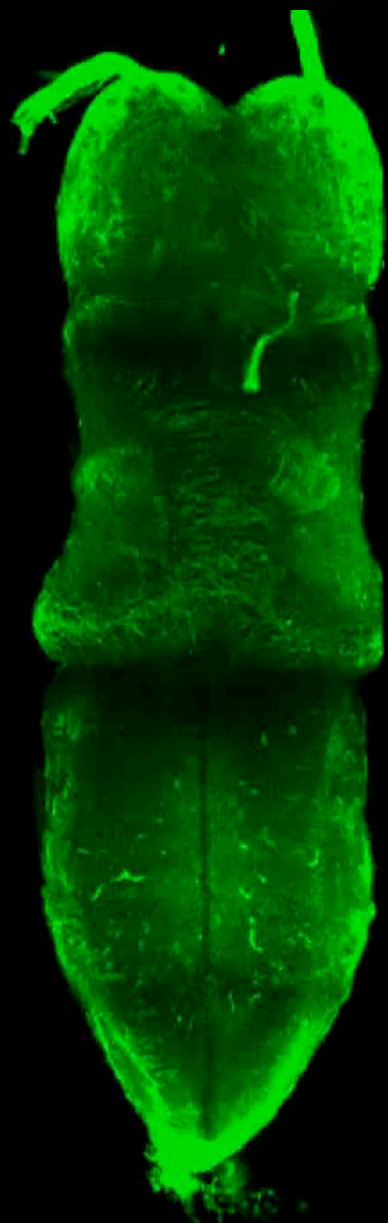
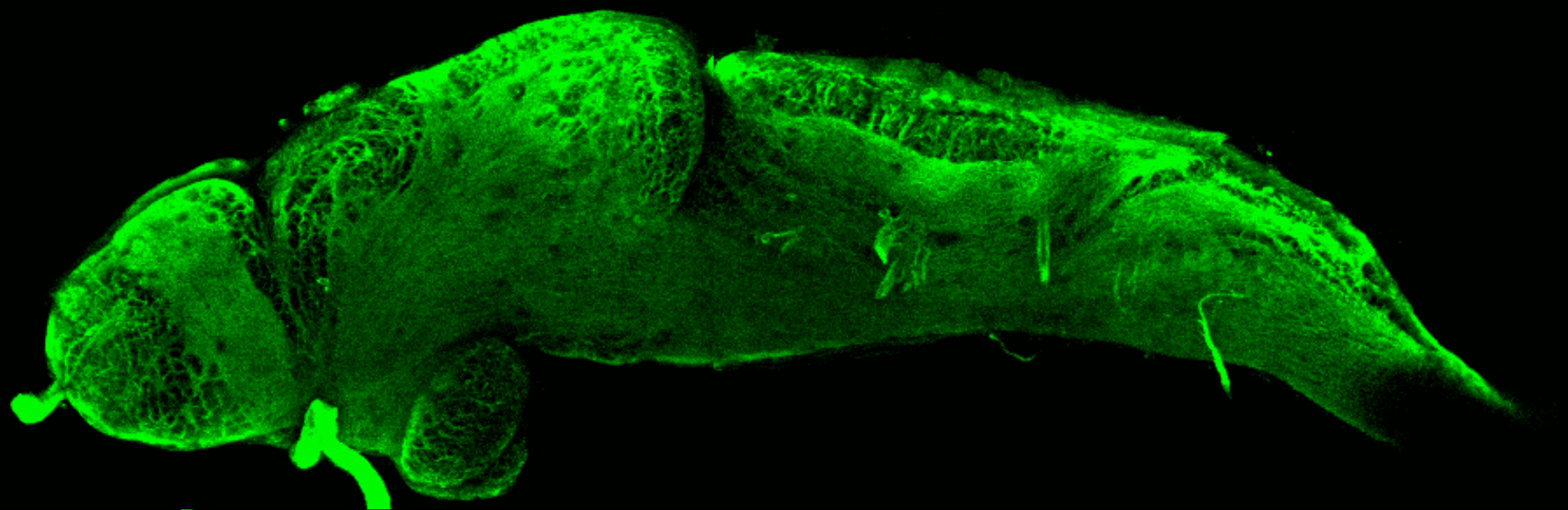


