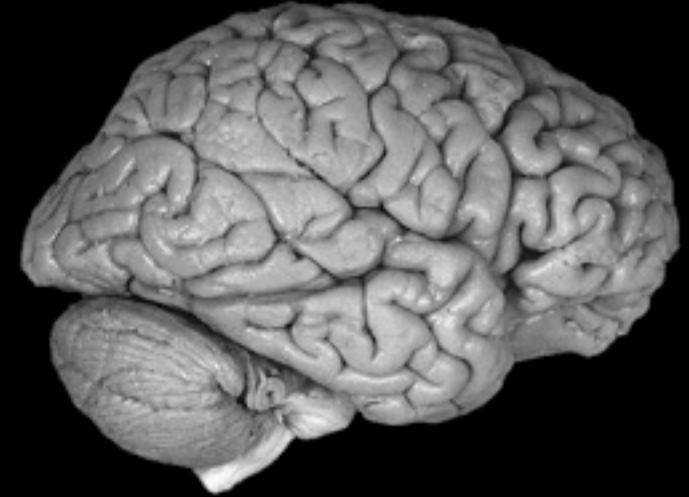


Bioinformatic analysis of familial Alzheimer's disease-like zebrafish

Nhi Hin (@nhihin)

Zebrafish Alzheimer's Disease Genetics Laboratory and Bioinformatics Hub
University of Adelaide

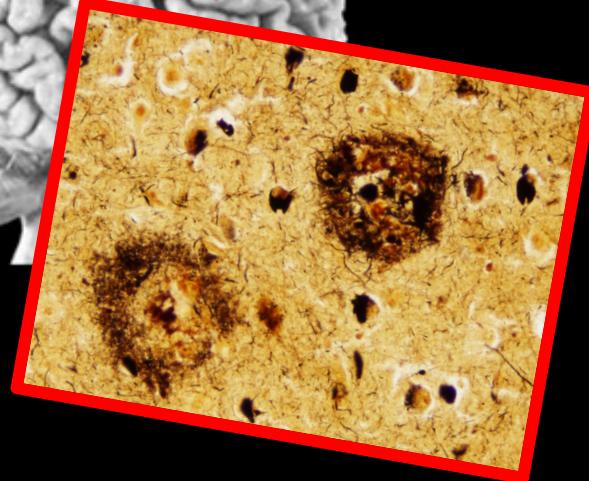


Healthy



Alzheimer's

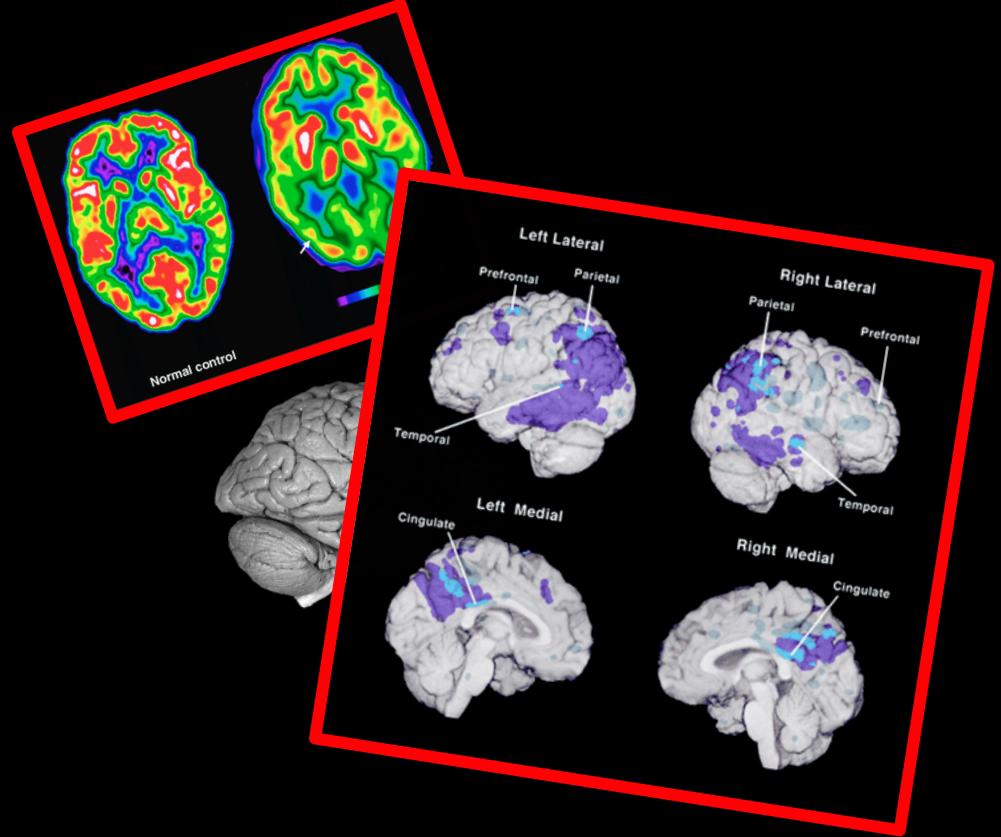
Upregulated by AD	#	PValue
cell adhesion	10	8.05E-04
response to wounding	7	1.17E-03
adherens junction	4	1.12E-03
cell death	18	7.47E-10
platelet activation	18	2.35E-05
iron ion binding	18	4.66E-05
protein oligomerization	11	9.92E-04
myeloid cell differentiation	29	9.95E-04
synaptic vesicle membrane	4	5.60E-03
synapse part	8	5.60E-03
CNS neuron development	3	2.87E-02
actin cytoskeleton	7	2.97E-02
mitochondrial matrix	6	4.77E-02



(Magistri et al. 2015)



Healthy



Before Alzheimer's

(Rabinovici et al. 2010)

