Single-cell transcriptomic and genomic changes in the ageing human brain

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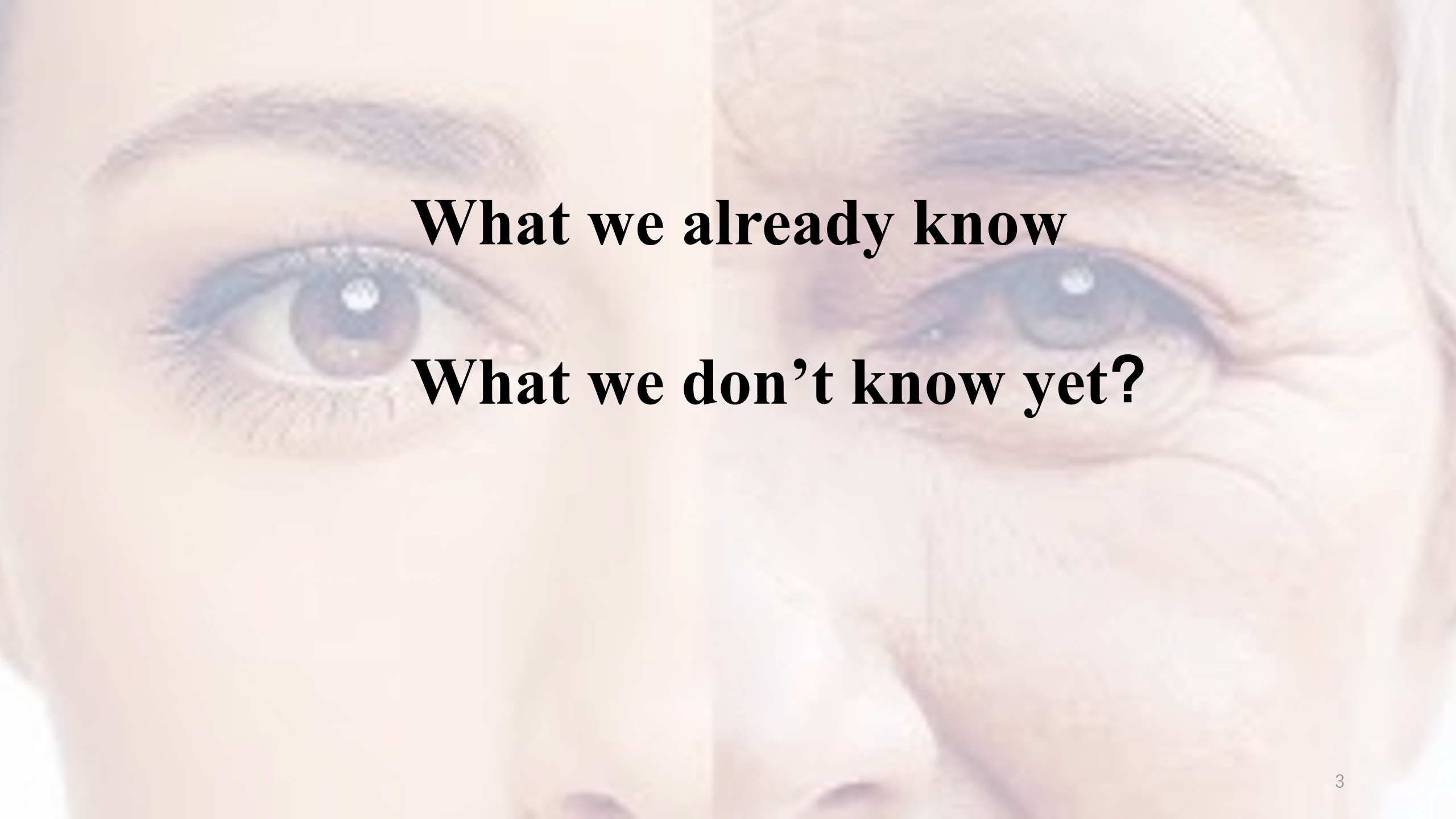
regulatory molecules and their interactions, such as regulatory proteins and their DNA/RNA target sites, small silencing RNAs and their RNA targets, and protein-protein interaction.

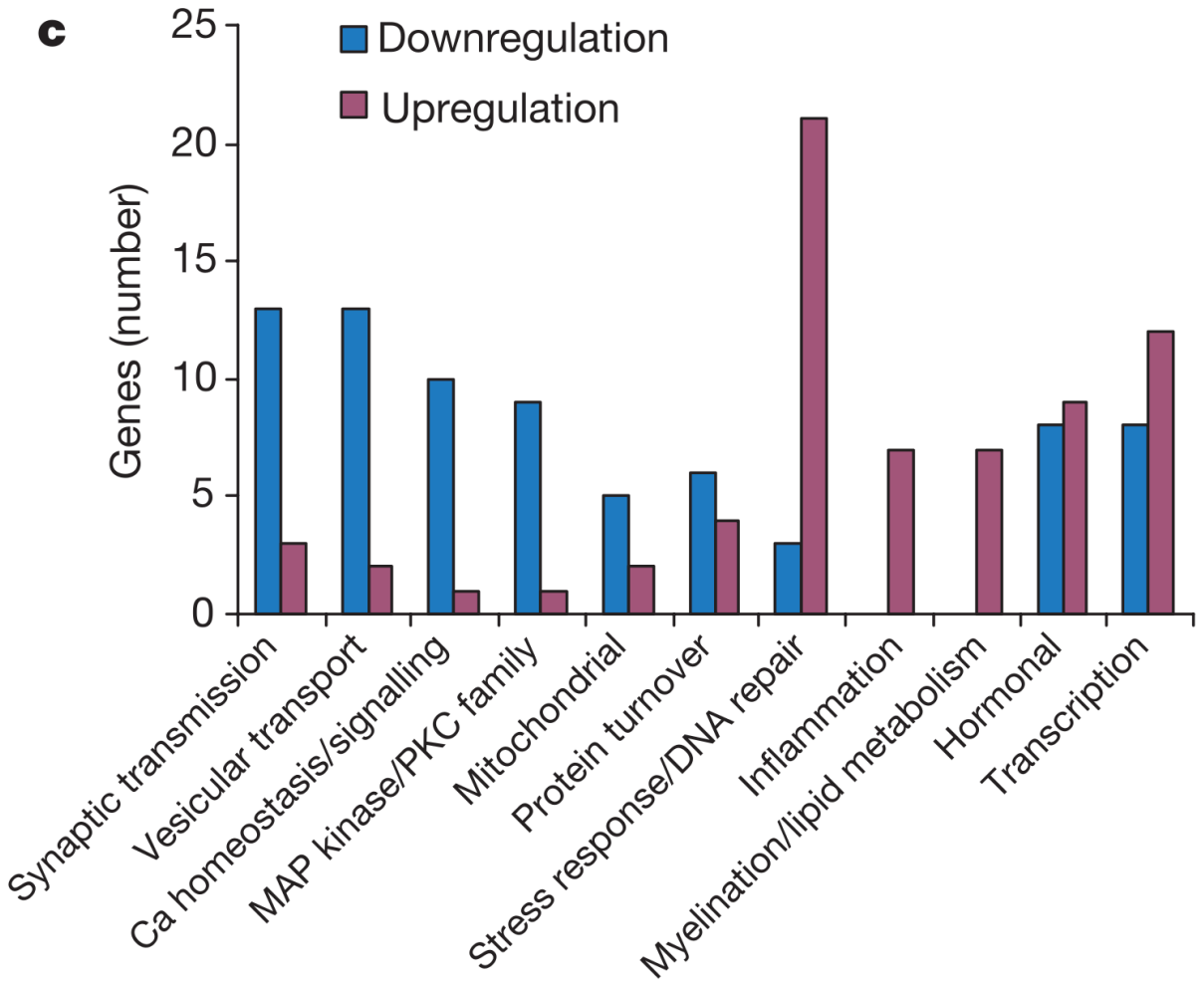
rates, causes, and consequences of somatic mutations in the human brain



What we already know

What we don’t know yet?