Astrocytes

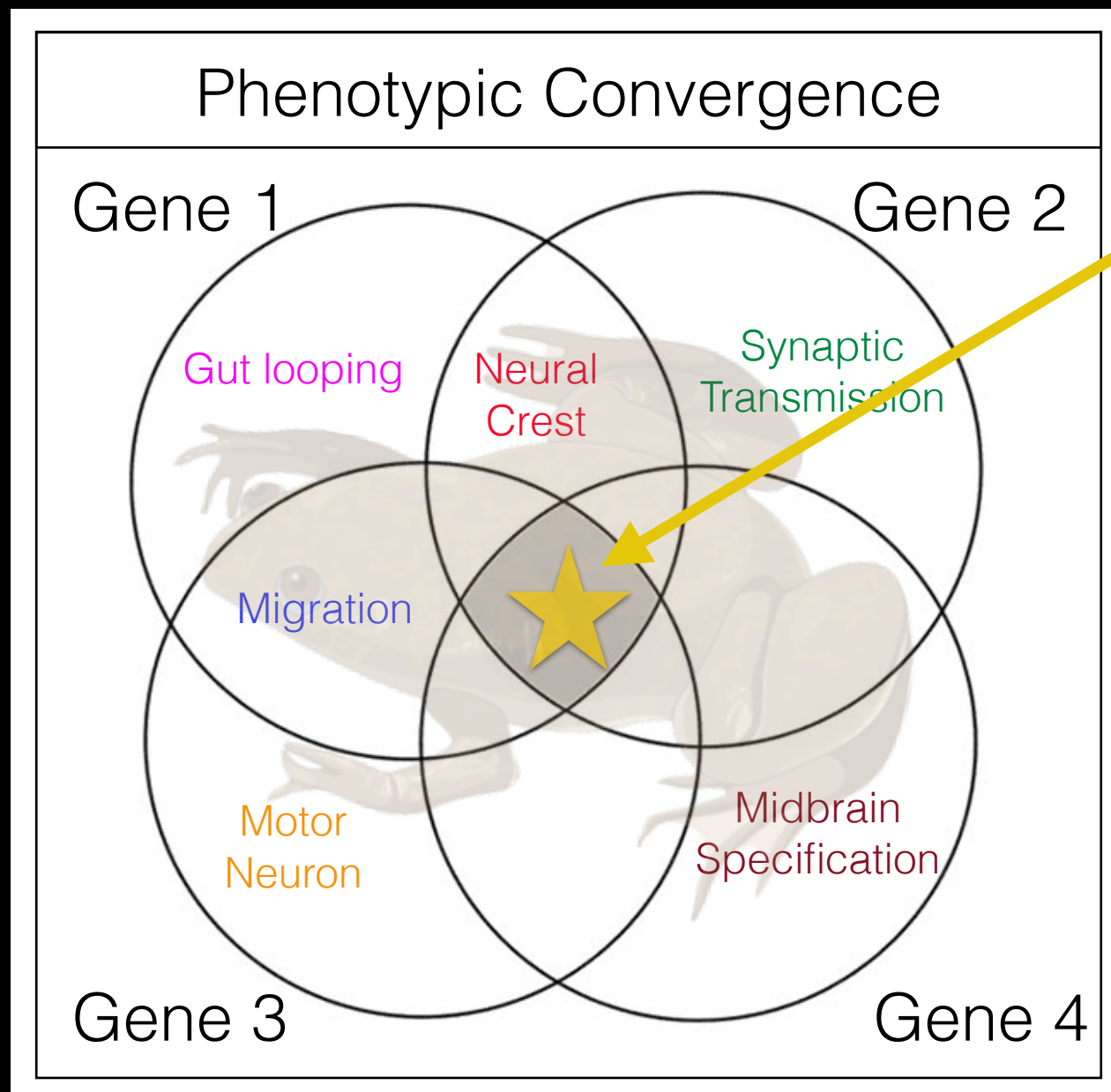


Microglia

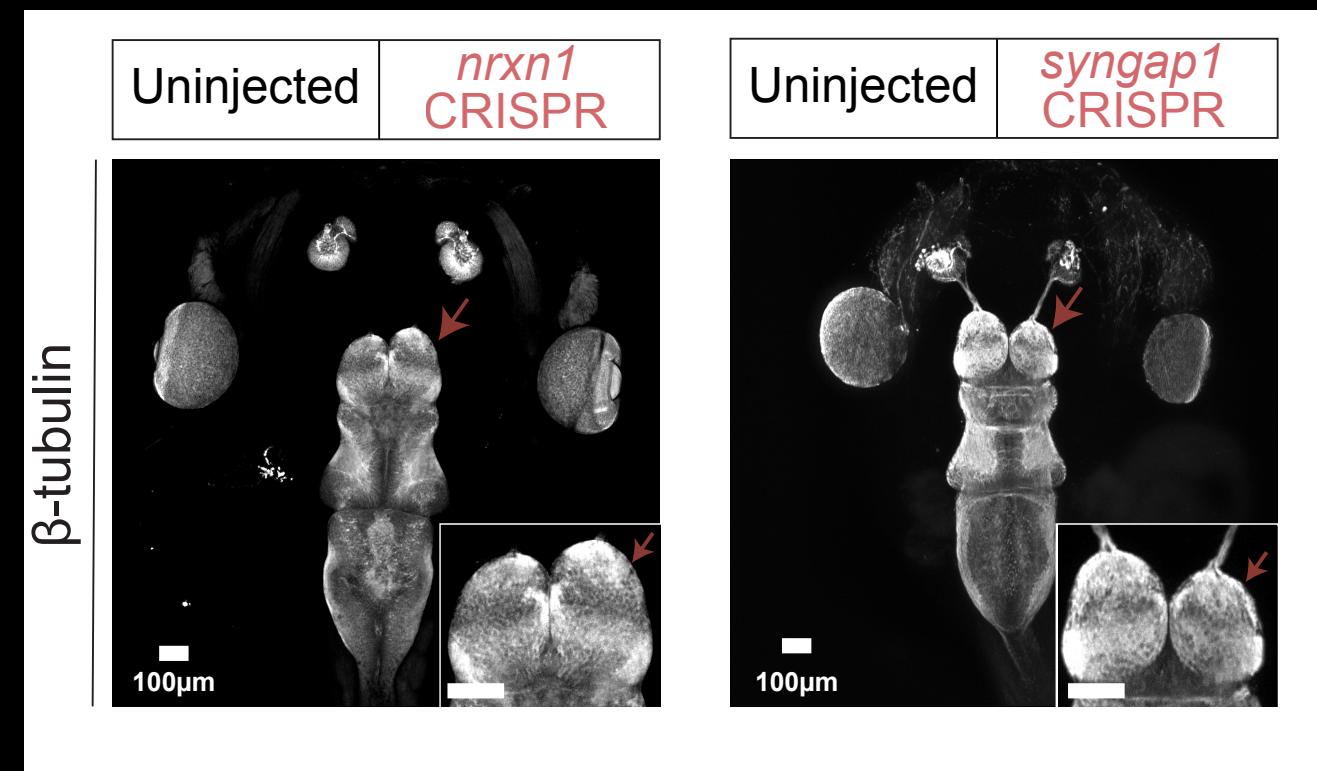




Top 10 Autism risk genes function in neurogenesis

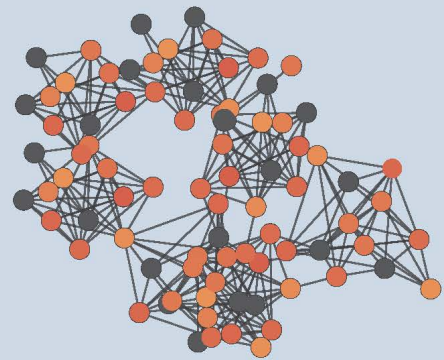