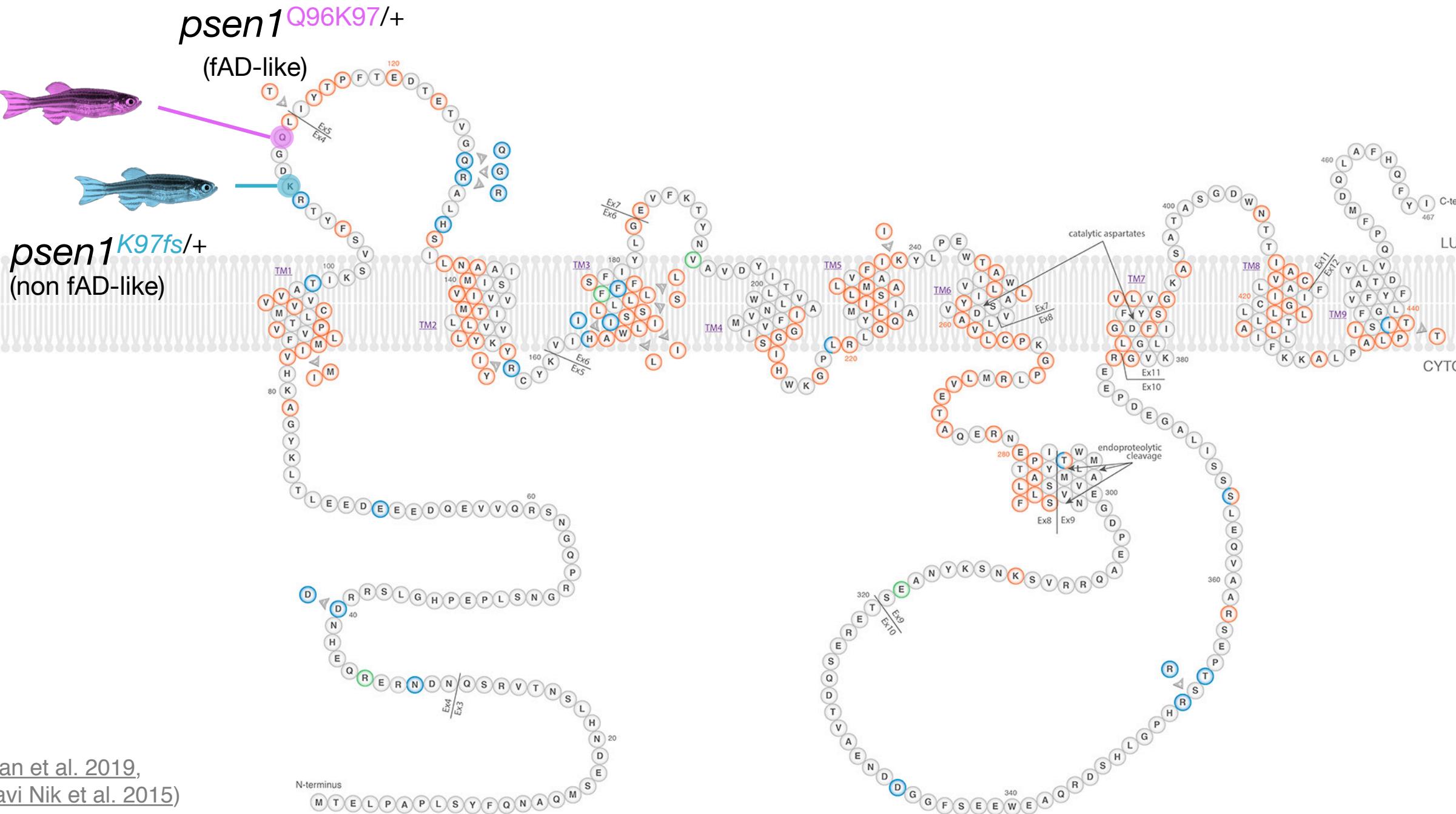


Healthy



Alzheimer's-like

**(Modelling genetic
state of familial AD)**



(Newman et al. 2019,
Moussavi Nik et al. 2015)

Compare between groups

to look for gene expression differences



Age: 6 months
psen1: $+/+$
(n=4)



Age: 6 months
psen1: Q96K97/+
(n=4)



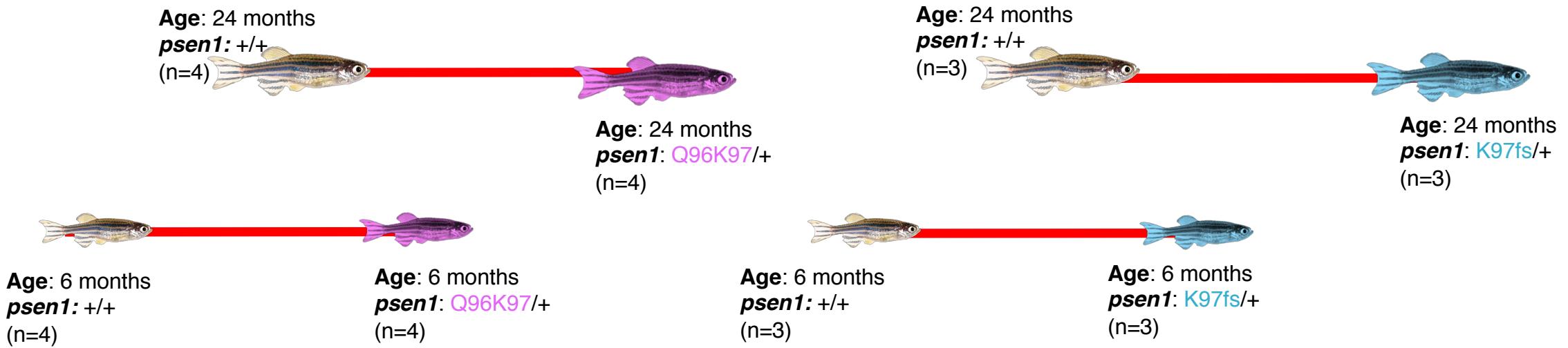
Age: 6 months
psen1: $+/+$
(n=3)



Age: 6 months
psen1: K97fs/+
(n=3)