Background transcriptional changes

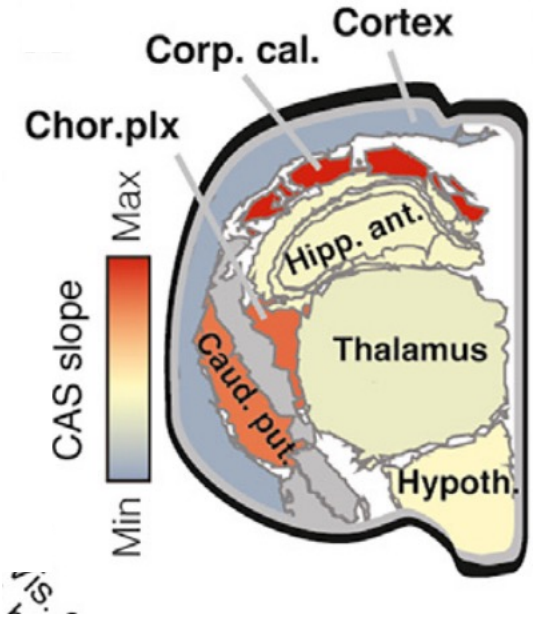


brain ageing affects many basic processes

2004_Nat_Tao Lu

Background

transcriptional changes



region-specific

Adult

Aged

cell-type specific

2023_Cell_Hahn, 2025_Nat_JinK

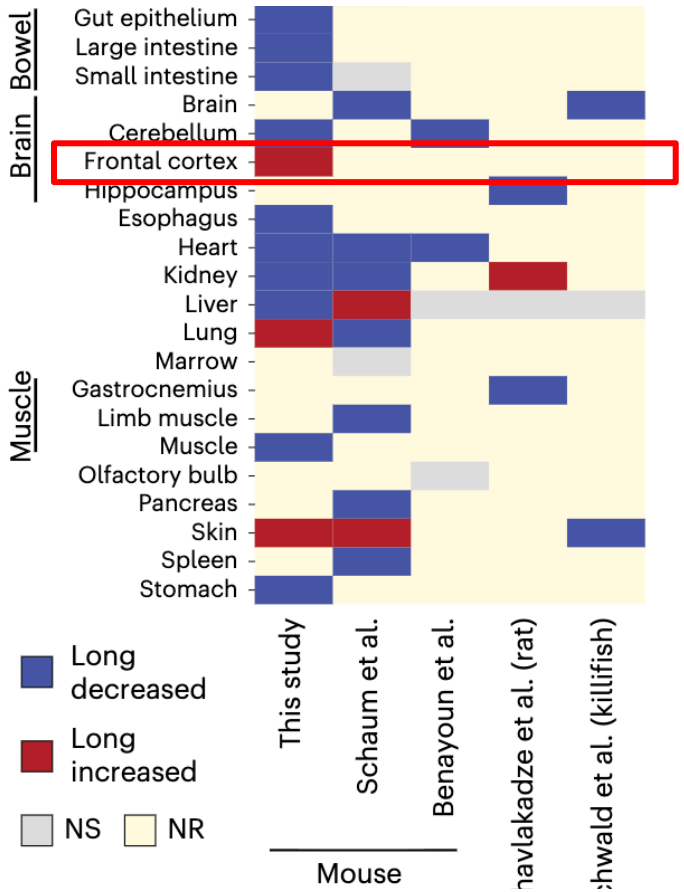
Background

While transcriptional changes during ageing are well documented,

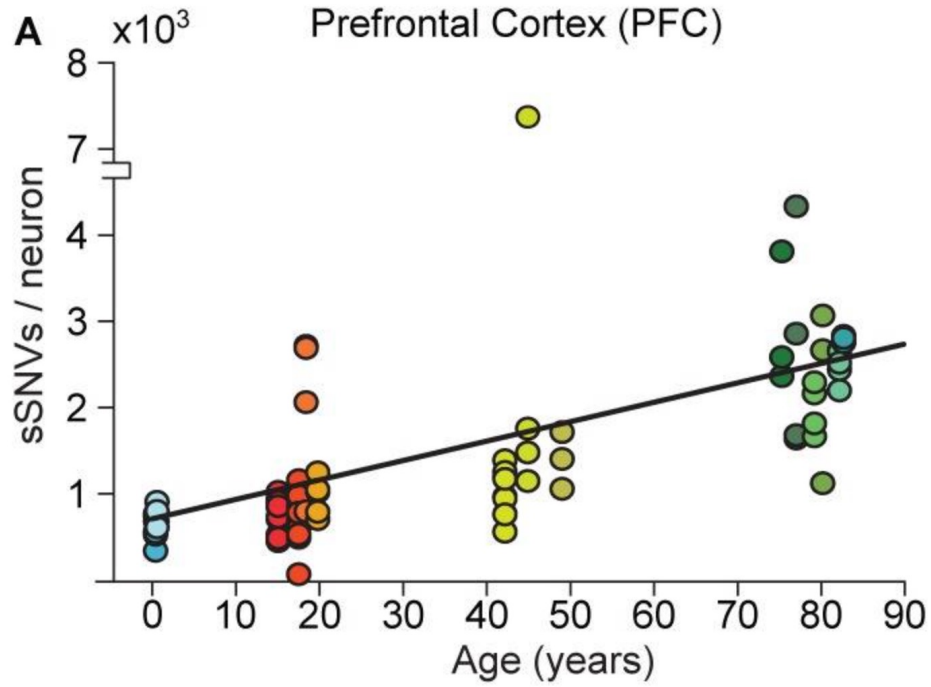
what happens at the genomic level underlying these changes
is much less understood.

Background

gene length



gene mutation



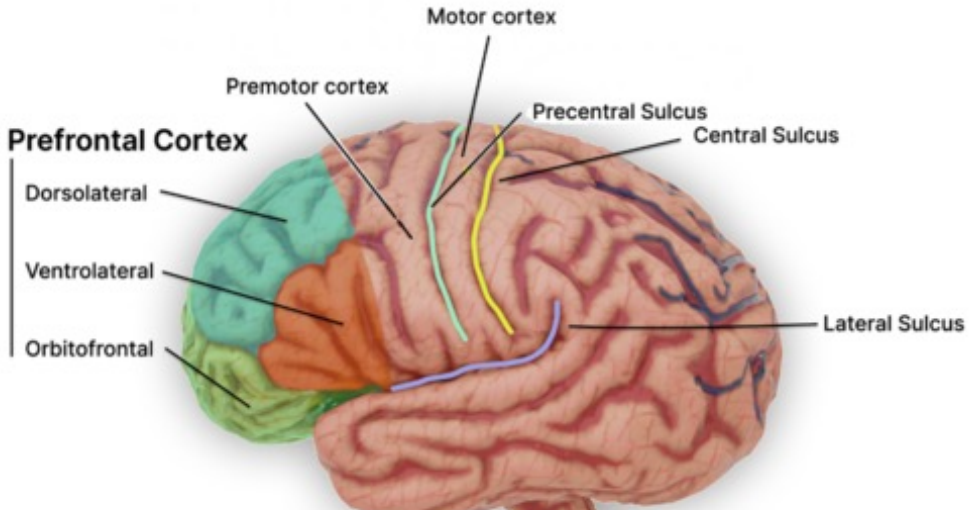
mouse frontal cortex:
long genes :upregulated ➡️
Neuron-specific genes : long
upregulated during ageing in the **human** brain?

neurons : post-mitotic cells
somatic mutations accumulate with age ➡️
how are these mutations related to
- gene length,
- gene expression?