Changes in Brain Growth (Neurogenesis)



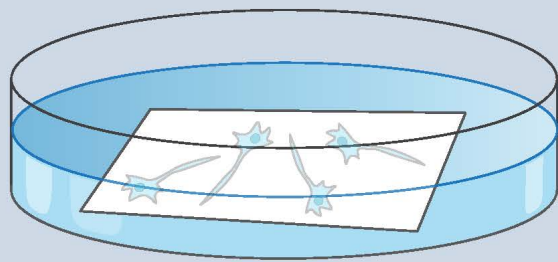
Estrogen Rescues

Validation in human *in vitro* models & datasets



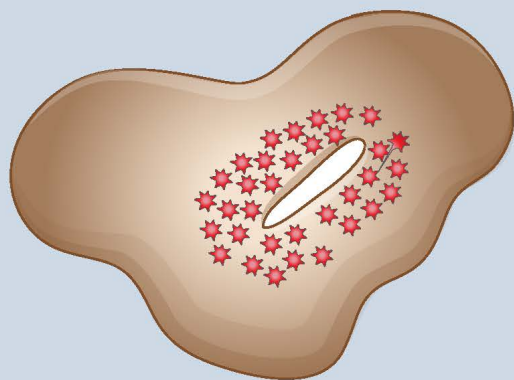
Cortical Layer-Specific
Network Connectivity