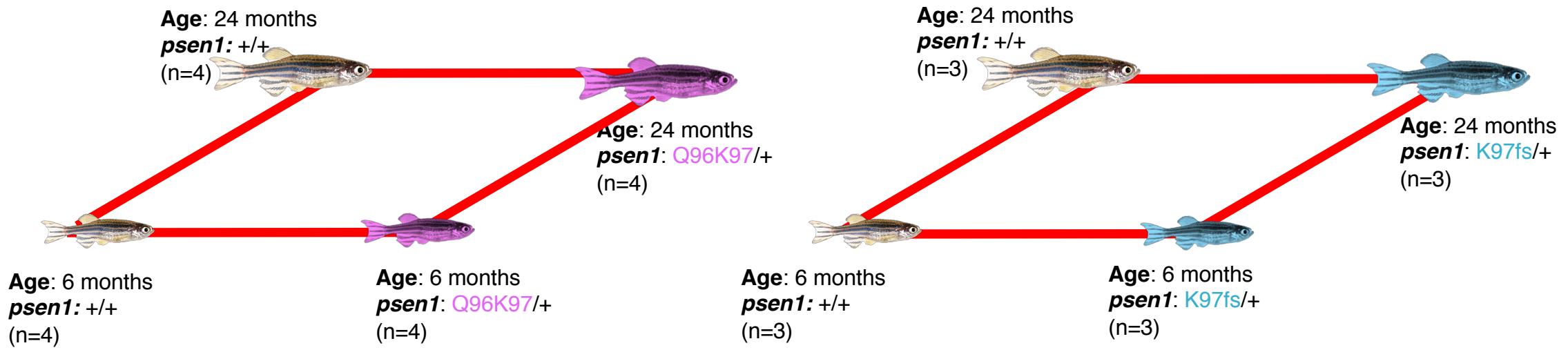
Compare between groups

to look for gene expression differences



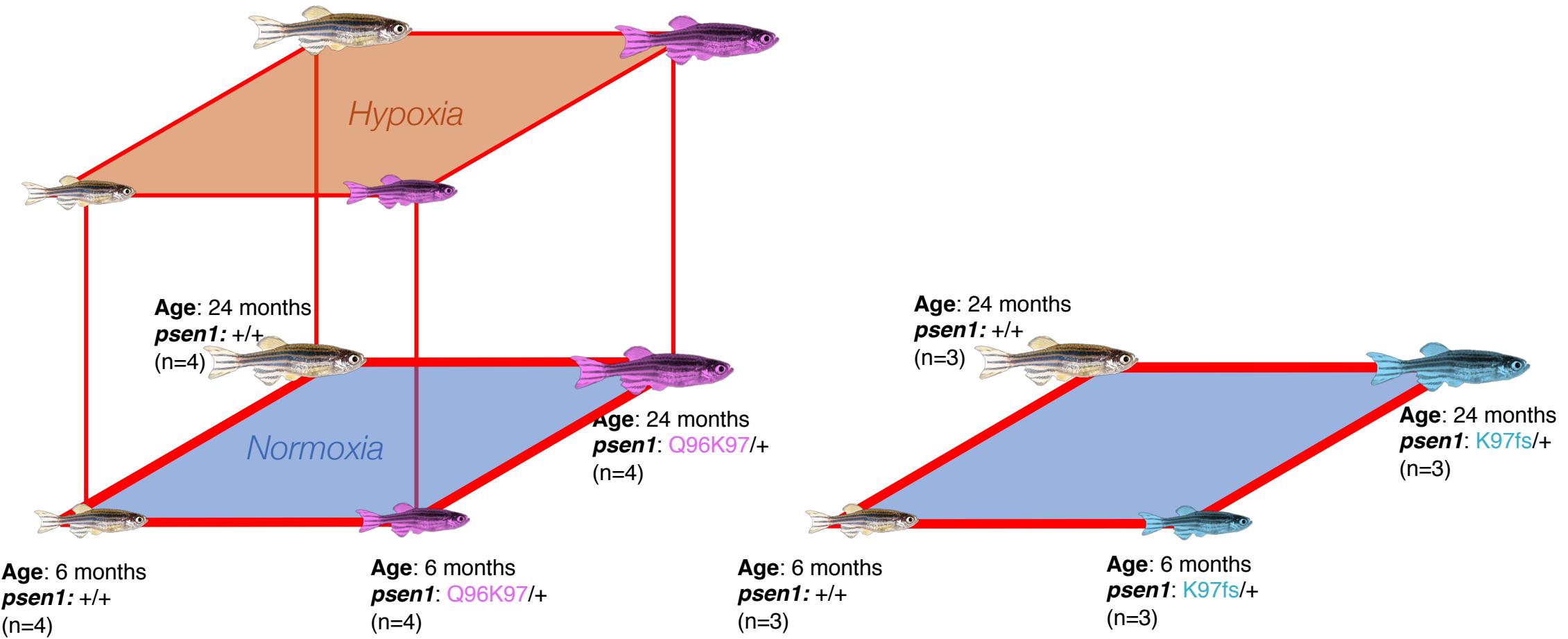
Compare between groups

to look for gene expression differences

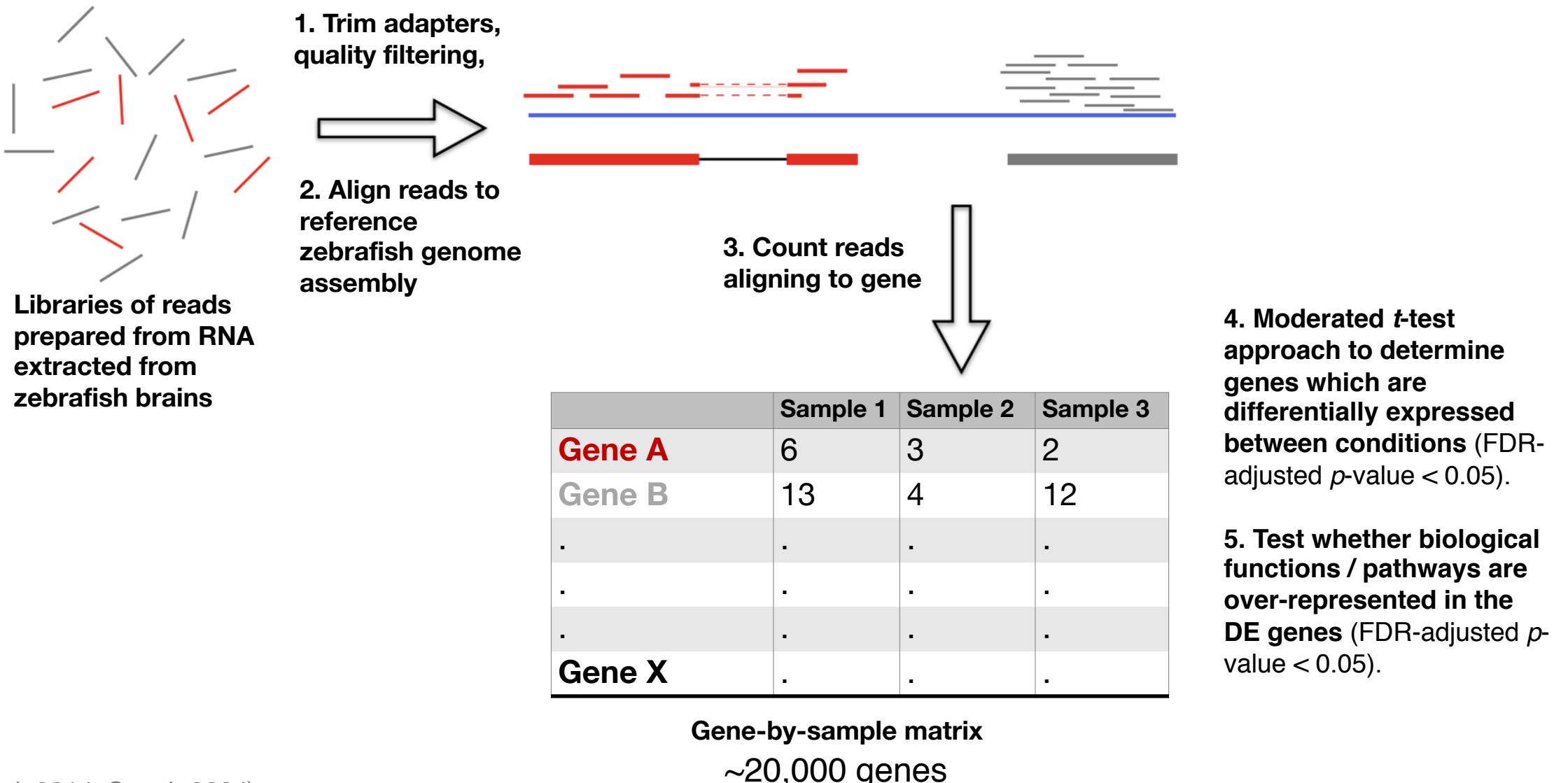


Compare between groups