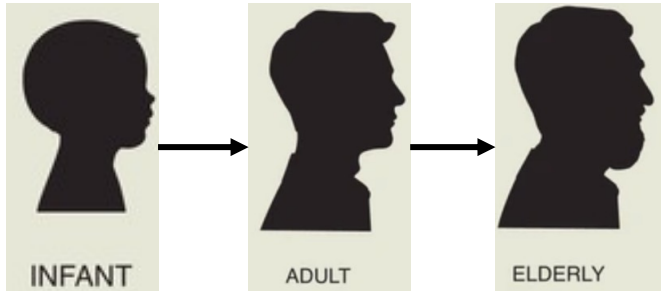
2018 Sci Lodato

Study design

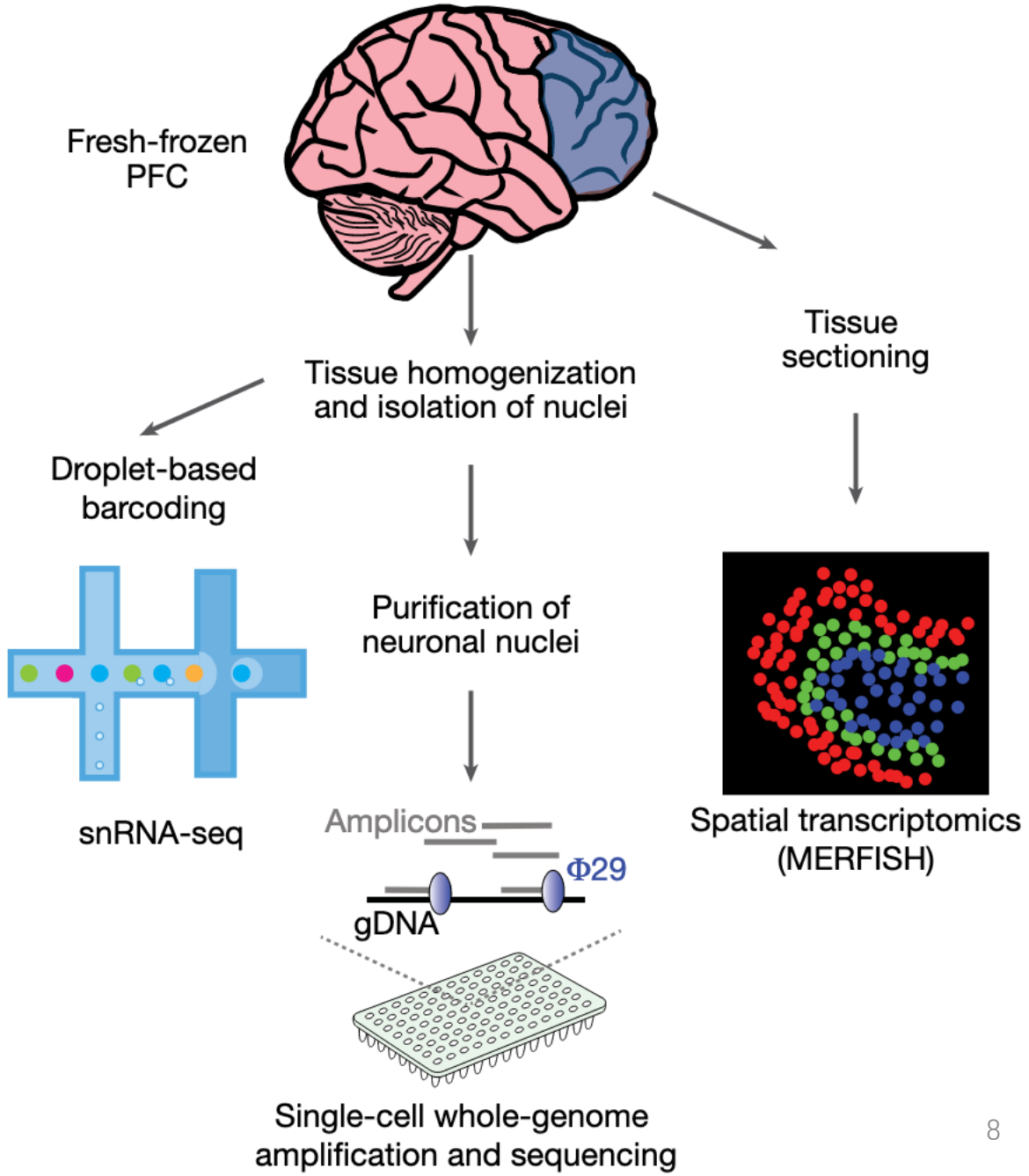
human prefrontal cortex (PFC)



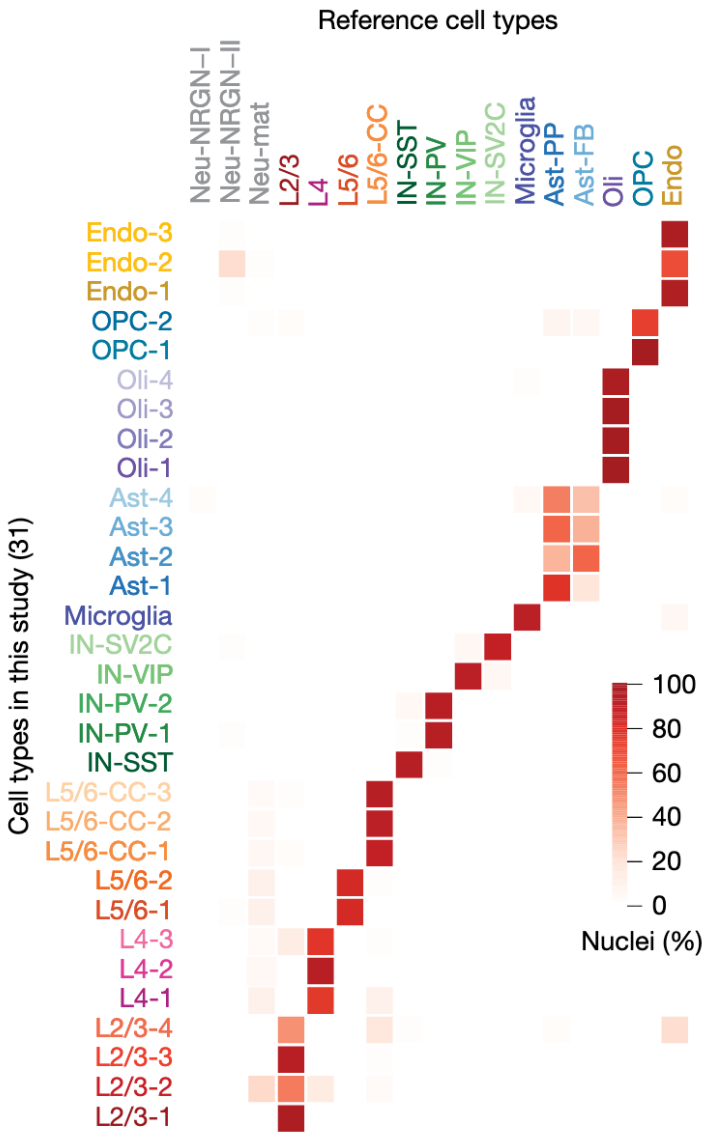
association cortex,
performs complex cognitive functions