**Highest network connectivity
in SVZi (neurogenic layer)**



iPSC-Derived
Neural Progenitor Cells

**Proliferation defect for
4 autism risk genes
(*CHD2*, *ADNP*, *NRXN1*, *DYRK1A*)**



iPSC-Derived
Cortical Organoids

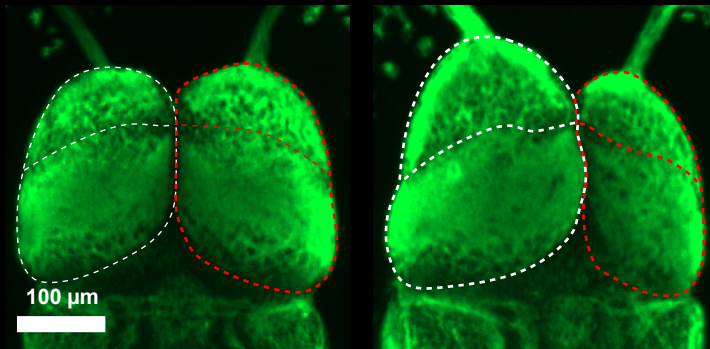
**Estrogen rescues
DYRK1A inhibition**

The future is frogs!

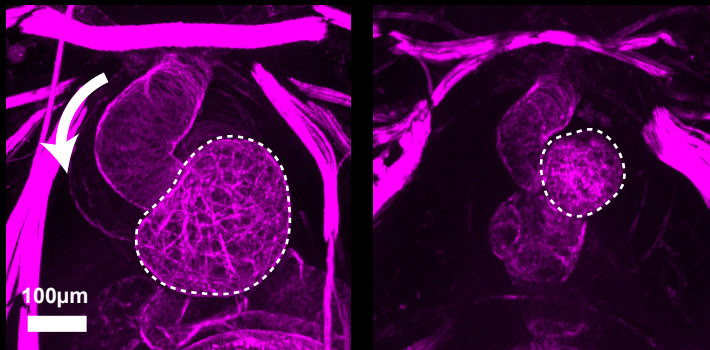
Overlap with CHD

Ideker, Willsey, Khokha Labs

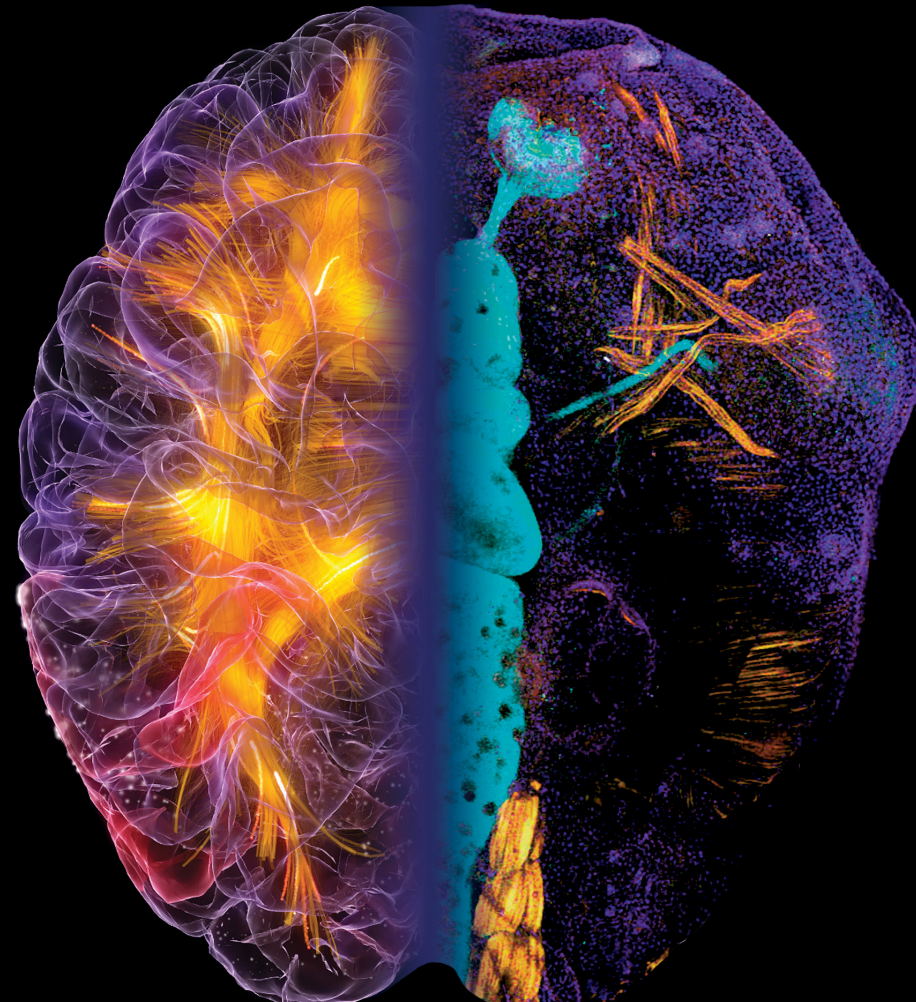
Brain



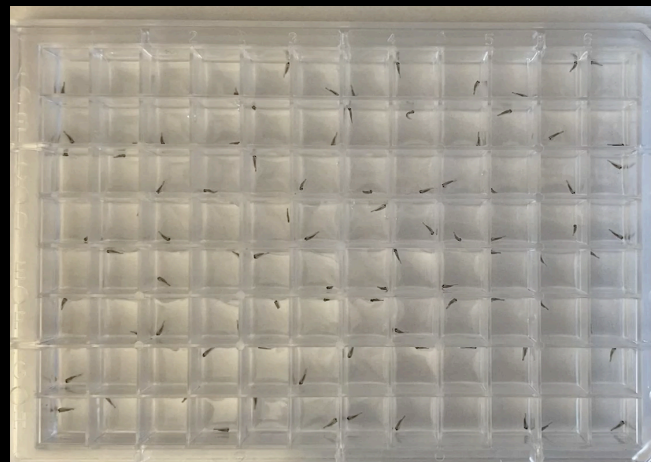