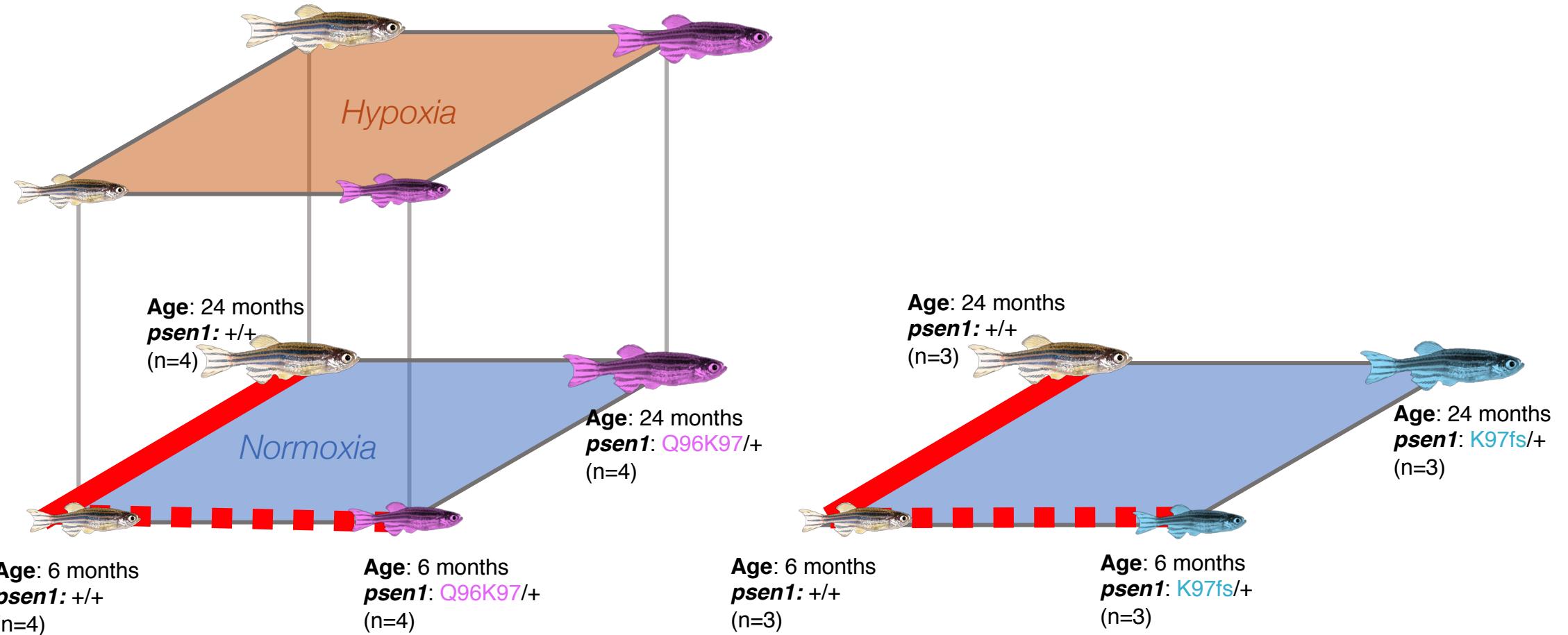
to look for gene expression differences



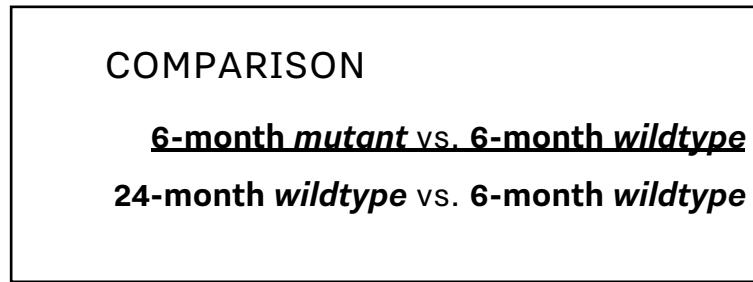
RNA-seq analysis



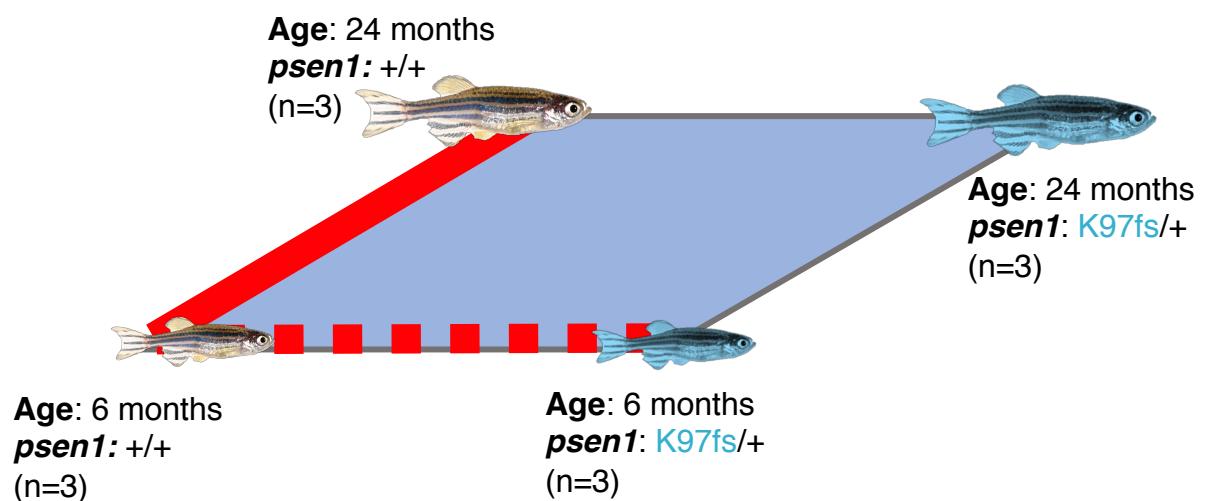
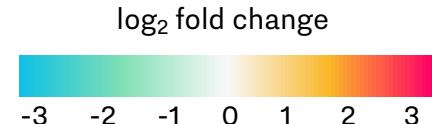
1. “Accelerated aging” in young adult mutants