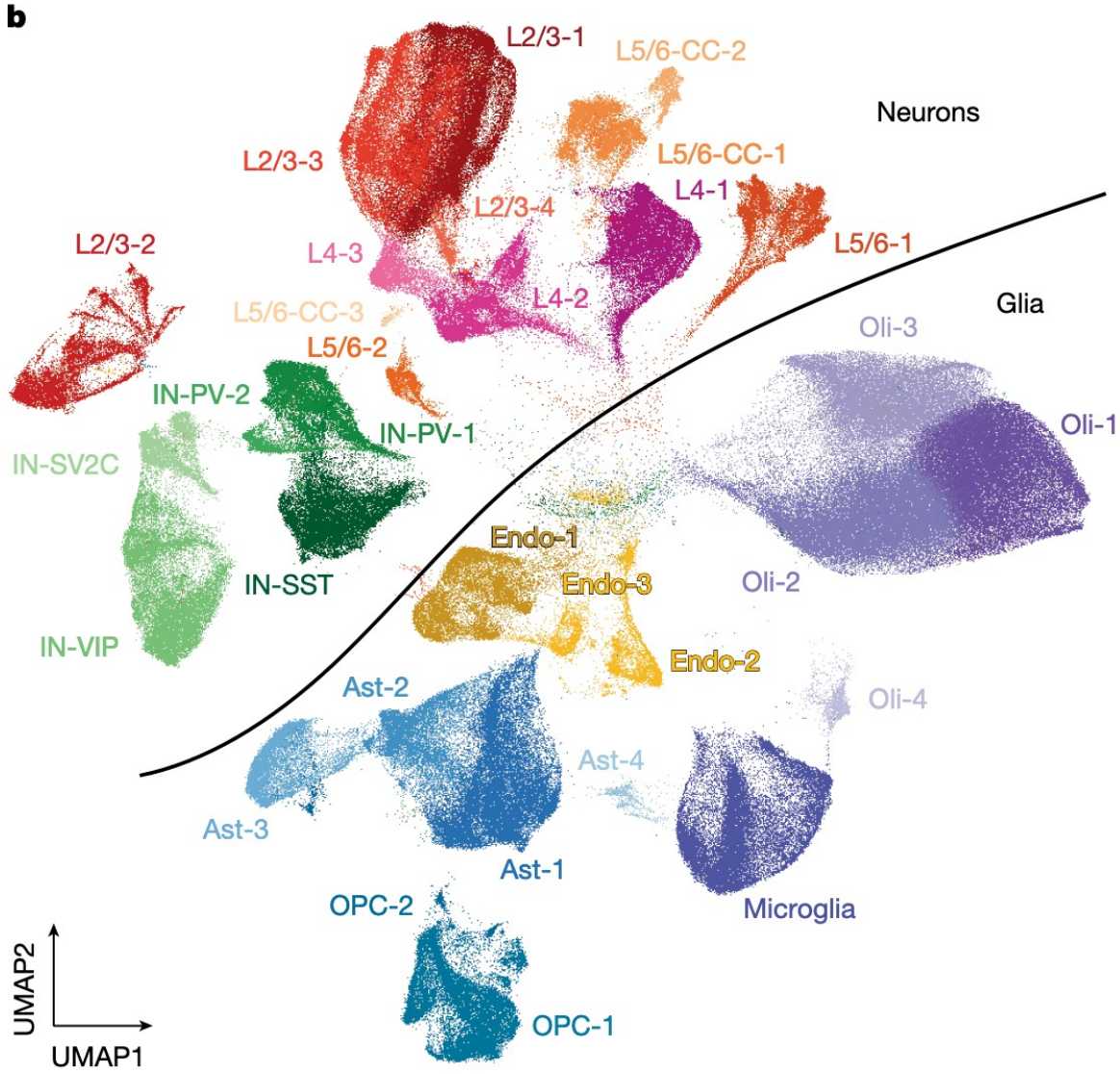


2 donors 10 donors 7 donors



1. Brain cell-type proportions during life





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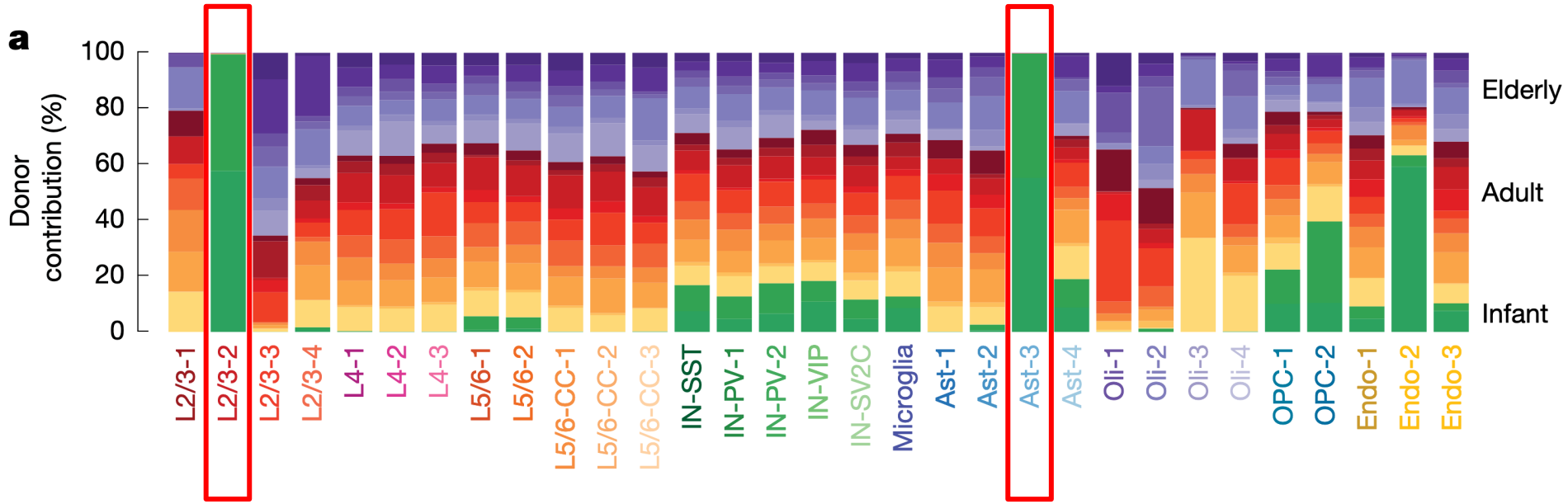

