UMass Chan MEDICAL SCHOOL

Genomics & Computational Biology

Linking single-cell transcriptomic and genomic changes in the aging human brain

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ASHG
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Financial Disclosure

I do not have any relationships to report within the last 24 months with ACCME defined ineligible companies.

Why study aging?

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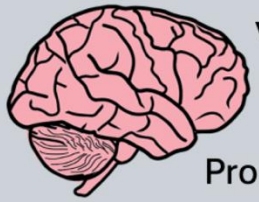
Physical	Molecular
Thinning skin and loss of elasticity	Telomere shortening
Graying and thinning hair	Changes in proteostasis
Loss of muscle mass	Epigenetic alterations
Reduction in height	Disrupted macroautophagy
Decreased joint mobility	Genomic instability

Cognitive
Processing speed
Verbal fluency
Recall
Prospective memory
Selective attention



- Aging is the primary risk factor for neurodegenerative diseases, cancers, and metabolic disorders.
- Study aging help extending lifespan and developing therapies for prevalent age-related disorders.

Aging and DNA damage

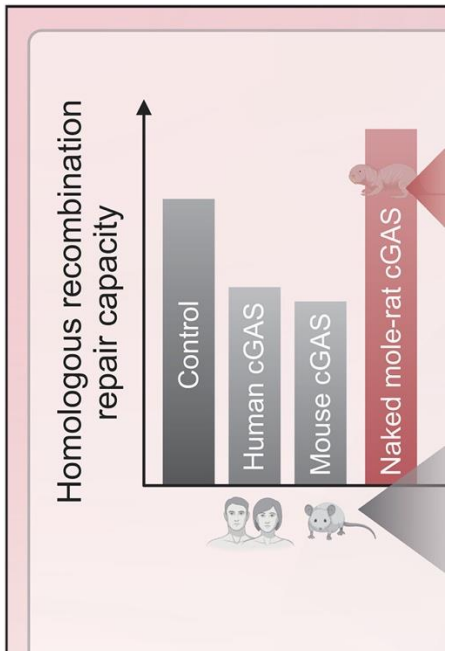
- Genetic disorders with defective DNA repair show premature aging, supporting the link between DNA damage and aging.

Cockayne Syndrome caused by ERCC6 or ERCC8 mutation

Vermeulen et al. 2013, *Cold Spring Harbor Perspectives in Biology*

Aging and DNA damage

- Genetic disorders with defective DNA repair show premature aging, supporting the link between DNA damage and aging.
- Species with enhanced DNA repair mechanisms, like naked mole rats, exhibit slower aging and lower cancer rates.



Picture from Akron Zoo
Chen et al. 2025, *Science*

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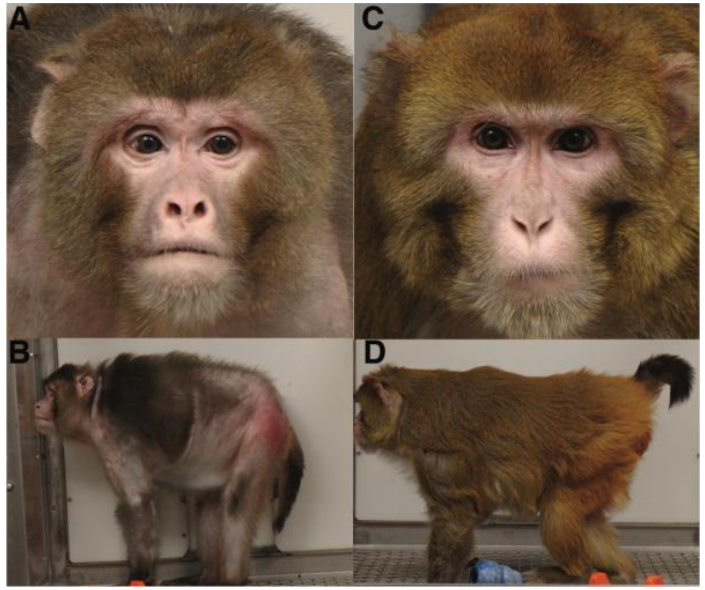
Aging and DNA damage

- Genetic disorders with defective DNA repair show premature aging, supporting the link between DNA damage and aging.
- Species with enhanced DNA repair mechanisms, like naked mole rats, exhibit slower aging and lower cancer rates.
- Caloric restriction can reduce oxidative stress and DNA damage, prolonging lifespan in various organisms.



Colman et al., 2009, *Science*

Genome and transcriptome in single-cell

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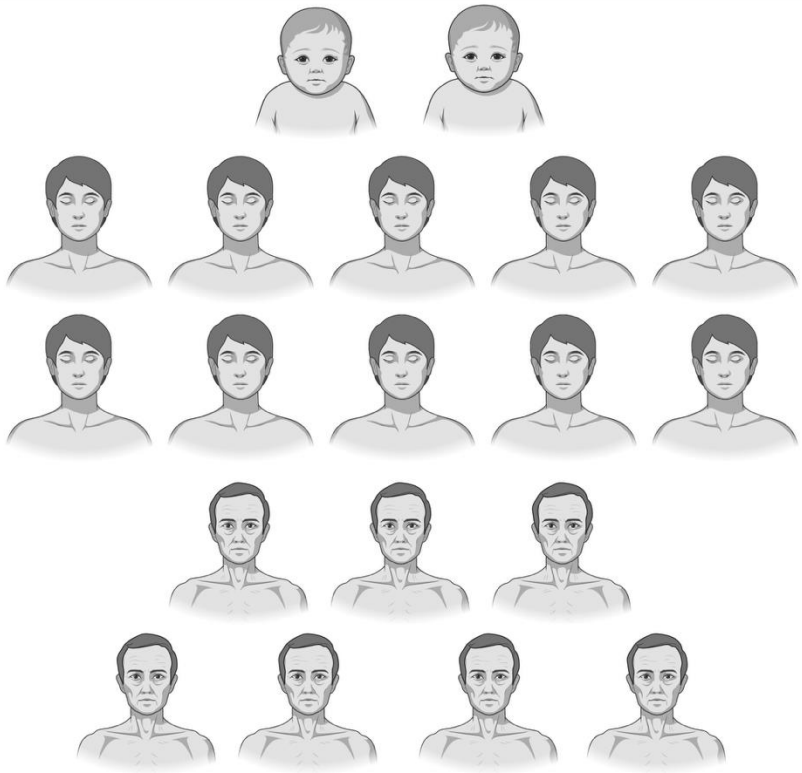
19 fresh frozen human prefrontal cortex

two infants

ten adults

seven elderly



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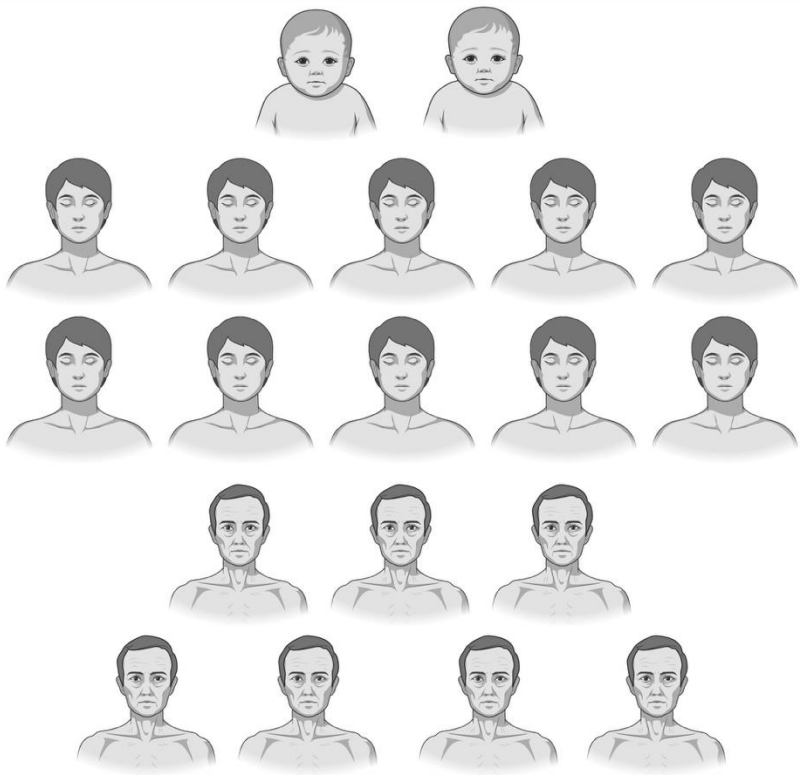