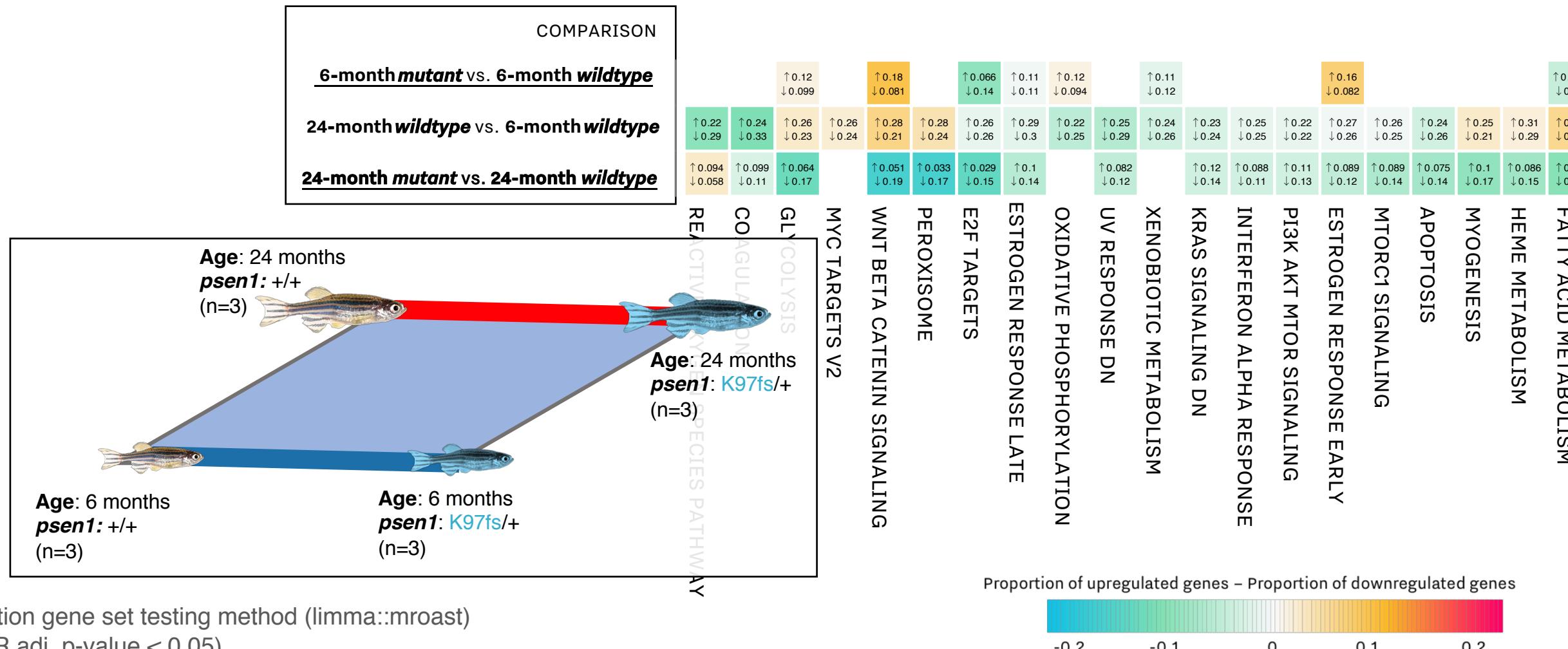
1. “Accelerated aging” in young adult mutants



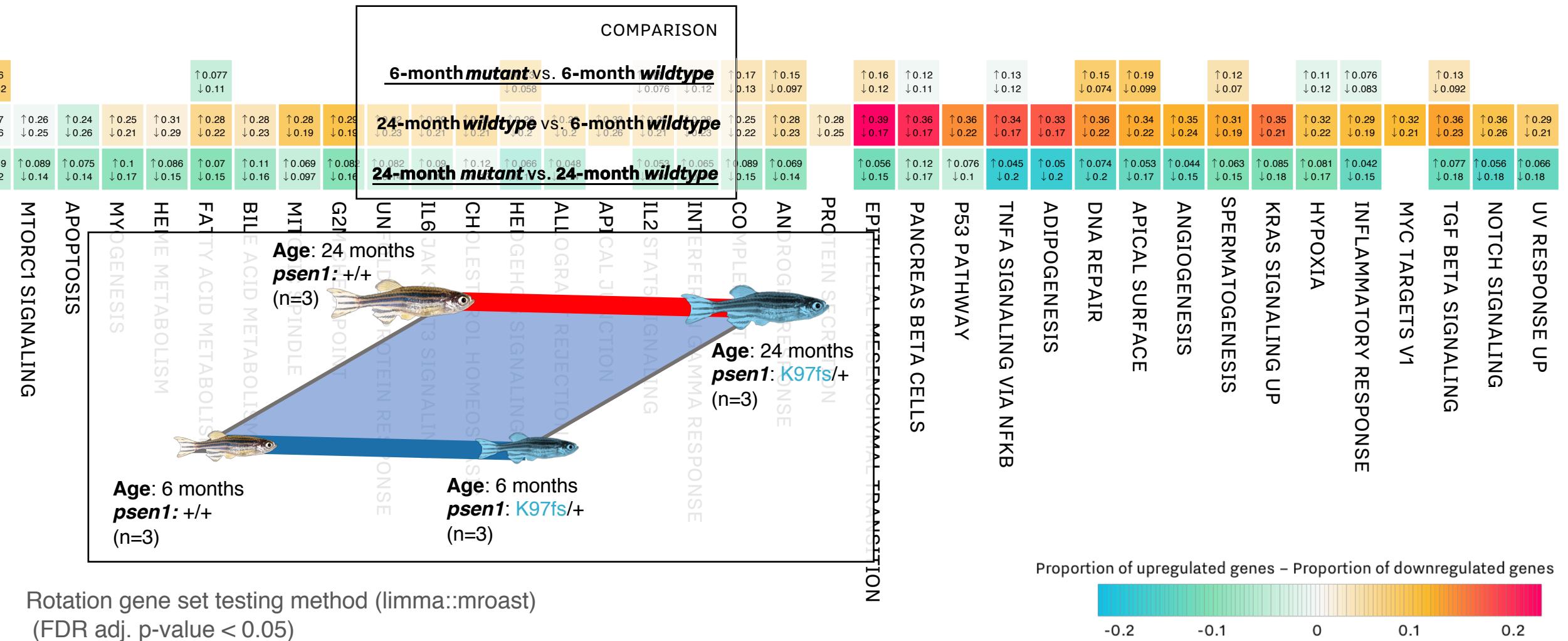
Differentially expressed genes between
K97fs/+ and +/+ at 6 months
(FDR adj. *p*-value < 0.05)