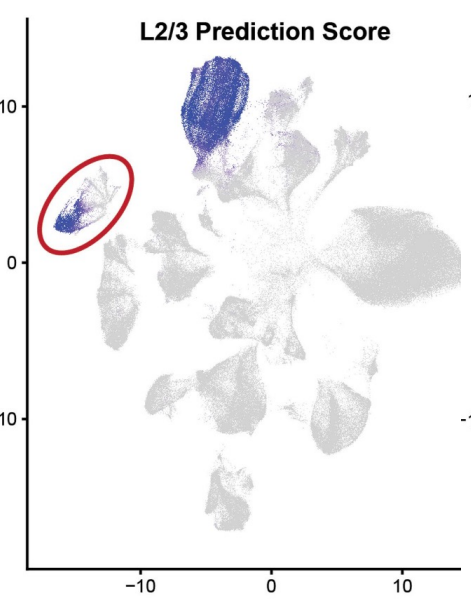

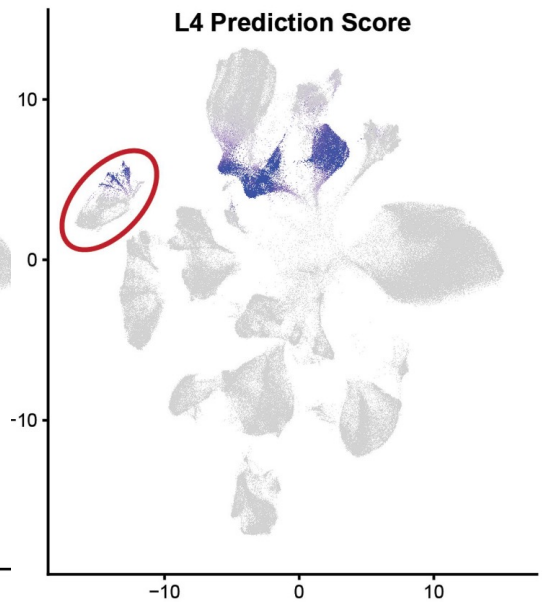

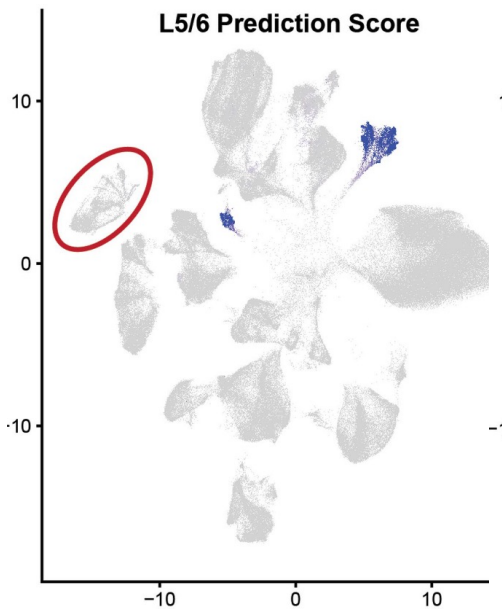

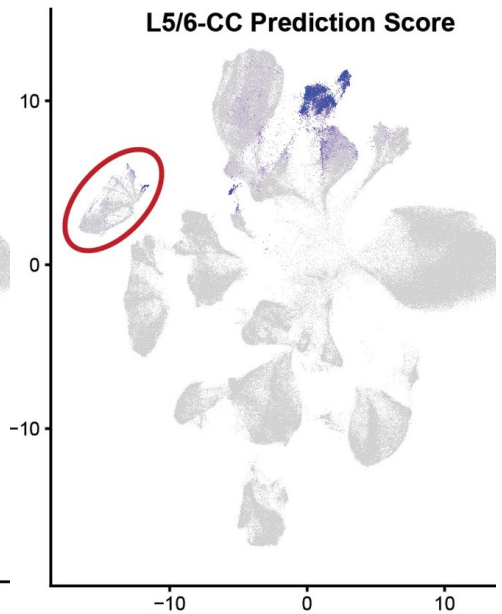

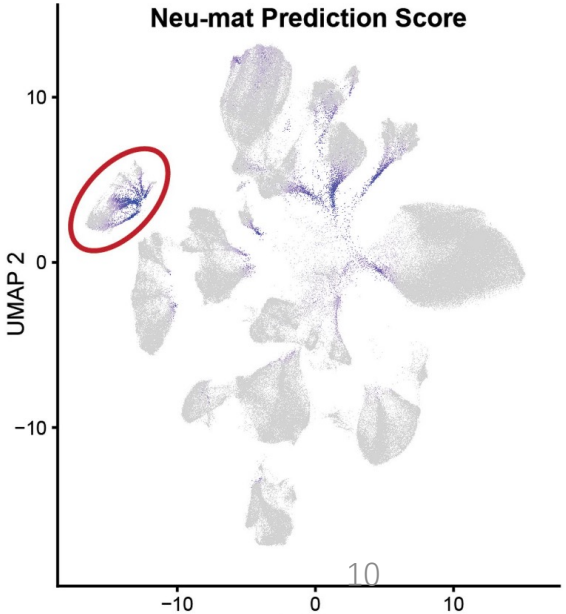

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