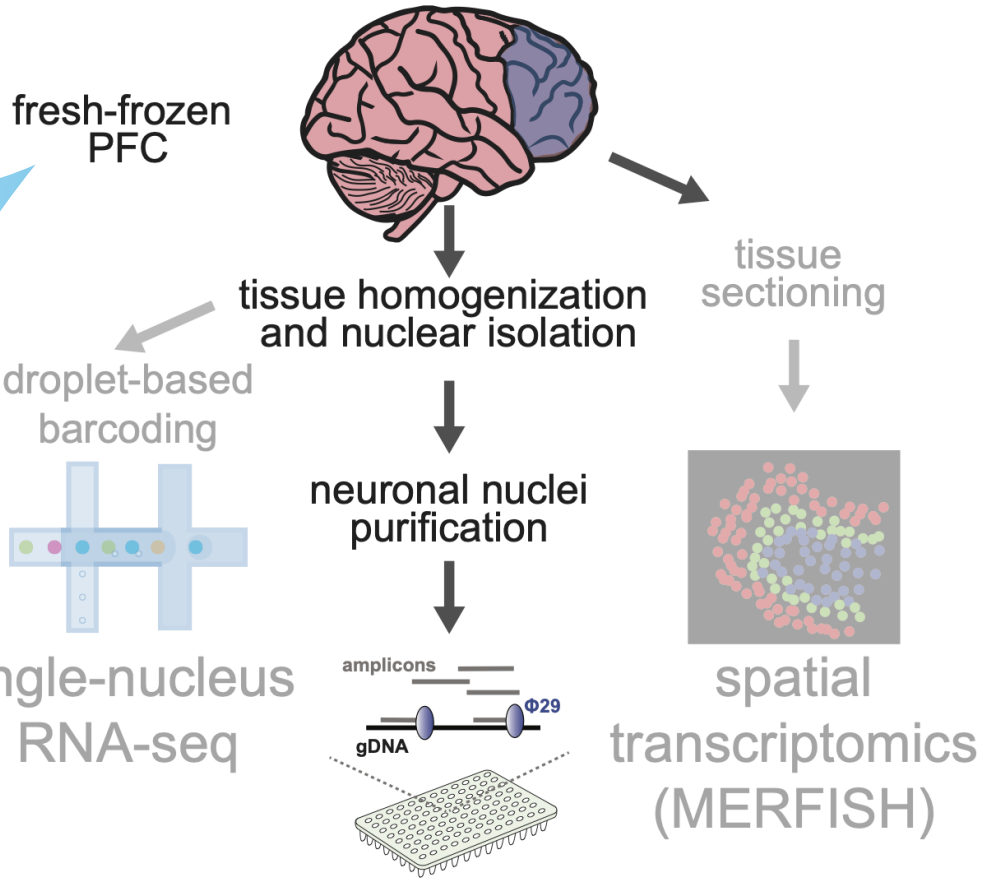

Experiments done by Ailsa and Jenn

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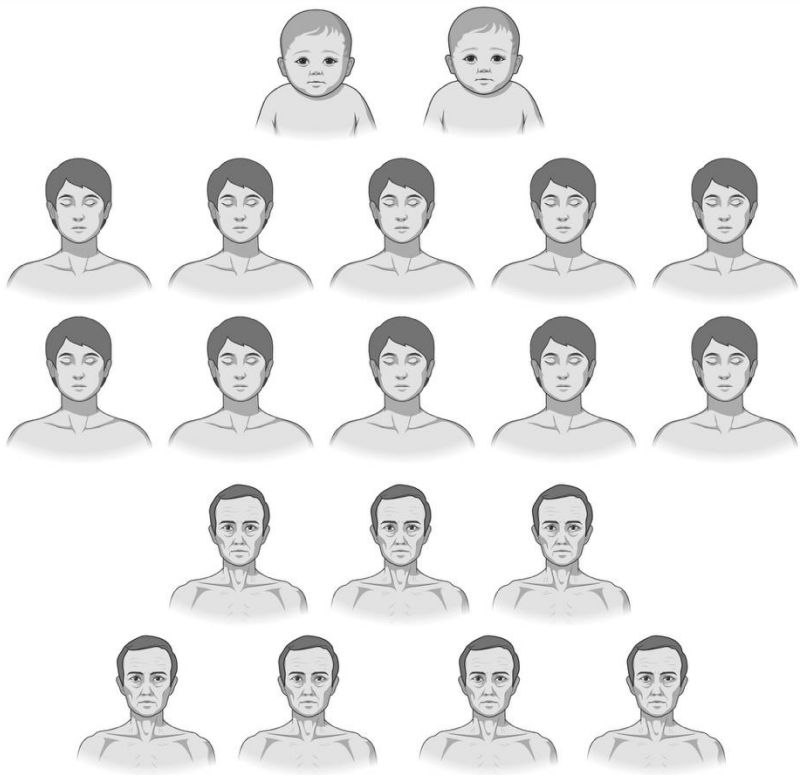

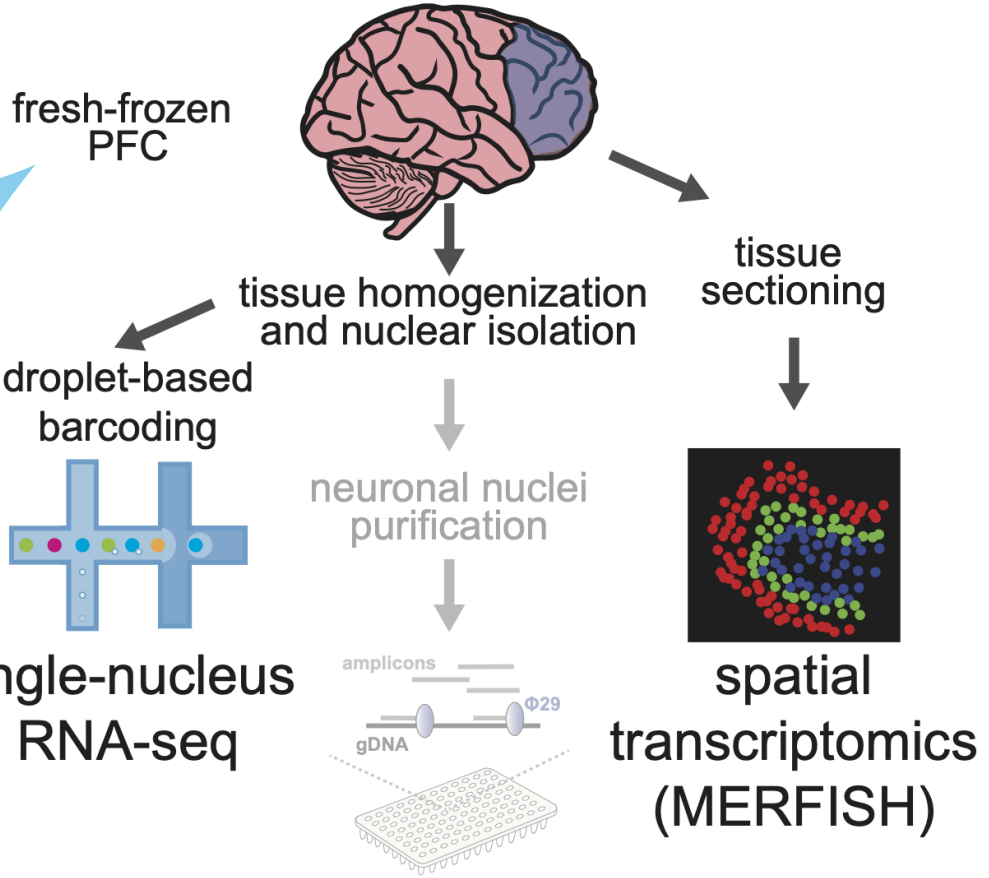

Experiments done by Ailsa and Jenn

How does somatic mutations accumulate in neurons during aging?

Somatic SNV accumulate in neurons

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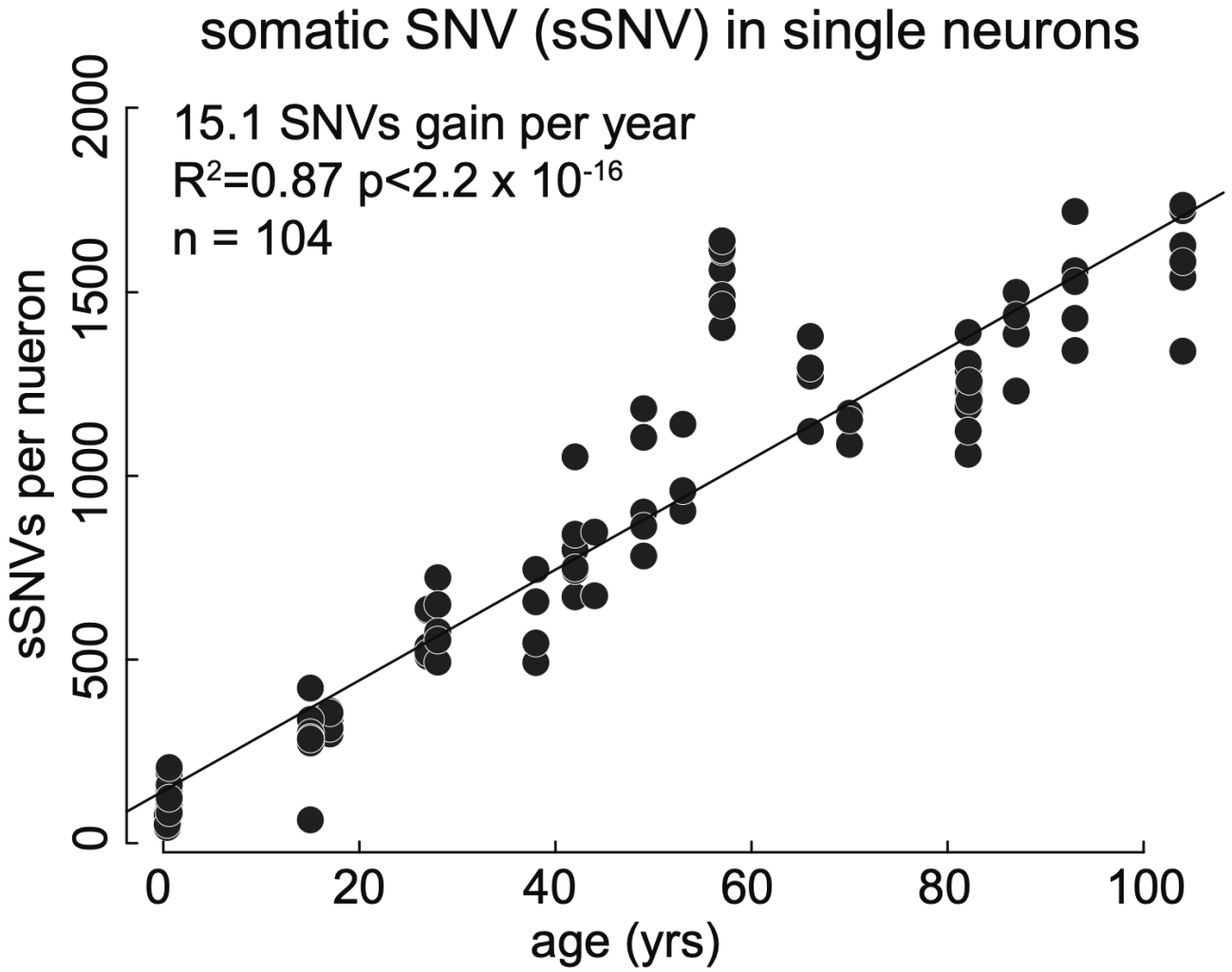

SNV: single nucleotide substitution

A signature associated with aging

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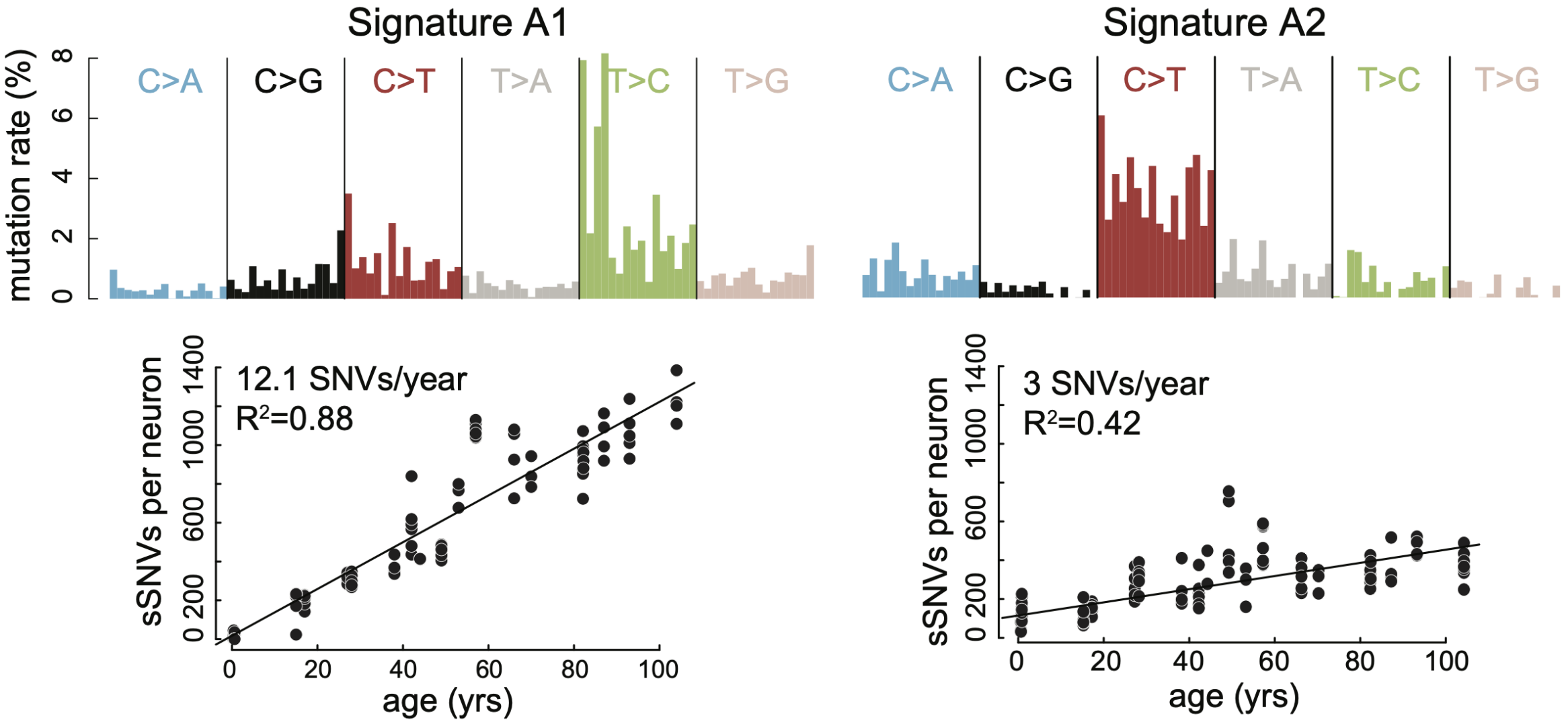