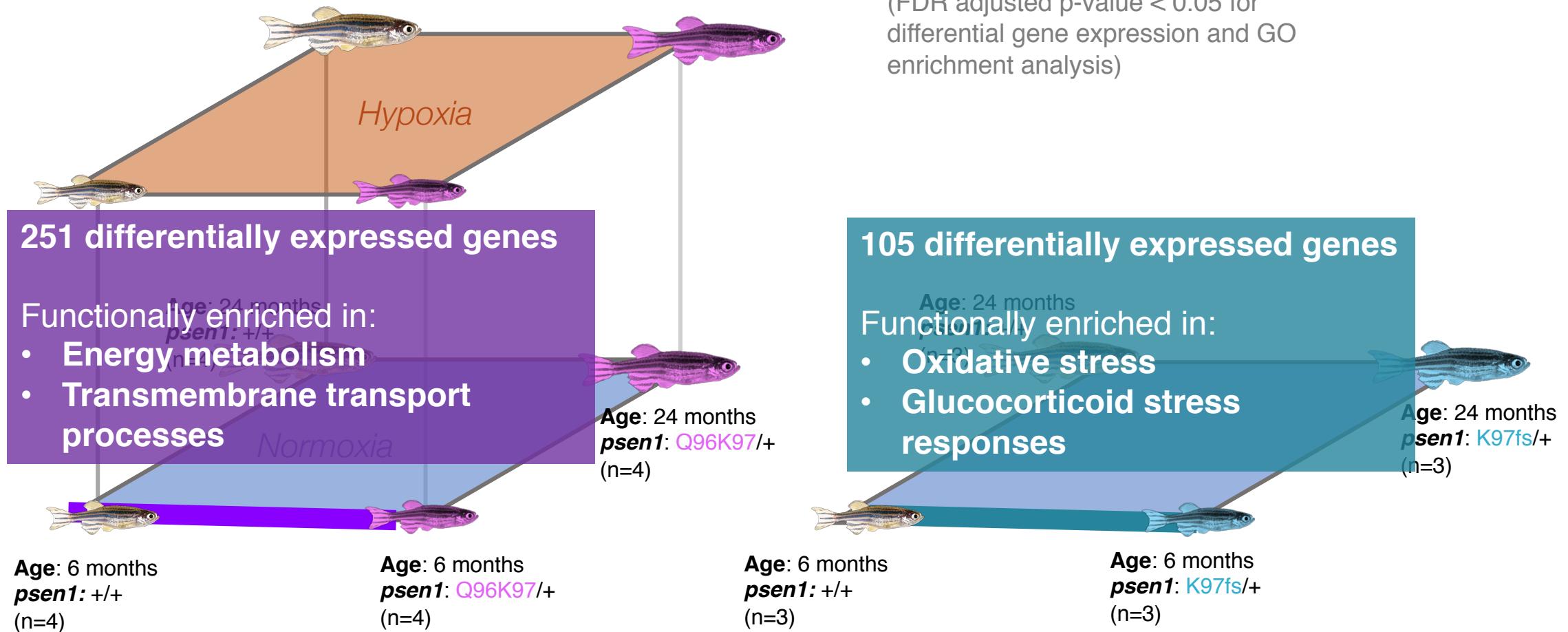
2. Gene expression changes in aged mutant brains, mostly distinct from young mutant brains



2. Gene expression changes in aged mutant brains, mostly distinct from young mutant brains



3. Q96K97 and K97fs mutations have different effects on gene expression at 6 months of age



HYPOTHESIS AND THEORY ARTICLE

Front. Neurosci., 13 August 2018 | <https://doi.org/10.3389/fnins.2018.00533>

Dysregulation of Neuronal Iron Homeostasis as an Alternative Unifying Effect of Mutations Causing Familial Alzheimer's Disease

 Amanda L. Lumsden^{1,2†},  Jack T. Rogers^{3†},  Shohreh Majd^{4†},  Morgan Newman⁵,  Greg T. Sutherland⁶,  Giuseppe Verdile⁷ and  Michael Lardelli^{5*}

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³Neurochemistry Laboratory, Department of Psychiatry-Neuroscience, Massachusetts General Hospital (East), Harvard Medical School, Harvard University, Charlestown, MA, United States

⁴Neuronal Injury and Repair Laboratory, Centre for Neuroscience, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

⁵Centre for Molecular Pathology, School of Biological Sciences, University of Adelaide, Adelaide, SA, Australia