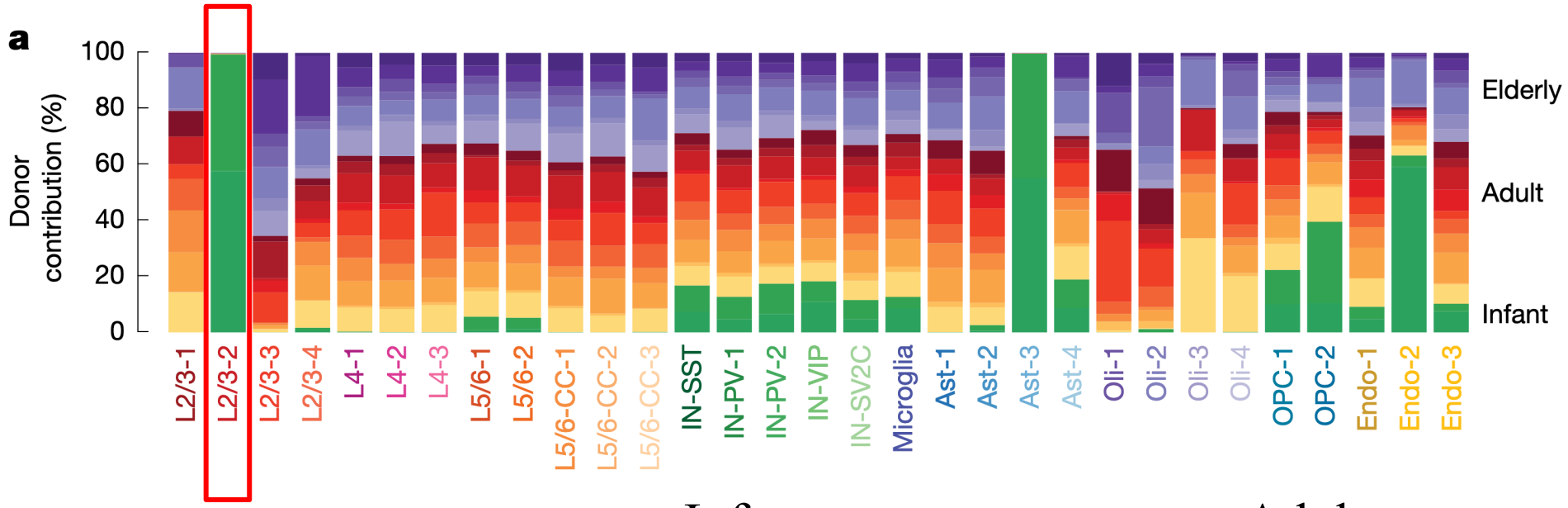
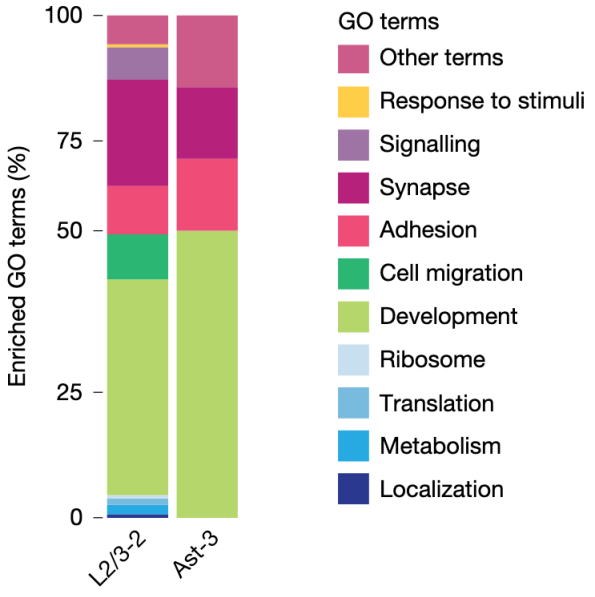
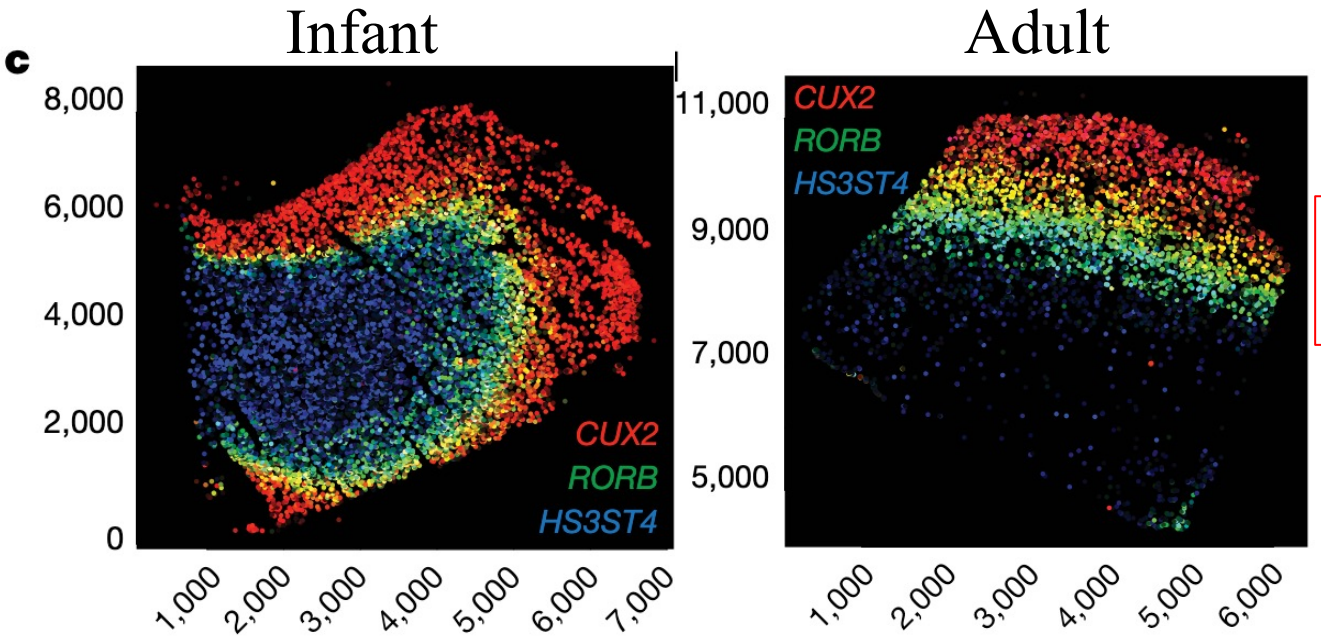
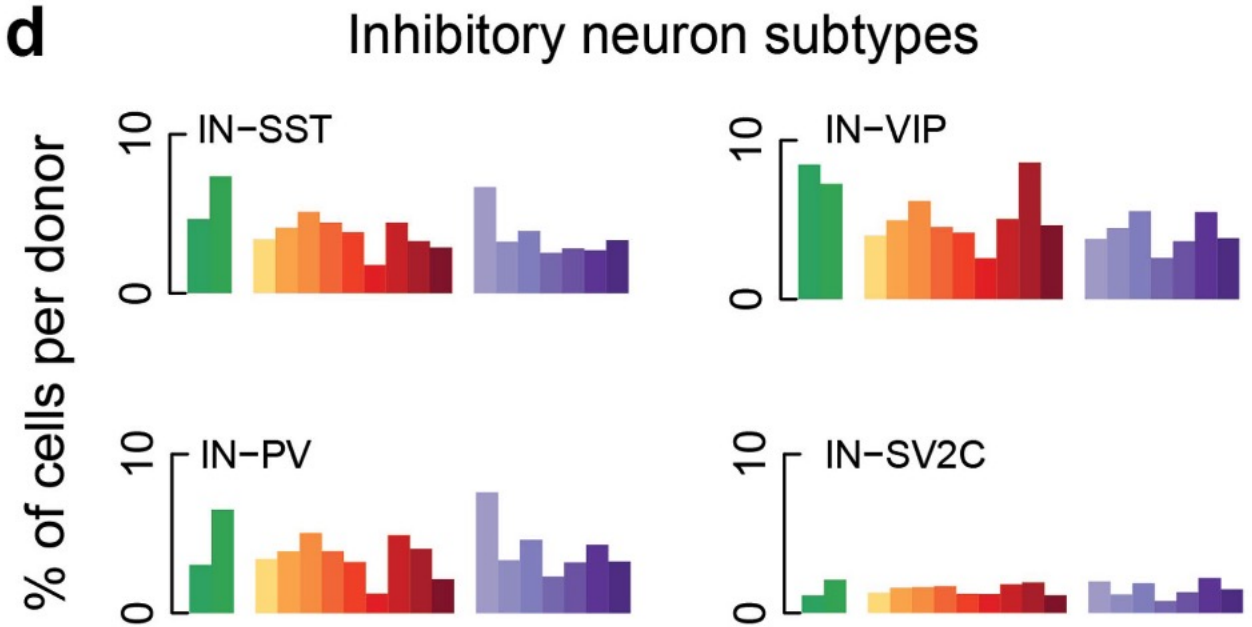






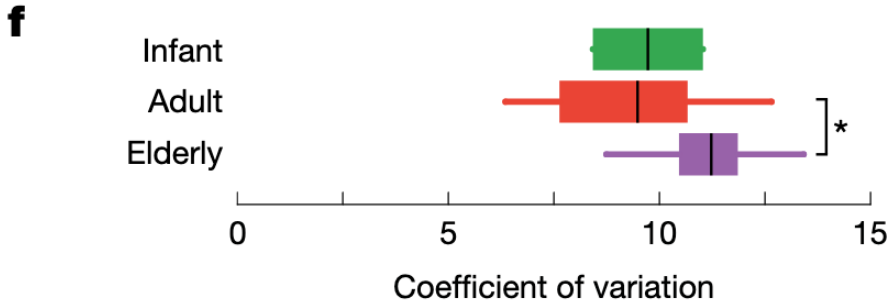
brain-cell development continues after birth