Signatures are fingerprints of certain mutagens

A signature associated with aging

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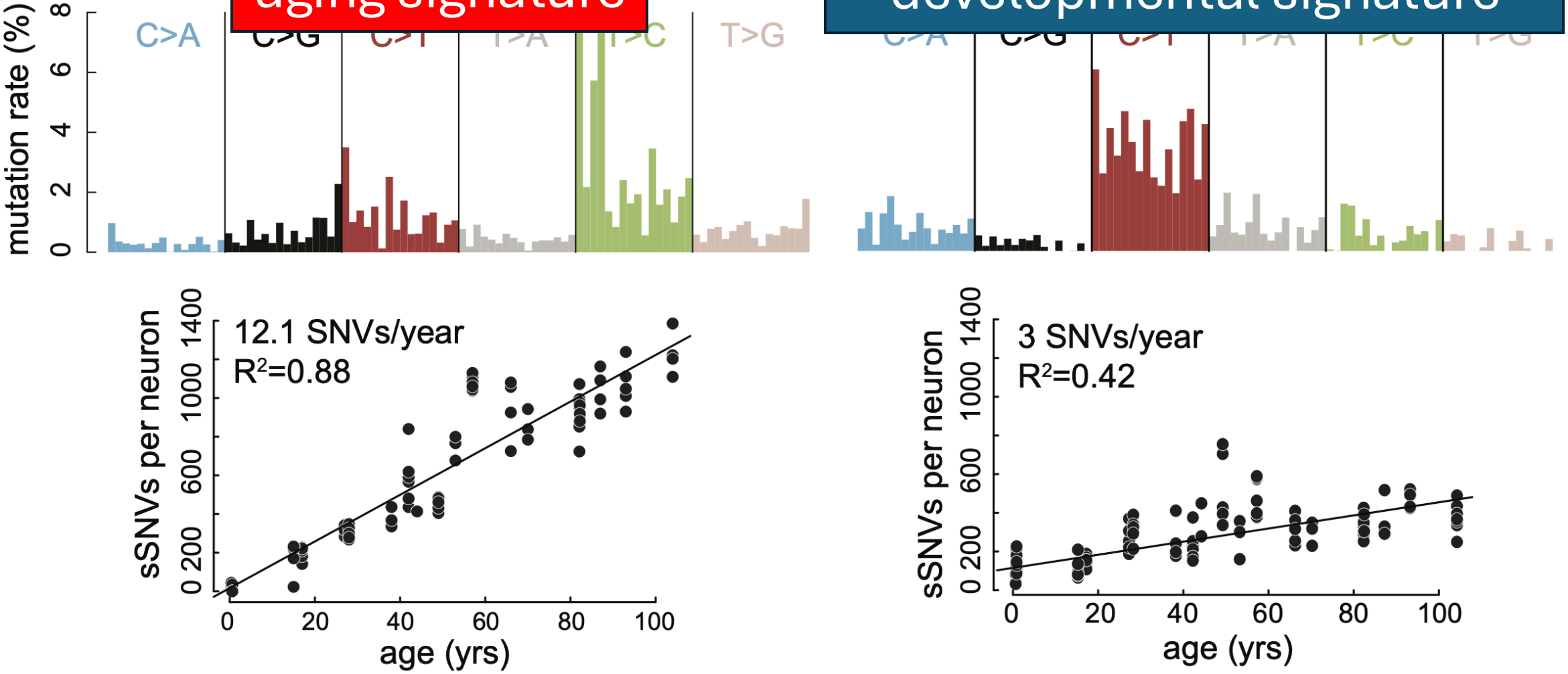
aging signature

developmental signature



Signatures are fingerprints of certain mutagens

Aging signature enrich at active genes

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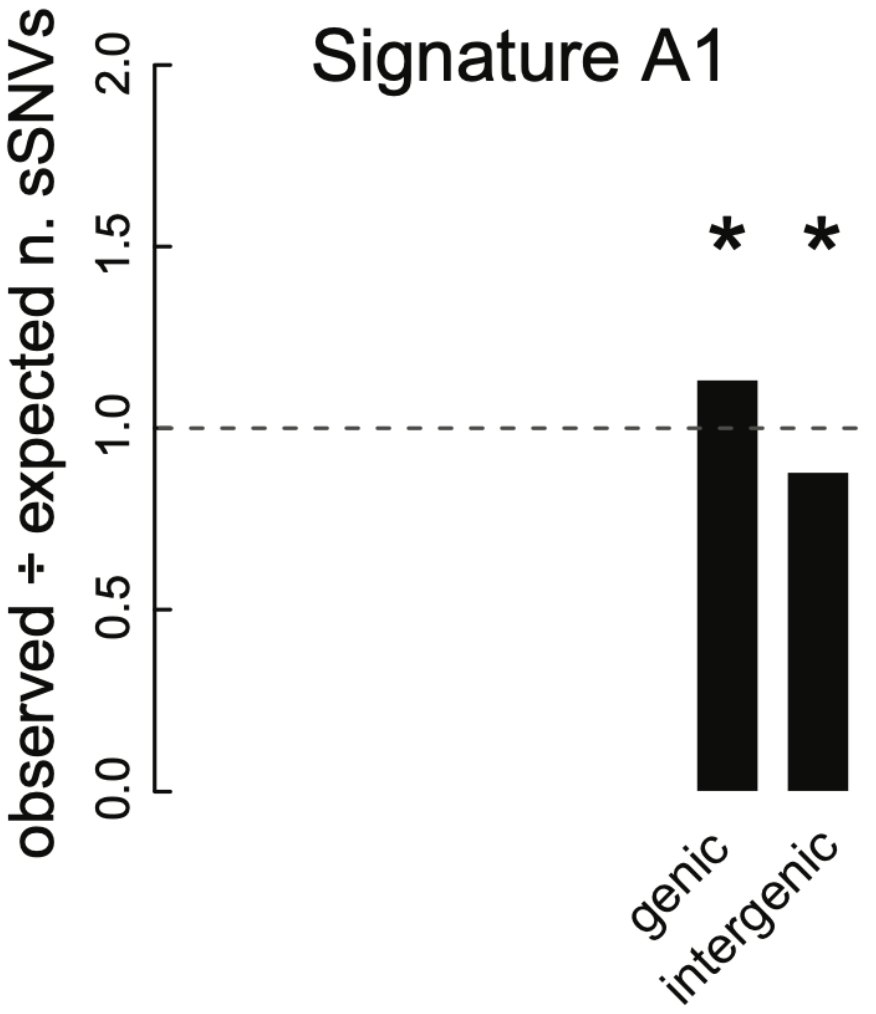

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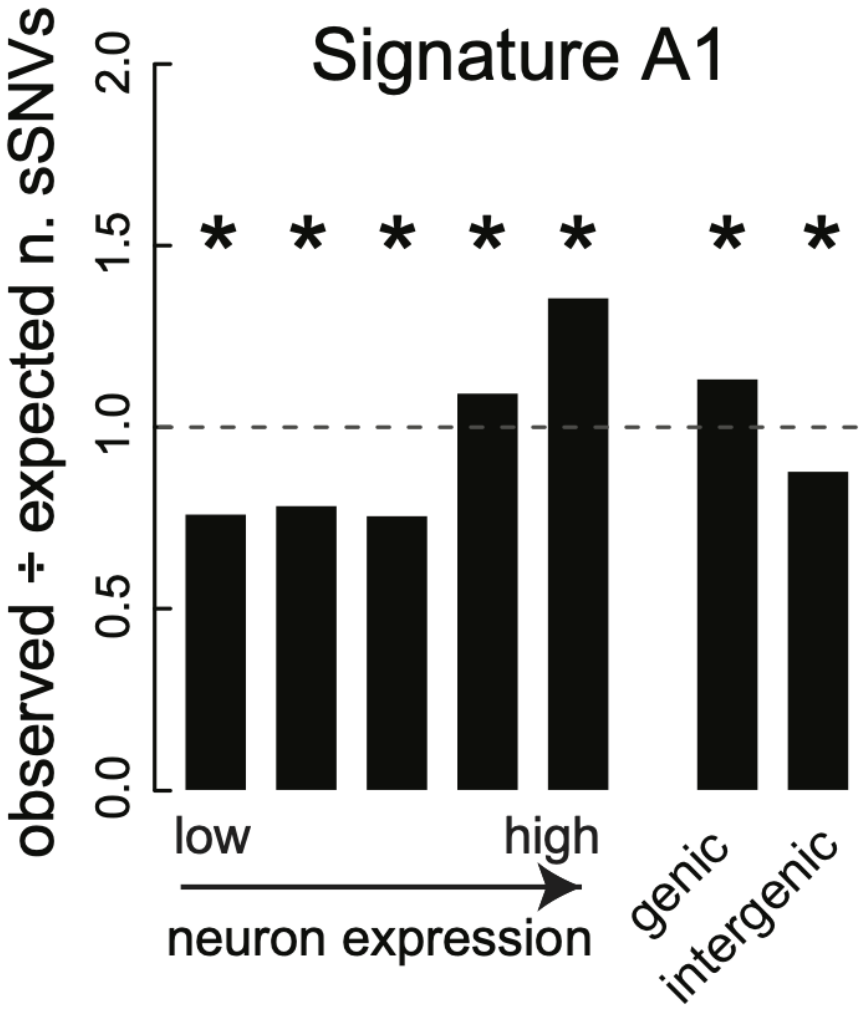

How does transcriptome change in PFC during aging?