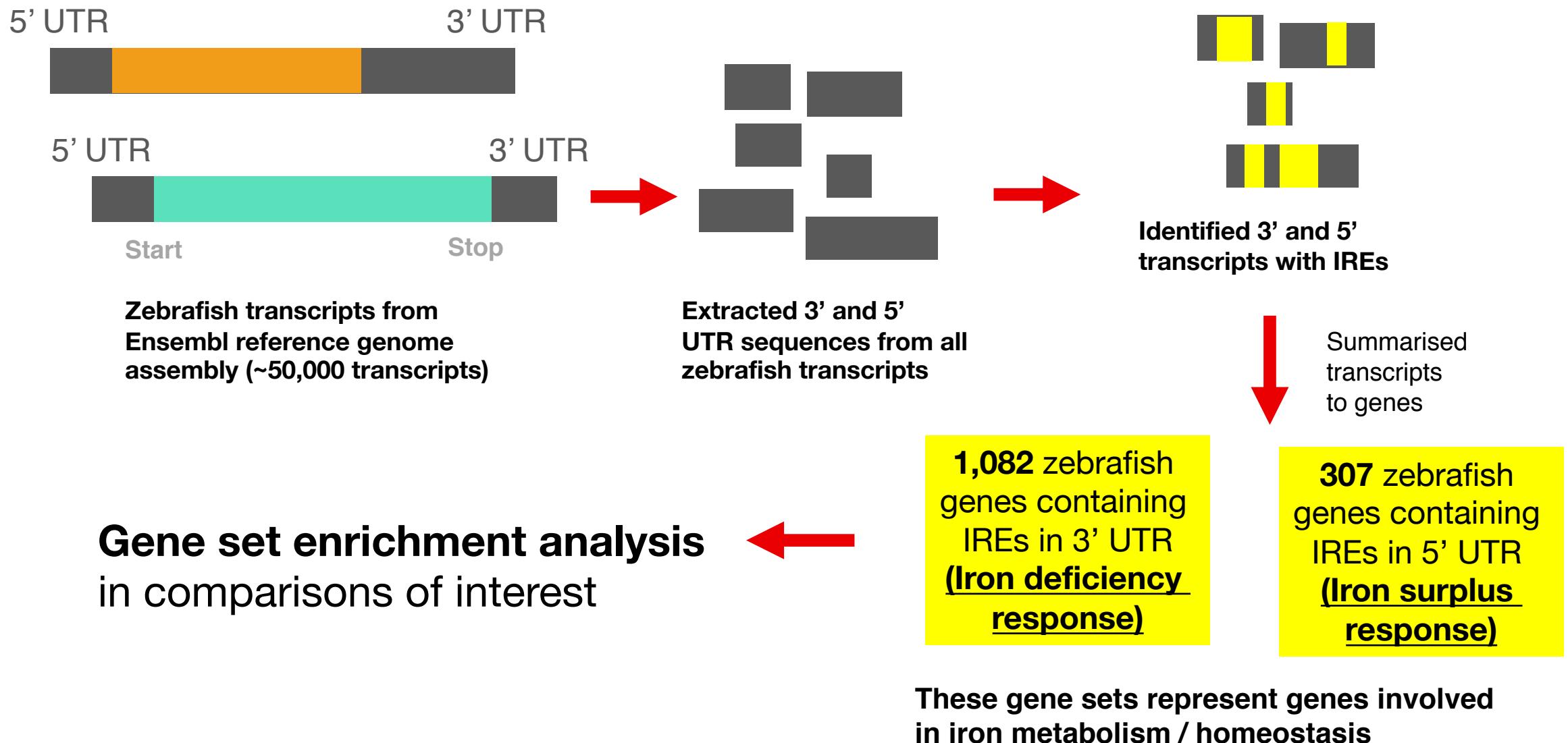
⁶Discipline of Pathology, Sydney Medical School, University of Sydney, Sydney, NSW, Australia

⁷School of Pharmacy and Biomedical Sciences, Faculty of Health Sciences, Curtin Health Innovation Research Institute, Curtin University, Bentley, WA, Australia

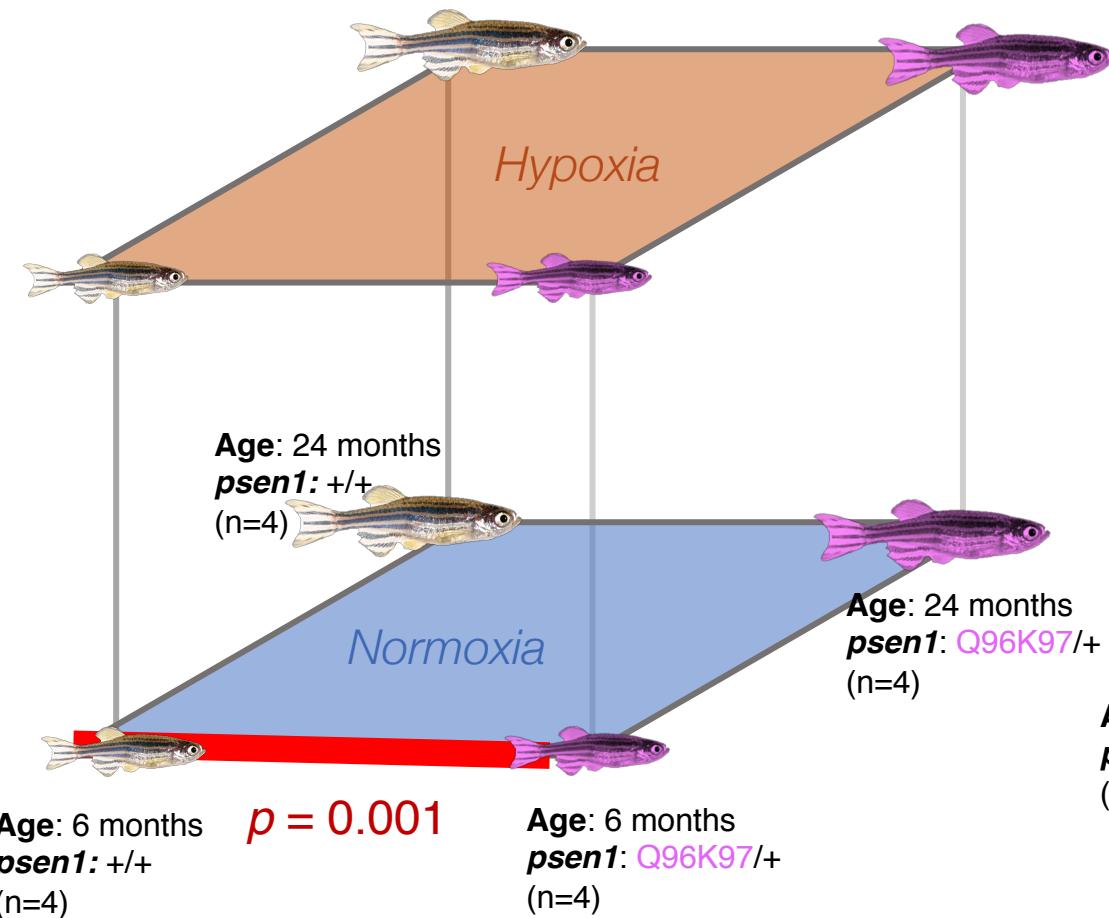
Is iron homeostasis disrupted in *Q96K97/+* (fAD-like) zebrafish? Can this be seen in the brain RNA-seq data?