Heart



*Rosenthal & Willsey et al.,
Cell Systems 2021*

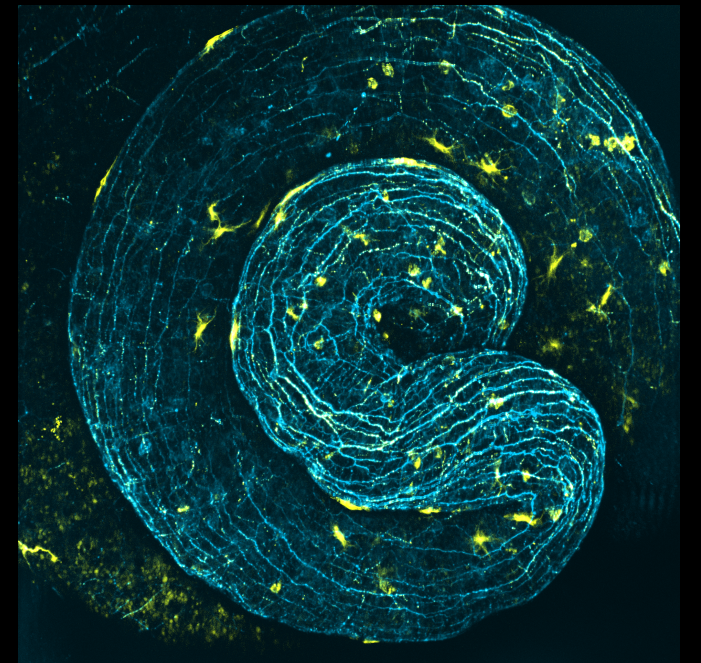


Behavioral Phenotyping
Mutant Lines from NXR



Overlap with GI Dysfunction

Kate McCluskey



Acknowledgements



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Jeremy Willsey (UCSF)

Richard Harland (UCB)

Mustafa Khokha (Yale)

Xenbase

CSHL *Xenopus* Course

National *Xenopus* Resource

Psychiatric Cell Mapping Initiative

NIMH 1U01MH115747

NIMH 1R21MH112158