snRNA-seq captured cells in PFC

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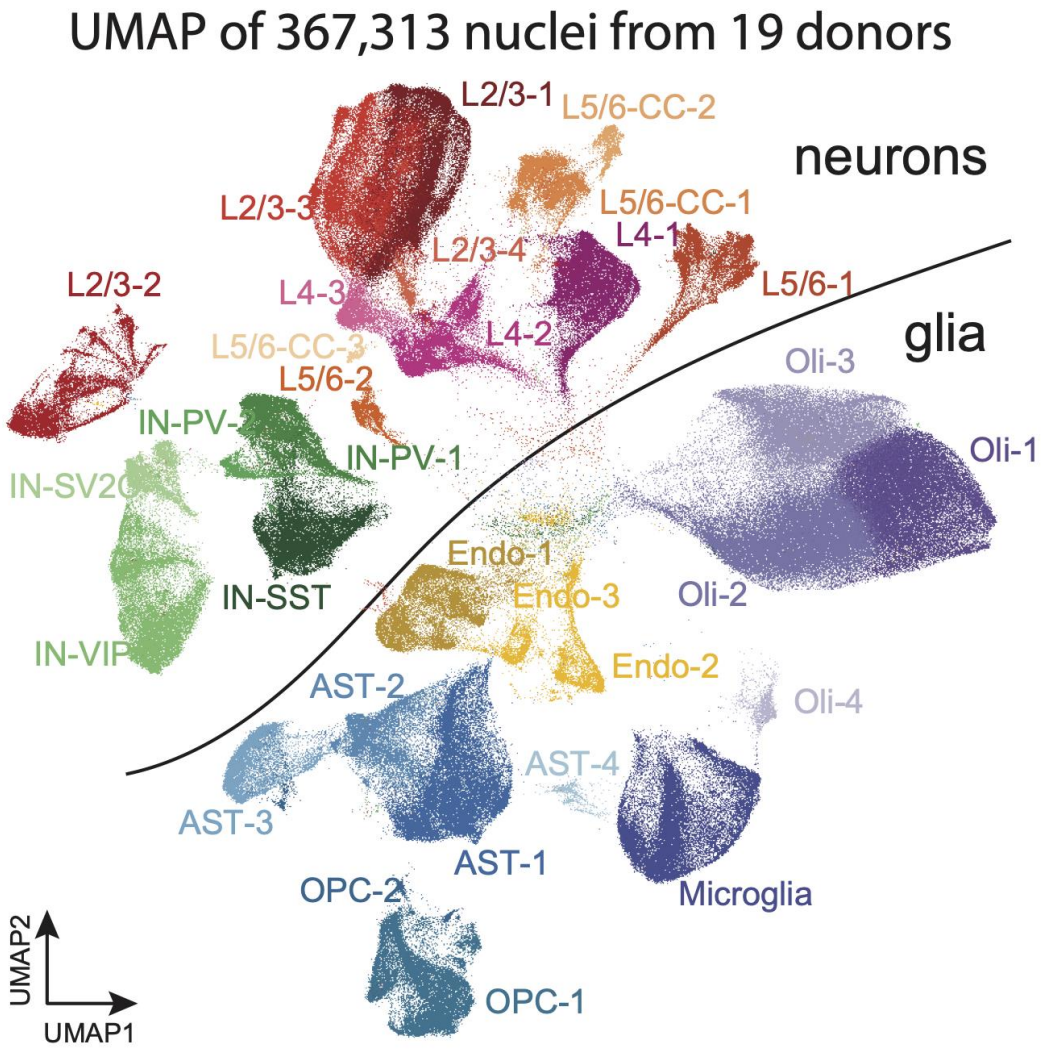

Many genes are commonly down during aging

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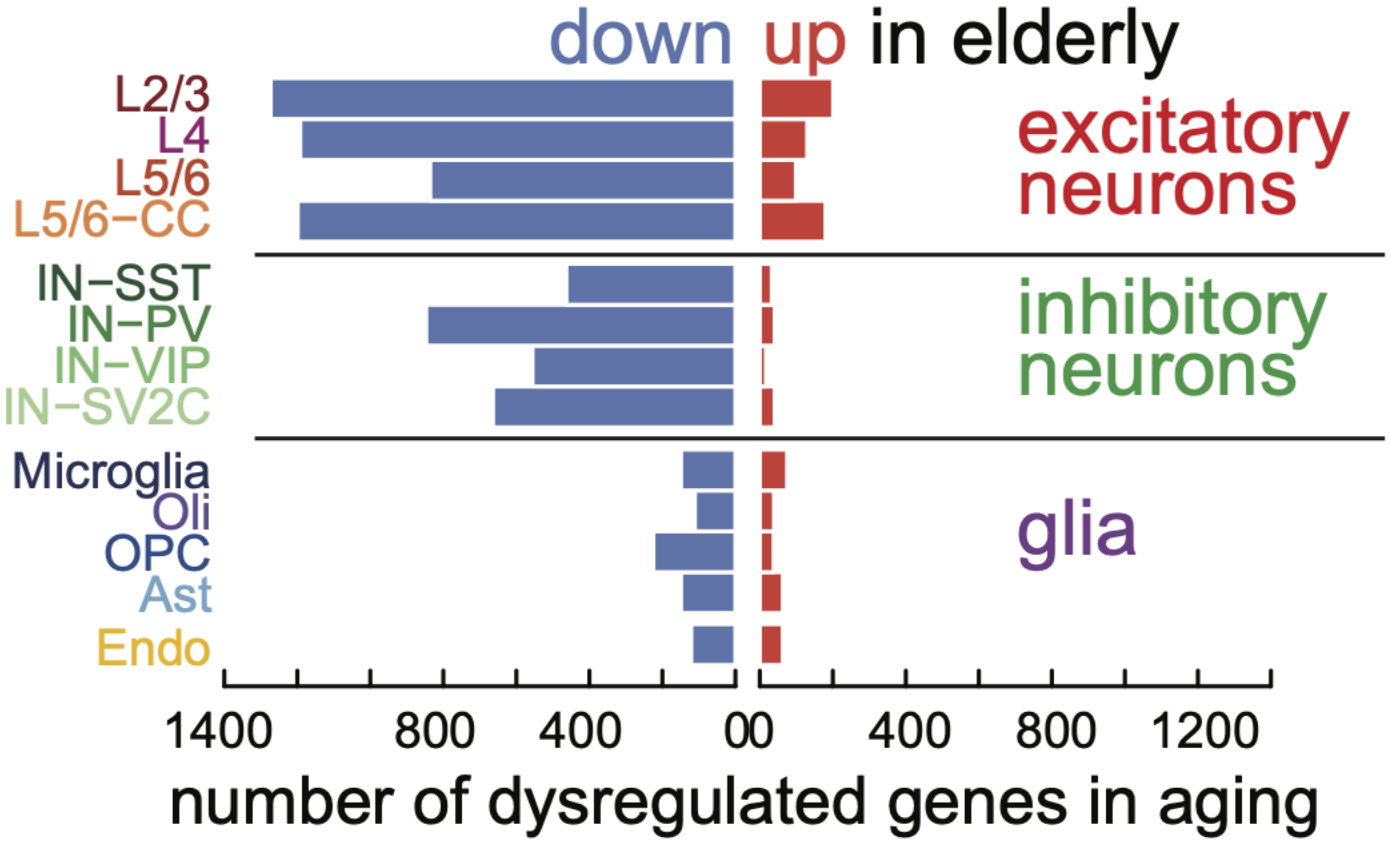

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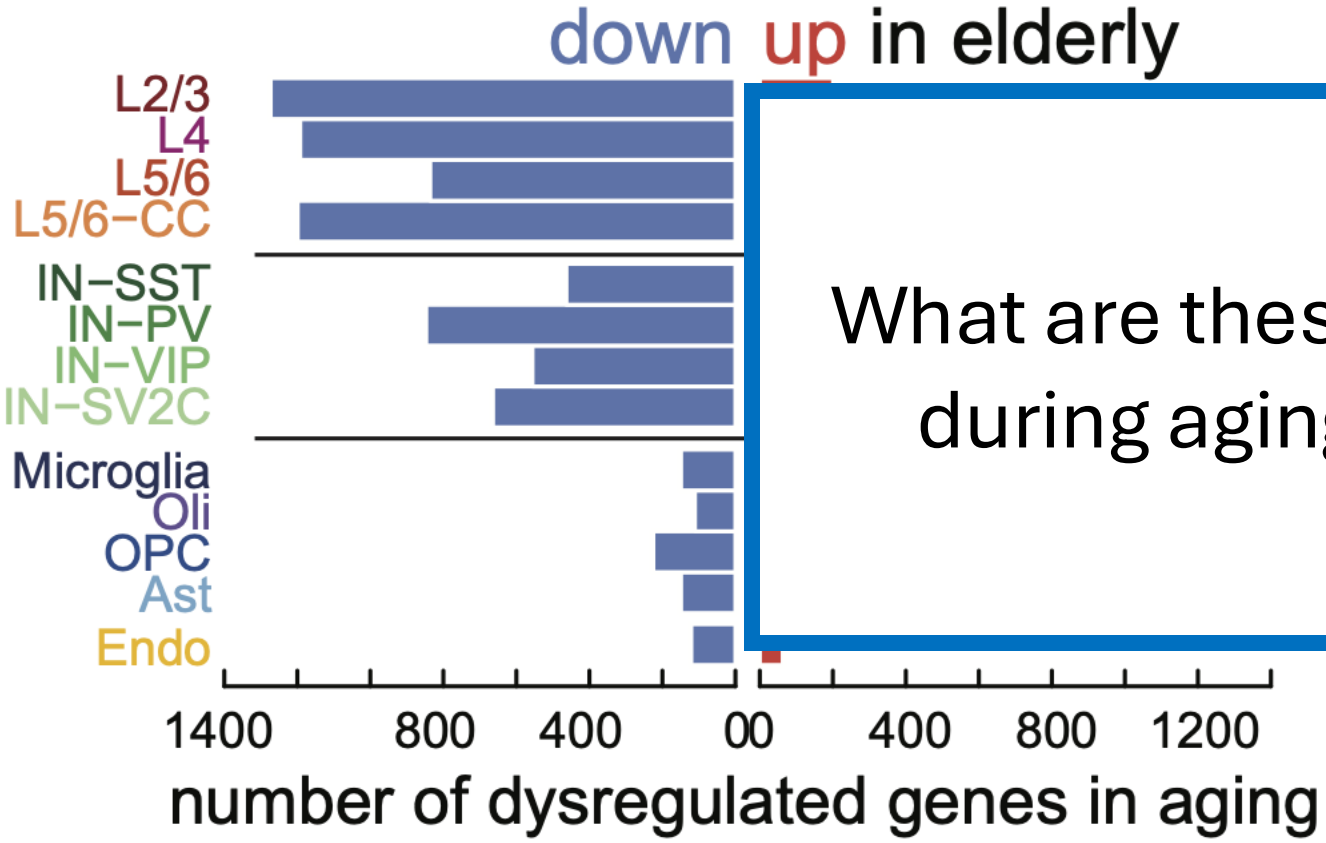

What are these gene down during aging process?

Common decrease of housekeeping program

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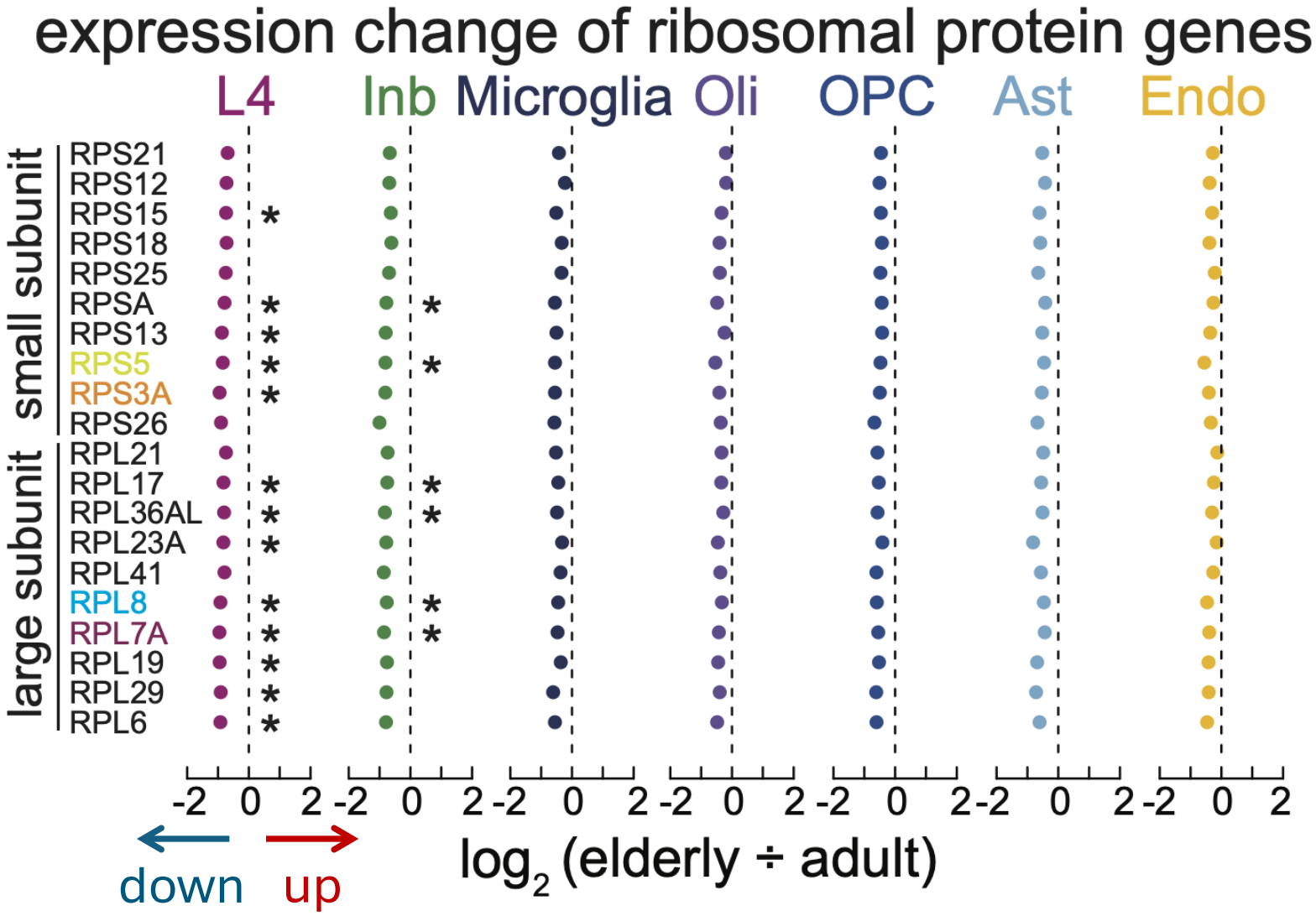