1. Define gene set representing iron homeostasis genes (genes containing Iron Regulatory Elements in their UTRs).
2. Apply gene set enrichment analysis to assess differences in iron homeostasis in the *psen1*^{Q96K97/+} fish vs. wild type siblings.

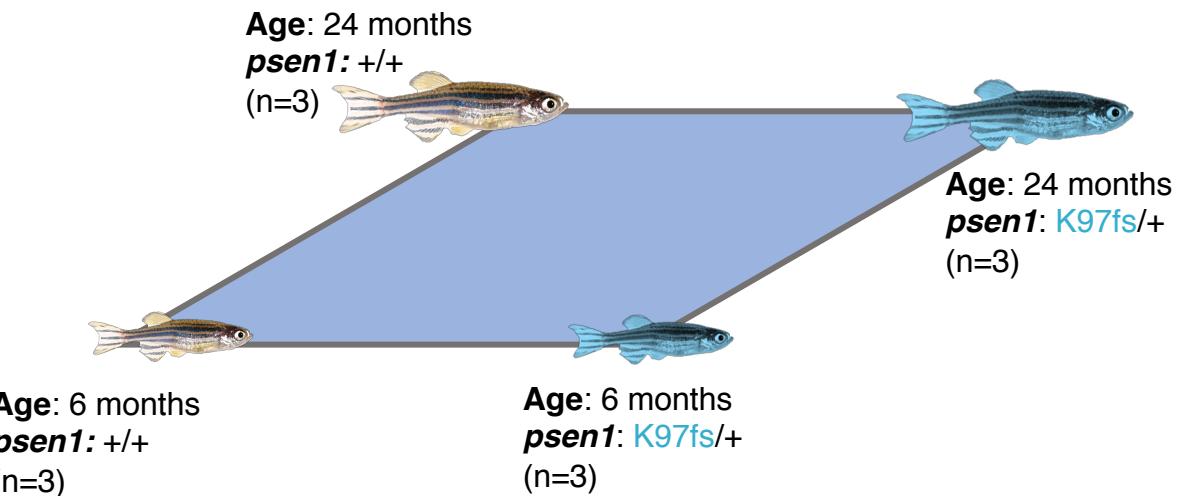
Defining sets of genes containing Iron Regulatory Elements



4. Evidence of iron deficiency response in Q96K97/+ brains at 6 months

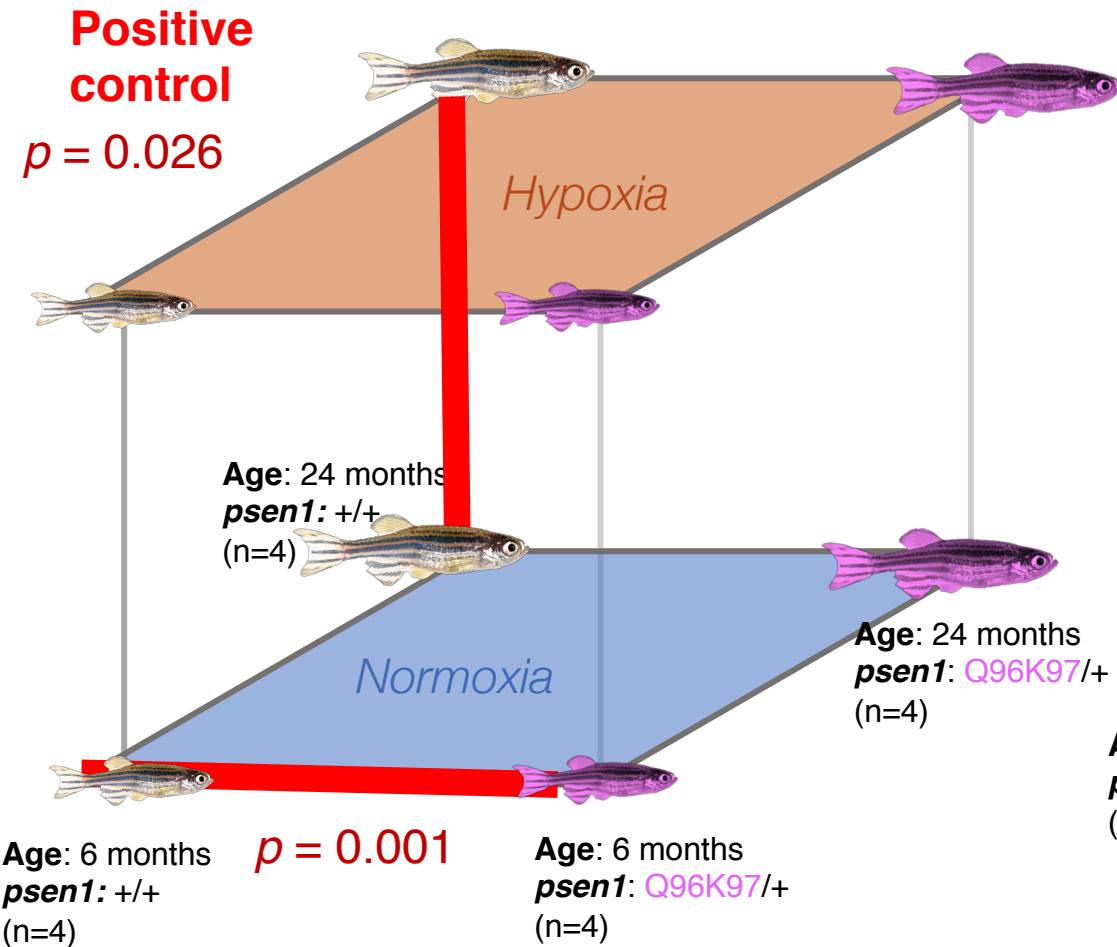


(Using gene set enrichment analysis,
p-values Bonferroni-adjusted)



1,082 zebrafish genes containing IREs in 3' UTR
(Iron deficiency response)

4. Evidence of iron deficiency response in Q96K97/+ brains at 6 months



1,082 zebrafish genes containing IREs in 3' UTR
(Iron deficiency response)

(Using gene set enrichment analysis,
 p -values Bonferroni-adjusted)

Summary

1. Analysing RNA-seq data can be an effective approach for detecting **broad patterns of gene expression changes** across the brain, and also more **targeted hypotheses** (with a representative gene set).
2. Gene set enrichment testing shows preliminary evidence to support iron dyshomeostasis in early stages of familial Alzheimer's disease (need to test other zebrafish models/mutations).

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+ Dave Adelson, Sabrina Ng, Shanice Mah, Arwa Nawaz