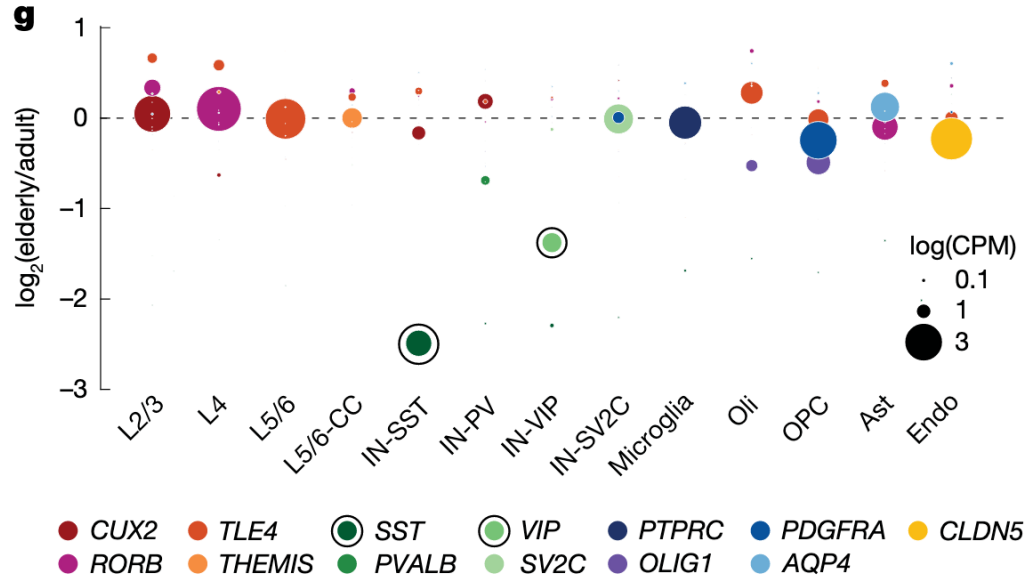
1. Brain cell-type proportions during life