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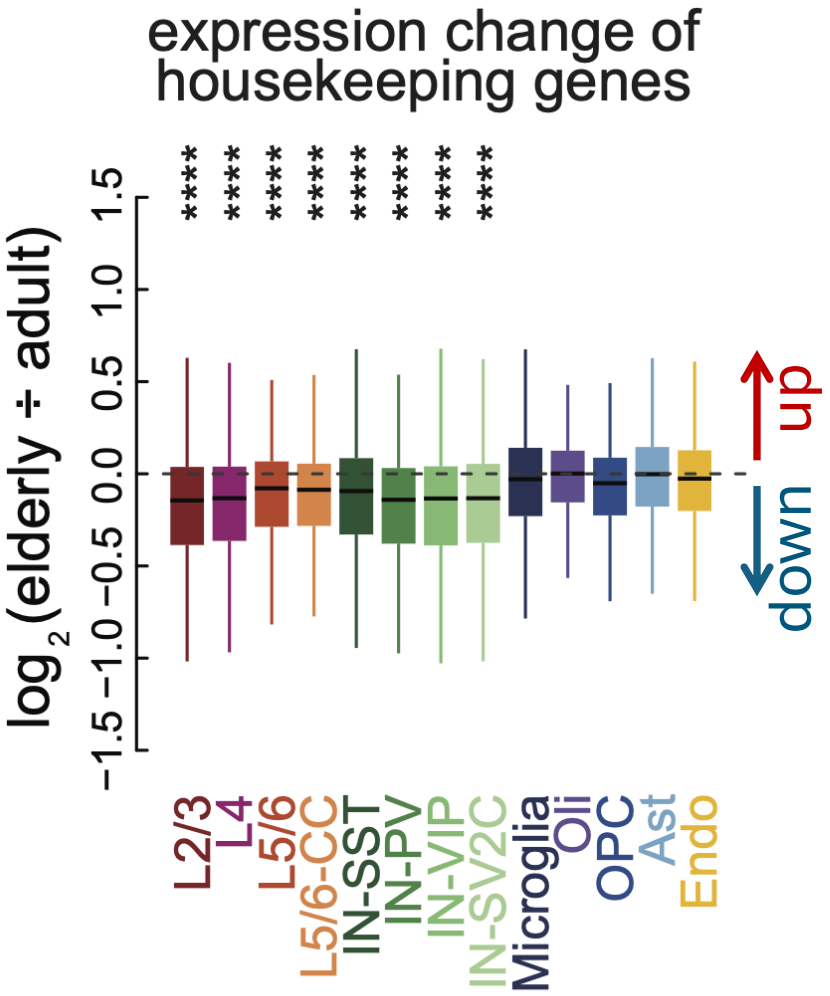

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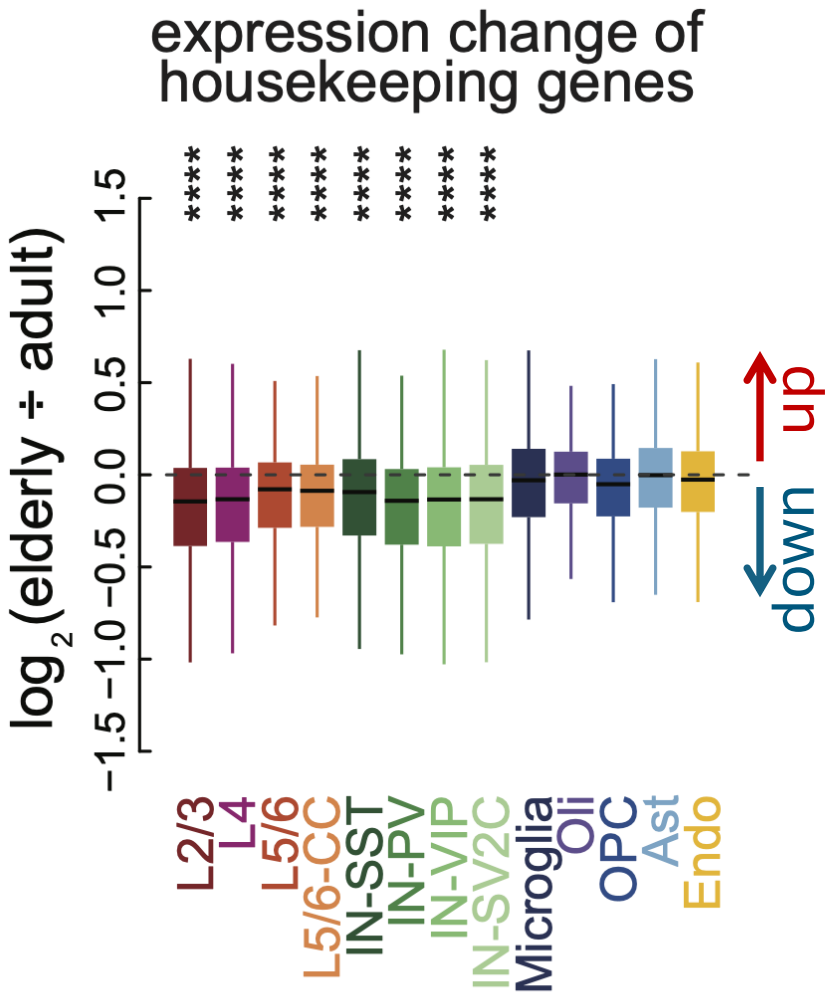

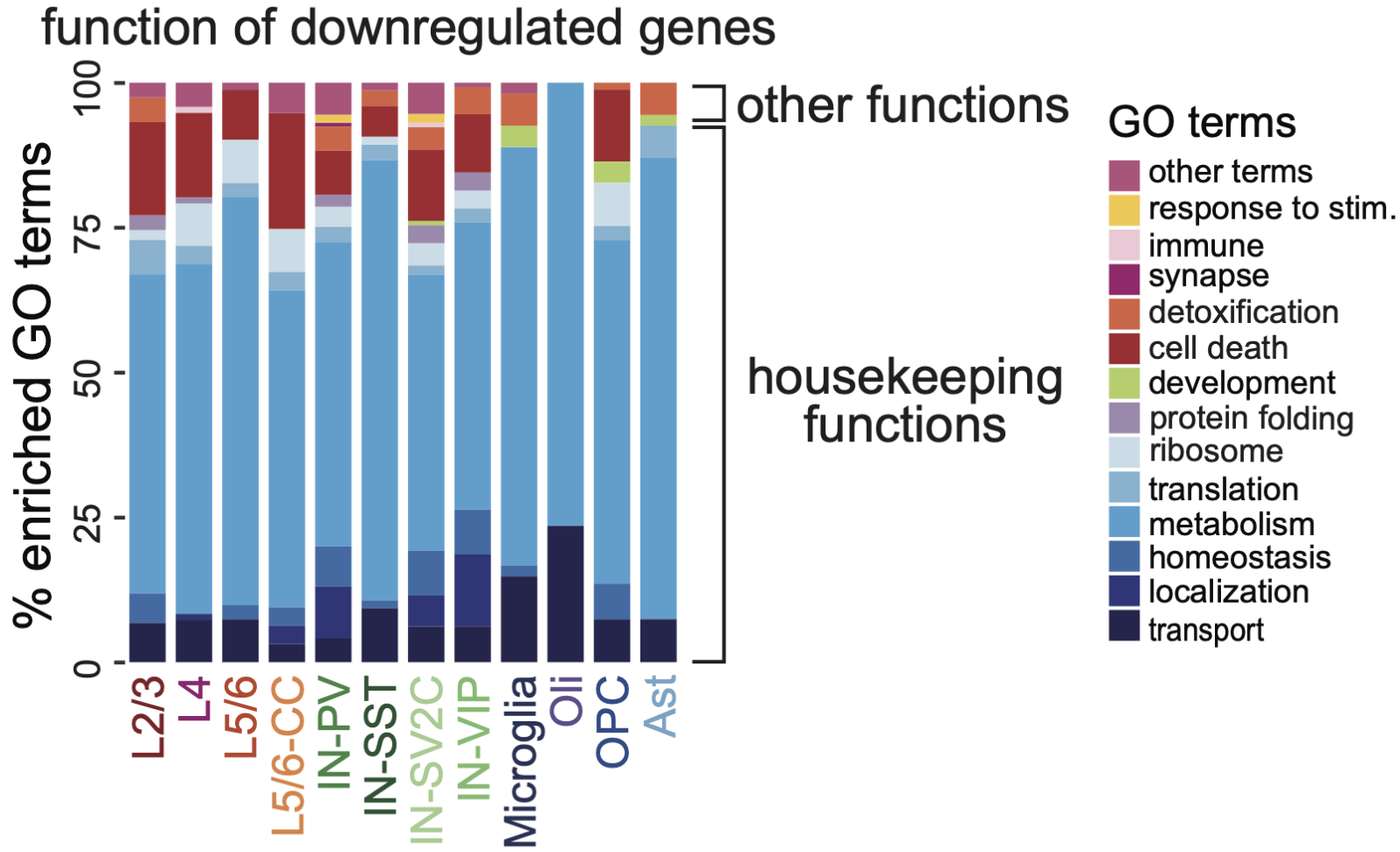

How does genomic changes link with transcriptomic changes during PFC aging?

Short and active genes go down during aging

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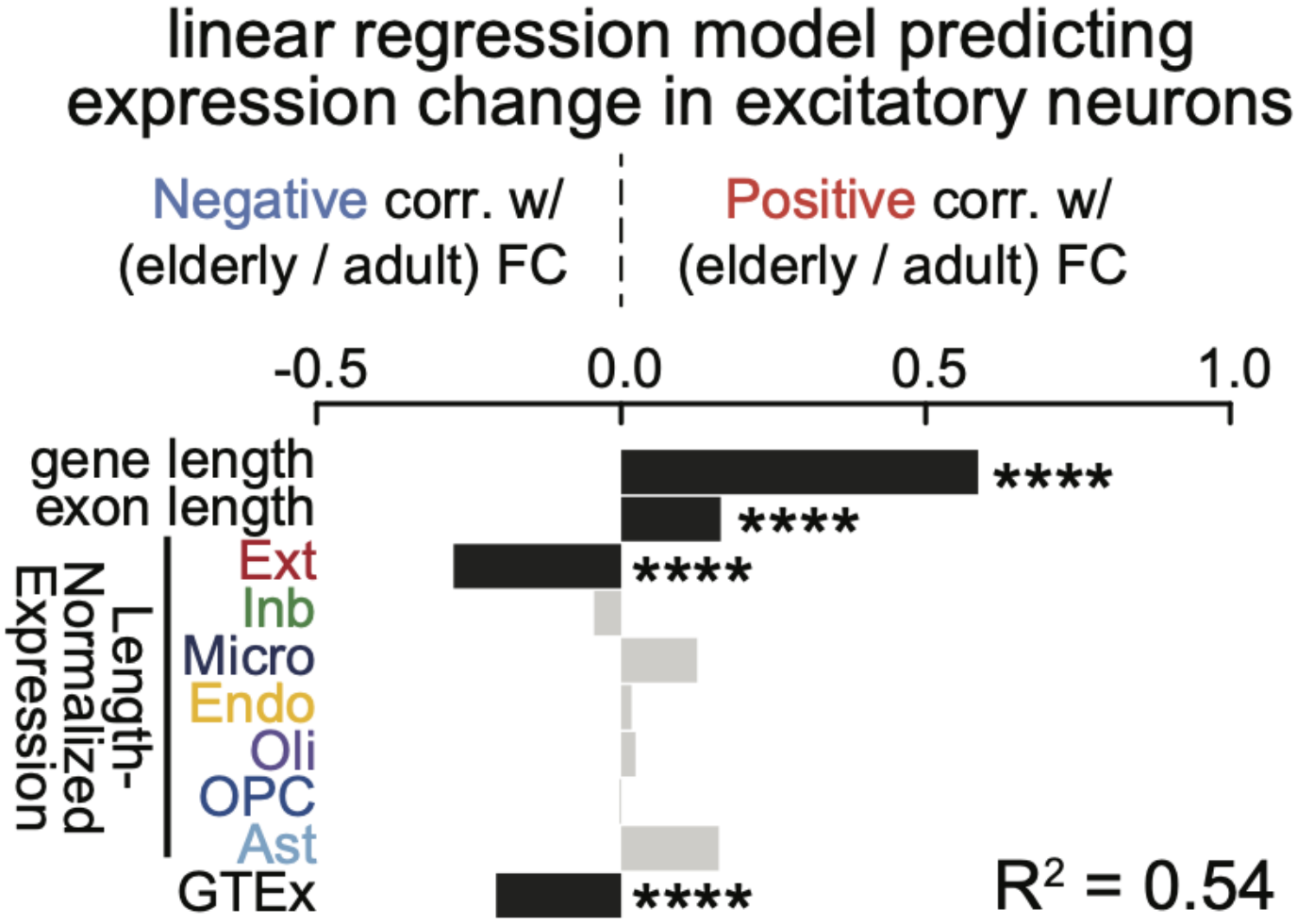

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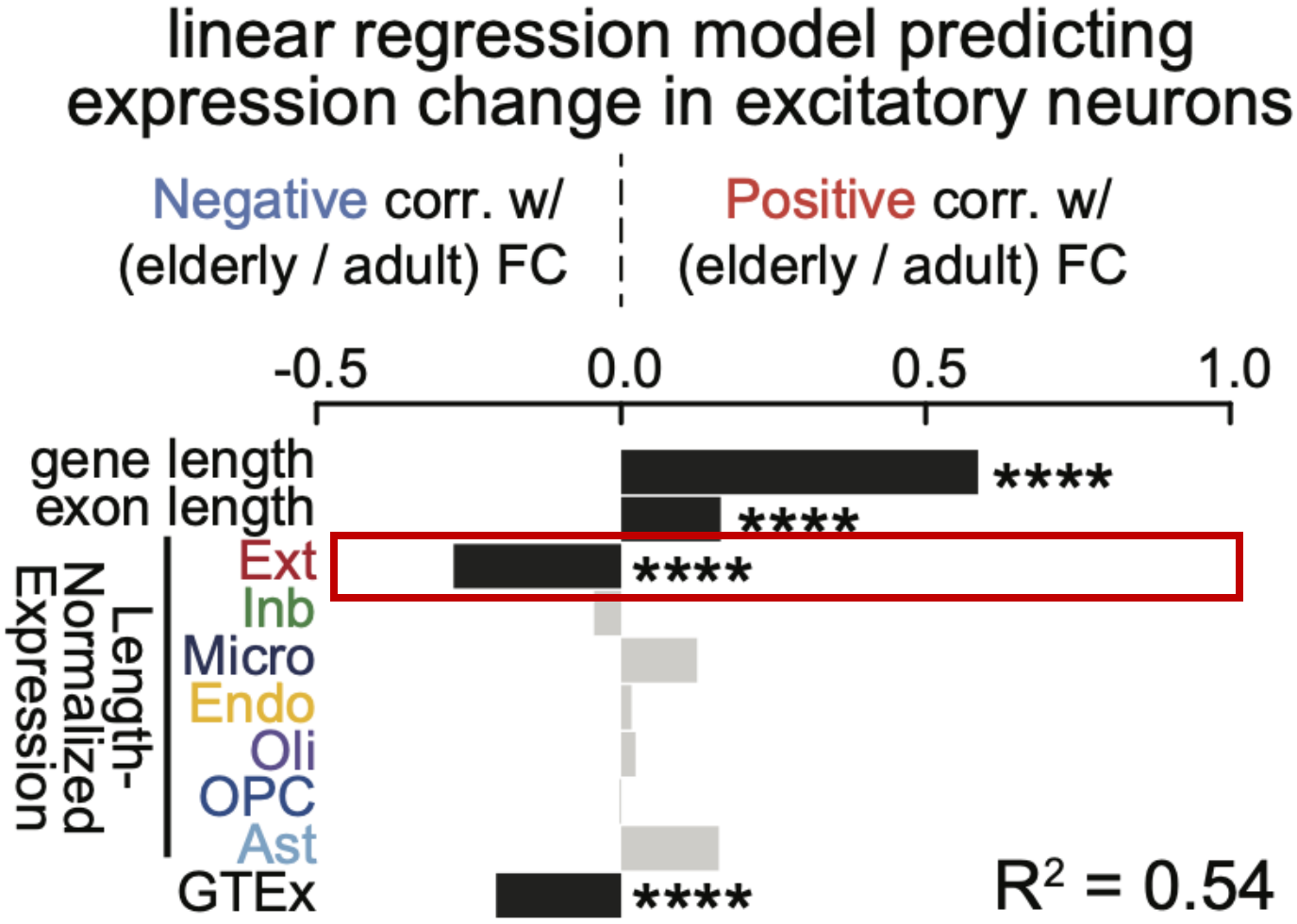

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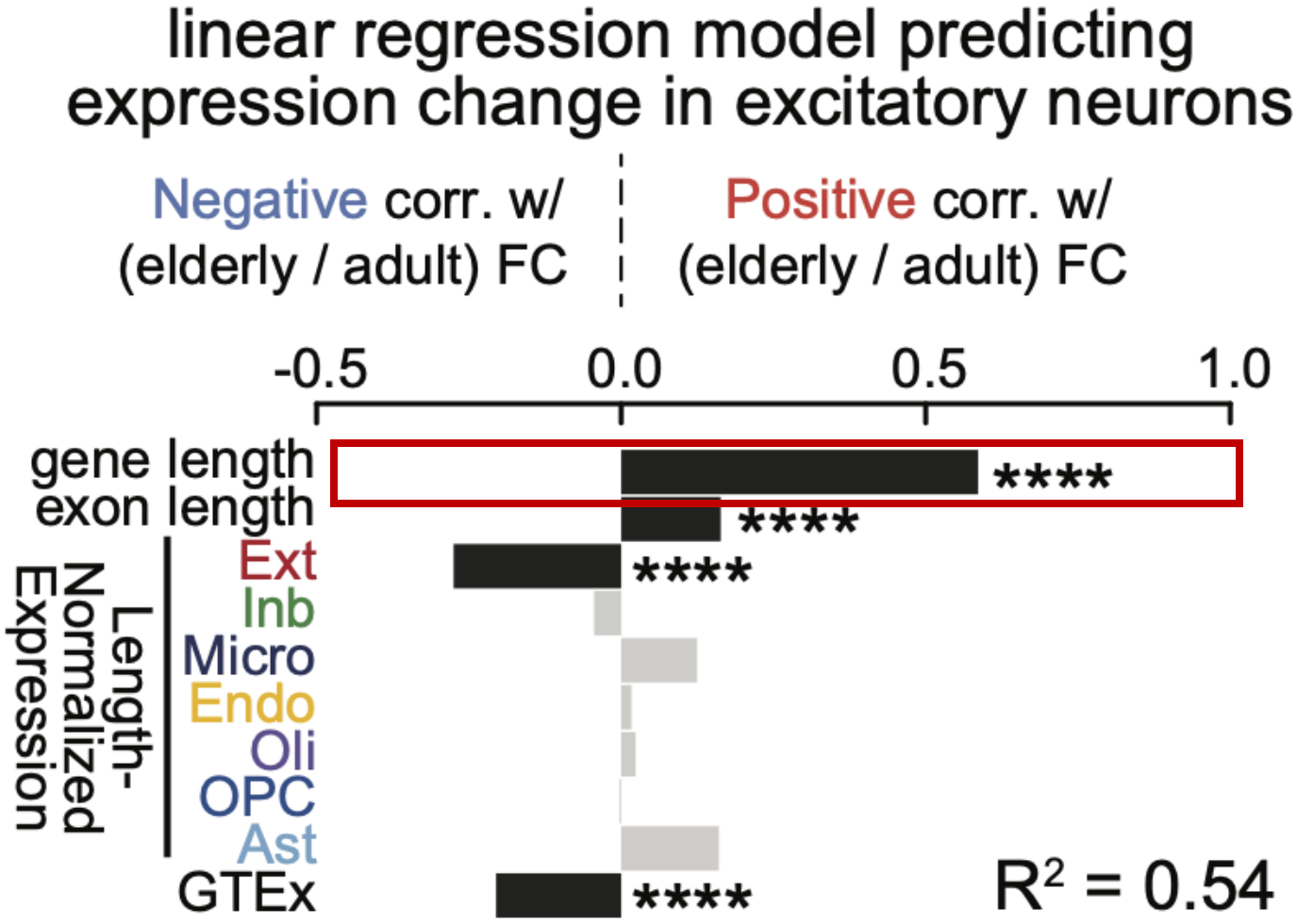

Housekeeping genes are short and active

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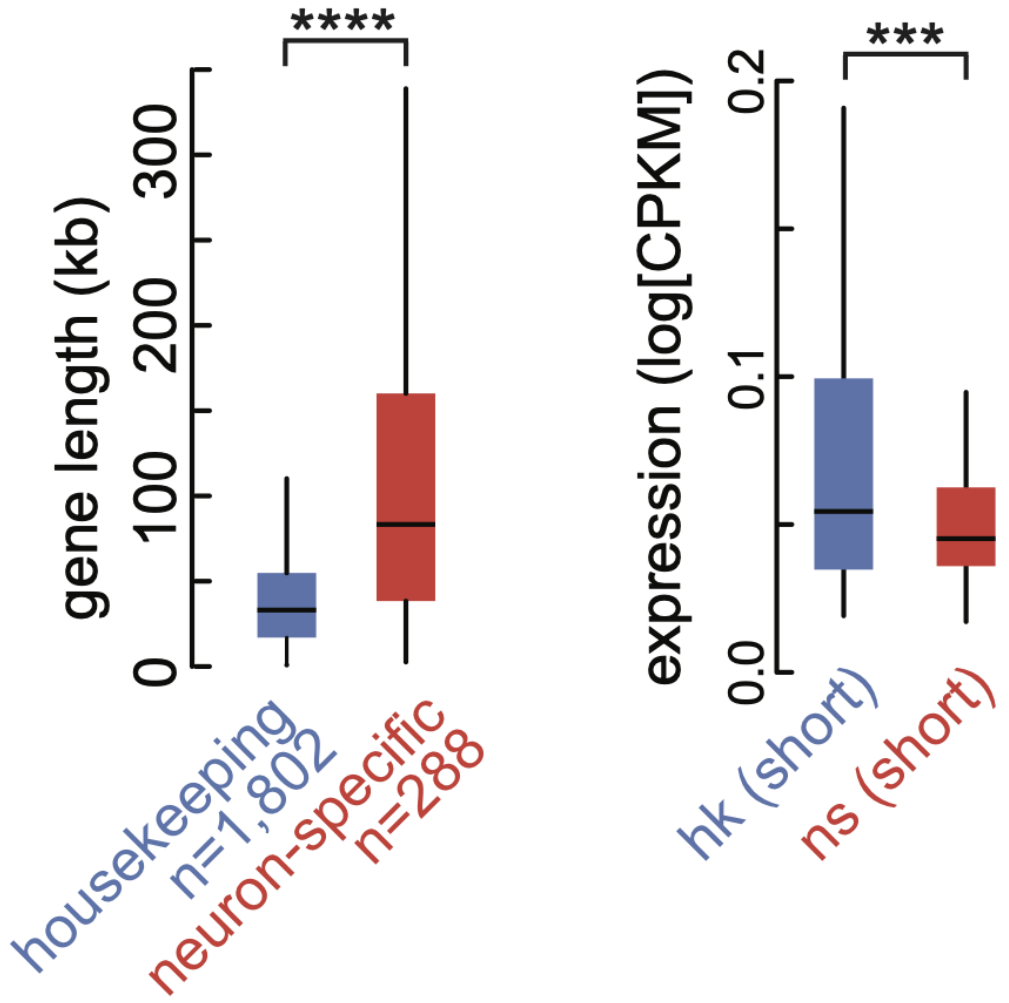

Shortest housekeeping genes down most

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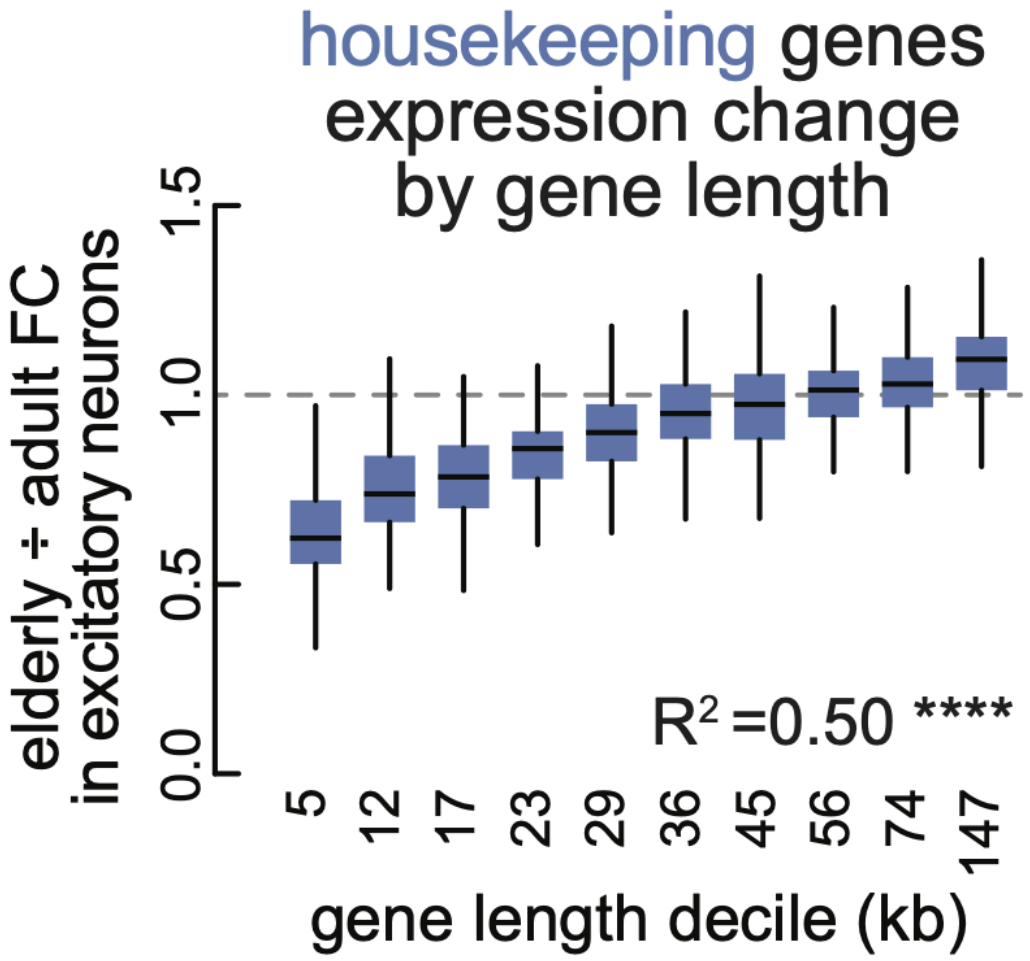

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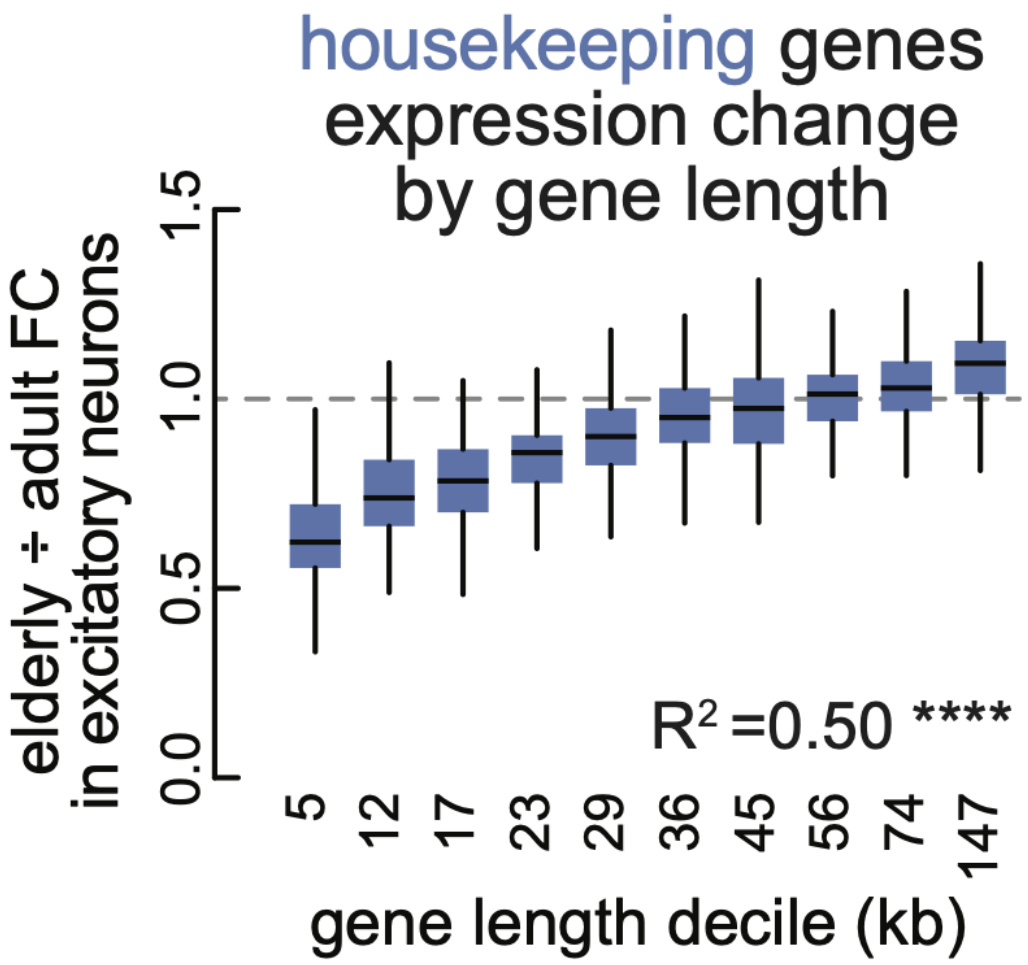

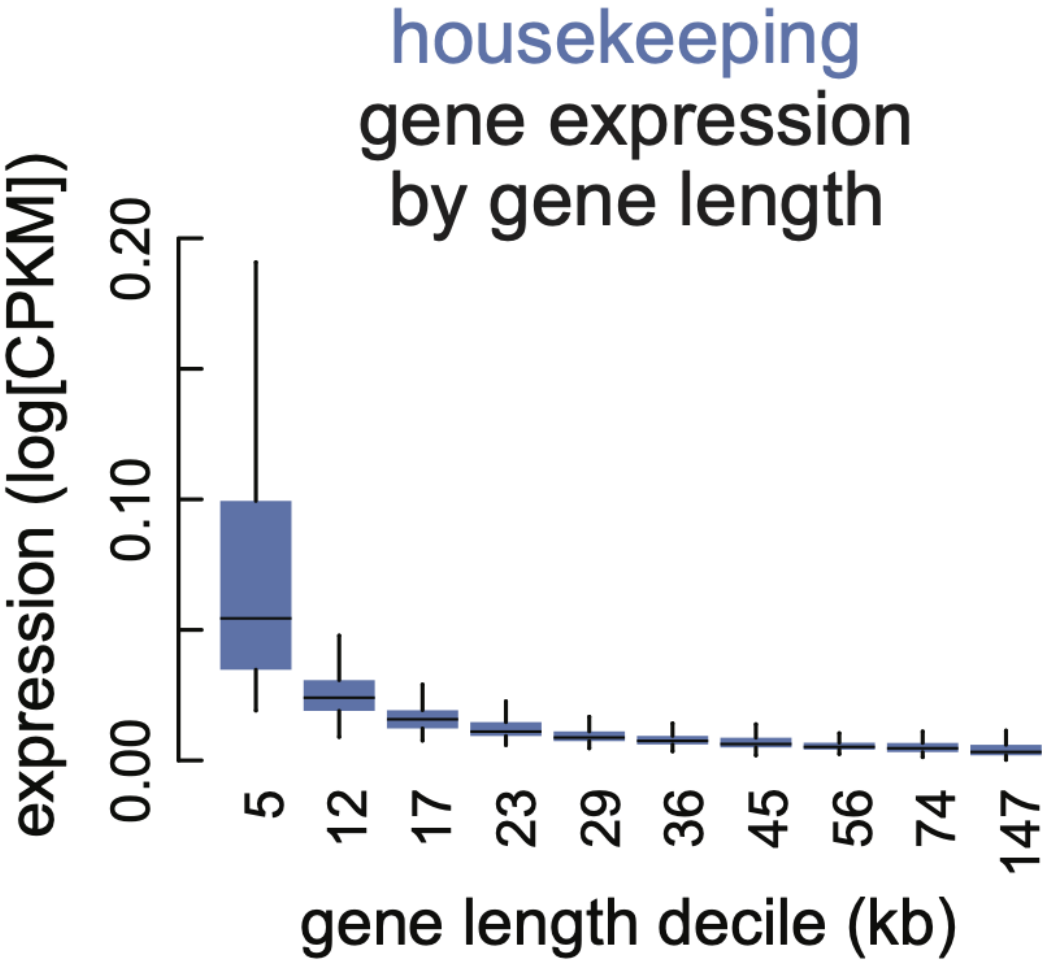

Short housekeeping genes bear more mutations

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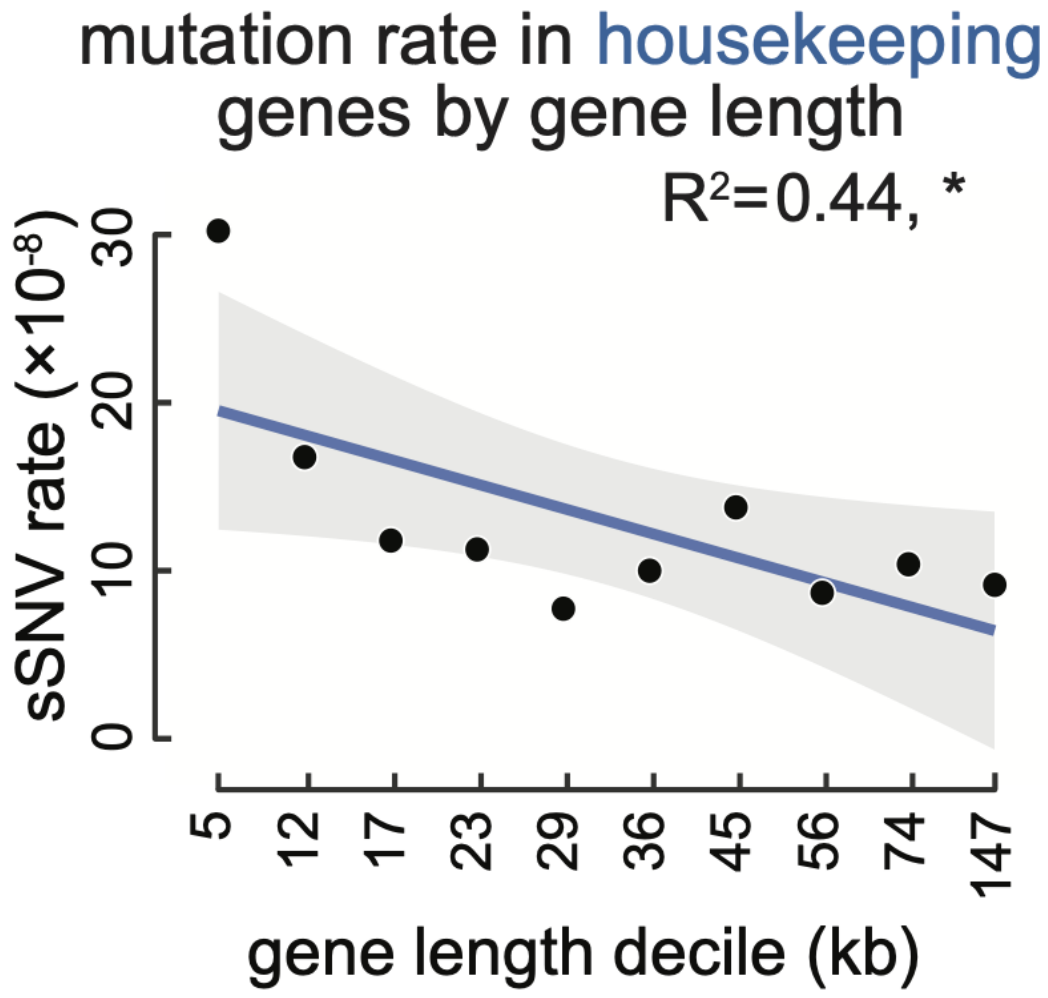

Proposed model

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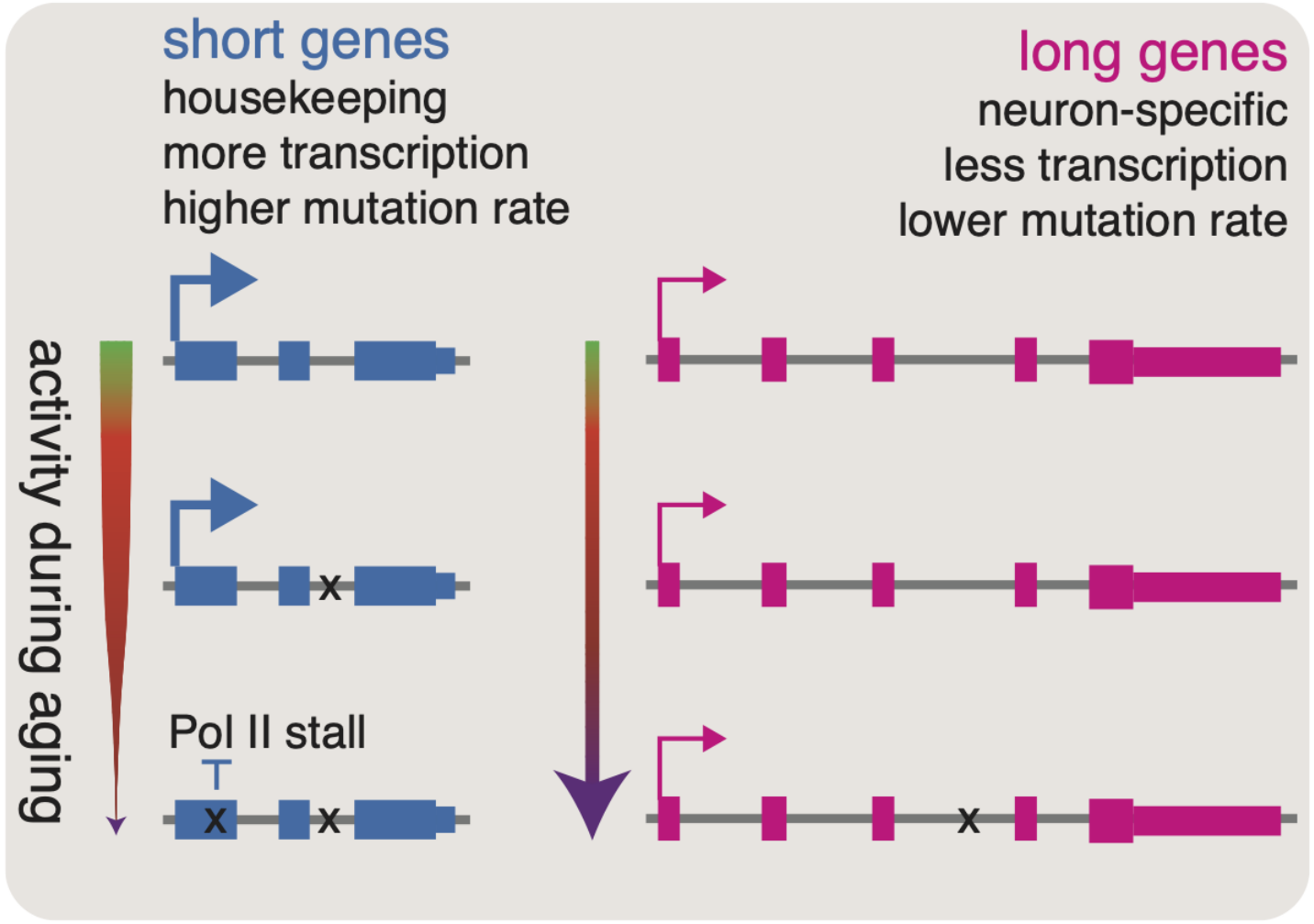
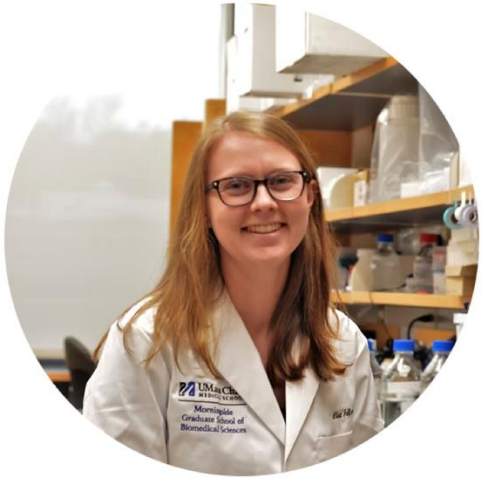


- Somatic SNVs accumulates in neurons with aging, faster in short and active genes.
- Short and highly active housekeeping genes are commonly downregulated in elderly human brain.
- **The more you use it, the more it wears out!**

Acknowledge



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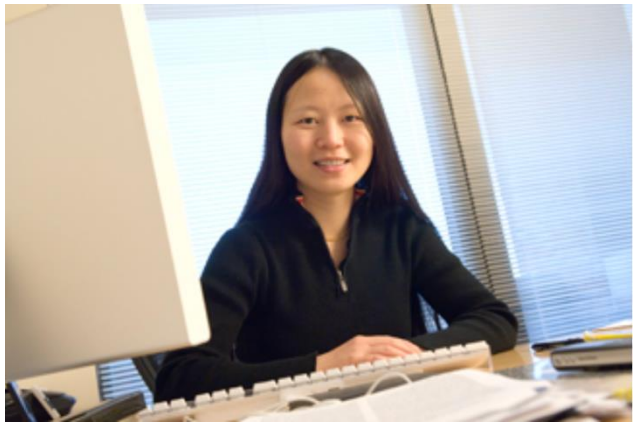

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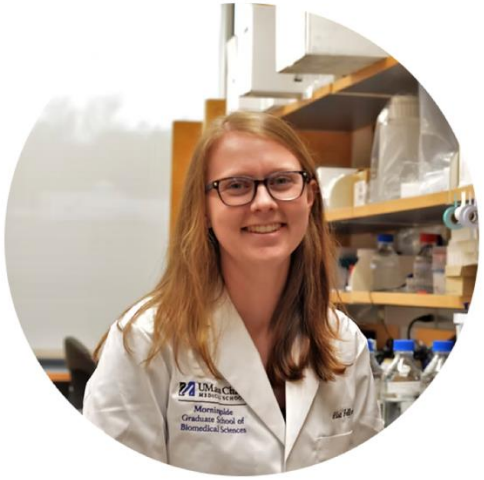

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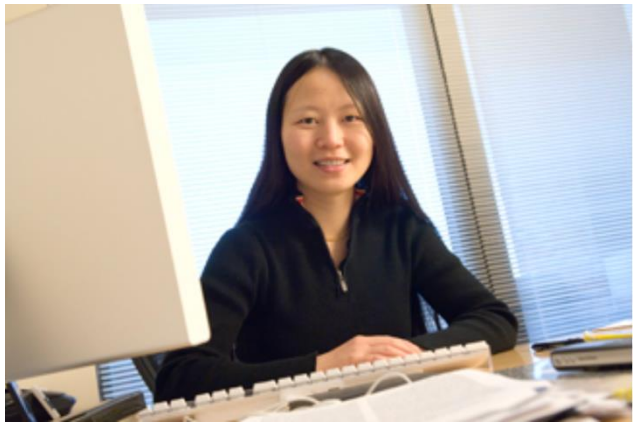

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