no decrease in IN-SST and IN-VIP inhibitory neurons

Inh SST

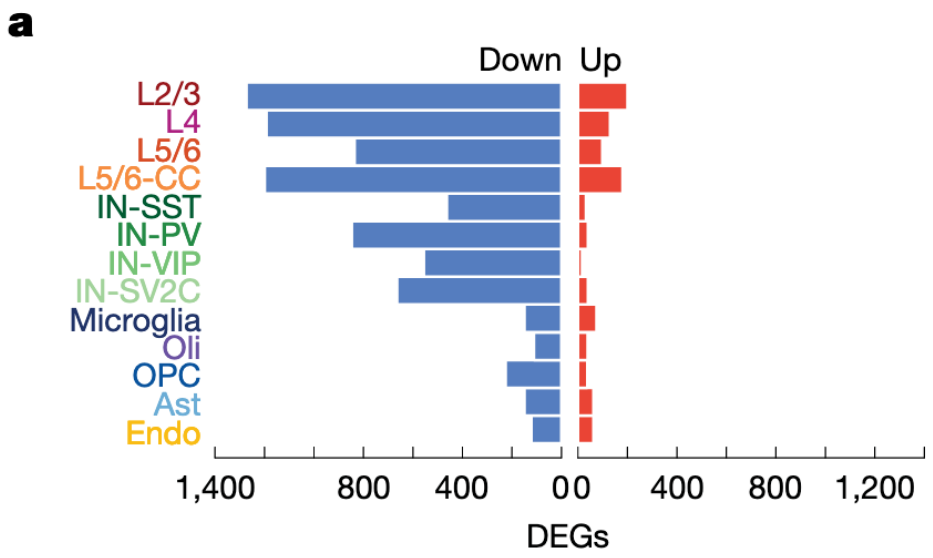


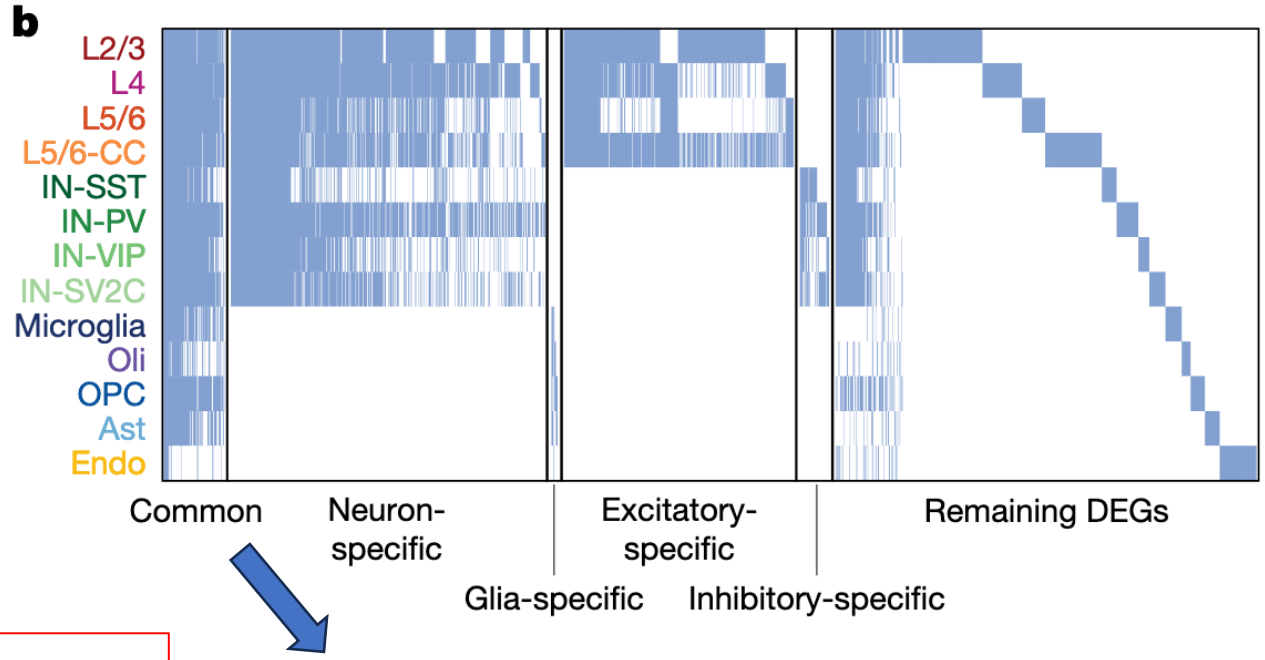


transcriptional variability ⬆️
marker expression of SST and VIP ⬇️

inhibitory signaling may be impaired

2. Housekeeping genes decrease in ageing



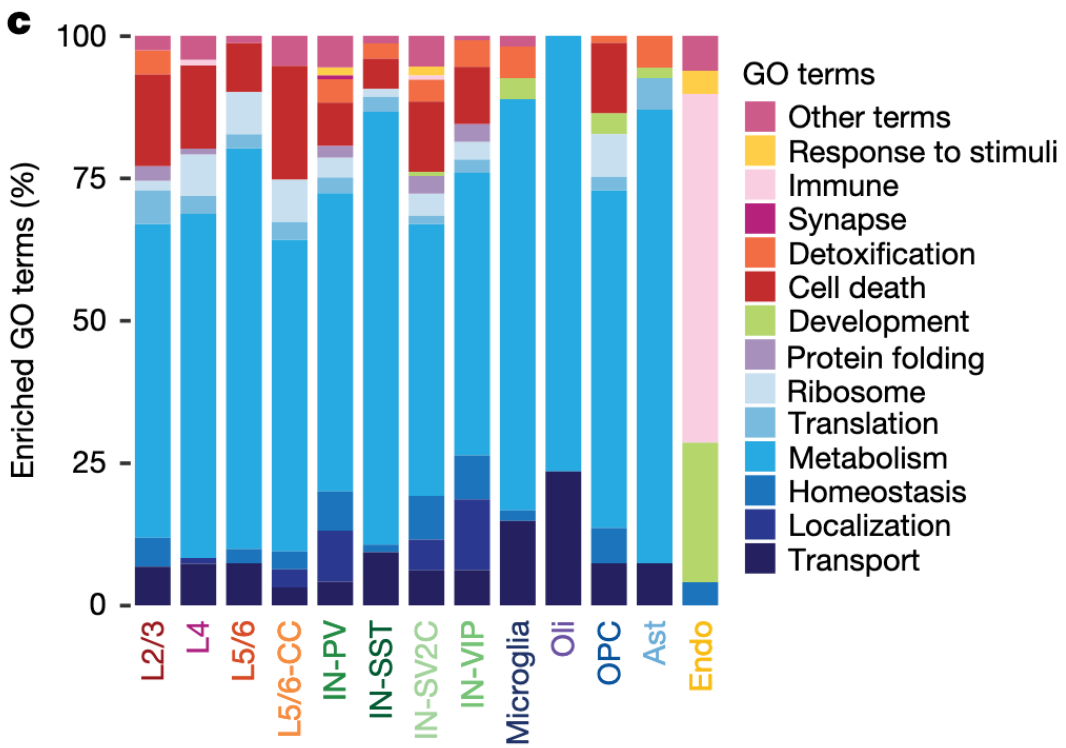


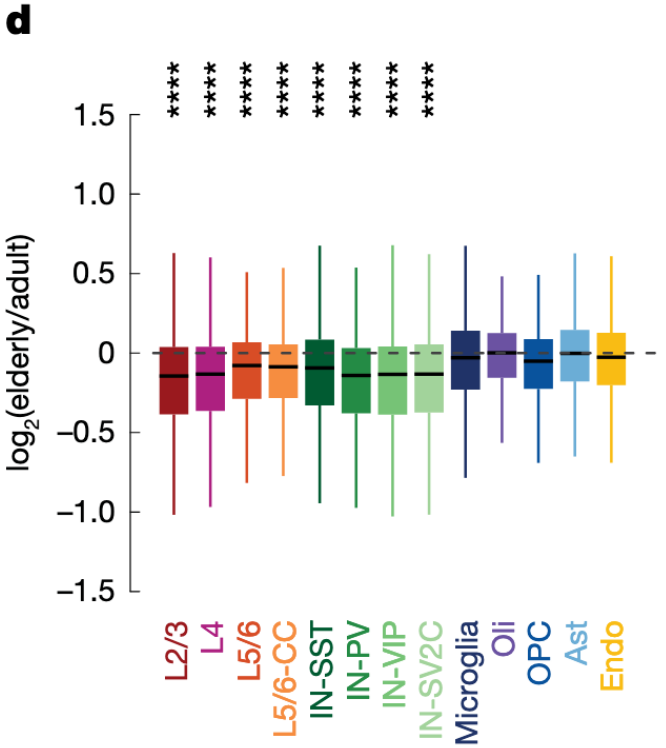
downregulated genes > upregulated genes

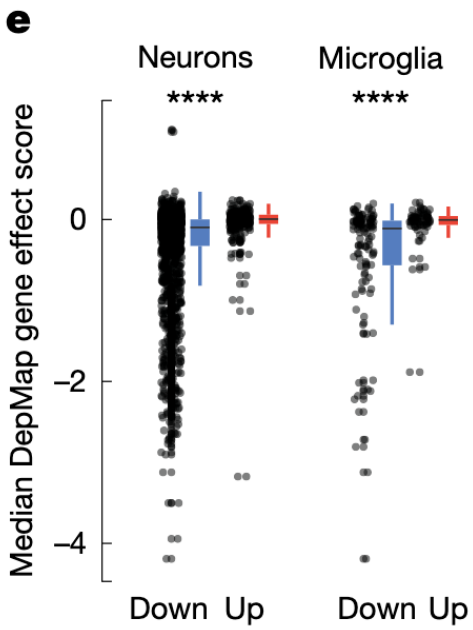
most downregulated genes are found in neurons

124 genes are commonly downregulated across multiple cell types

2. Housekeeping genes decrease in ageing





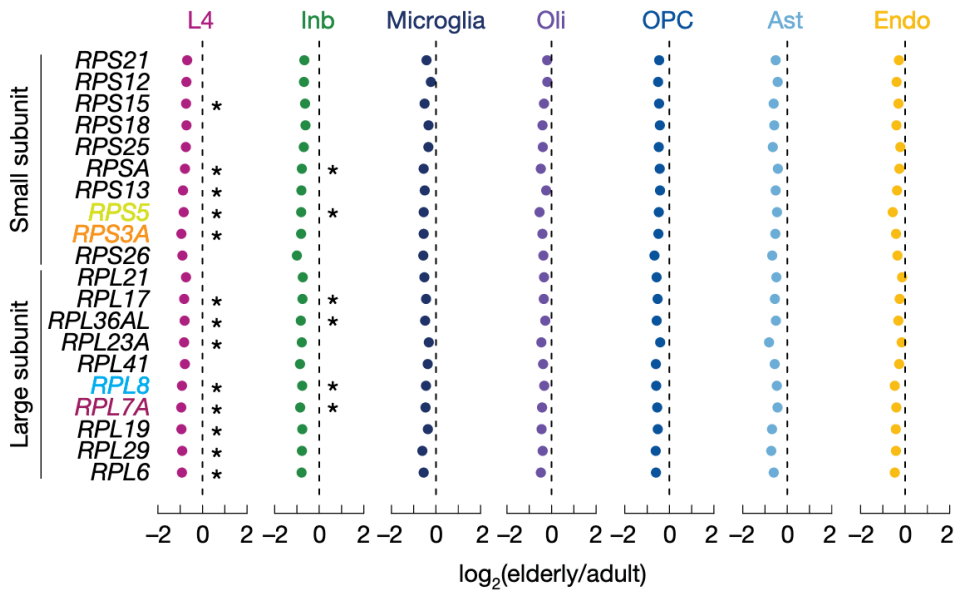


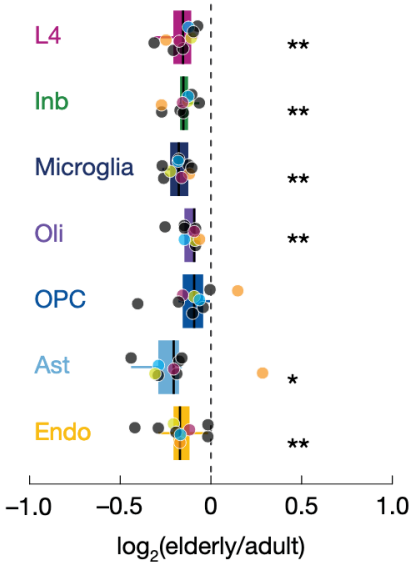
downregulated genes ⇄ housekeeping gene

DepMap: downregulated genes more essential for cell survival

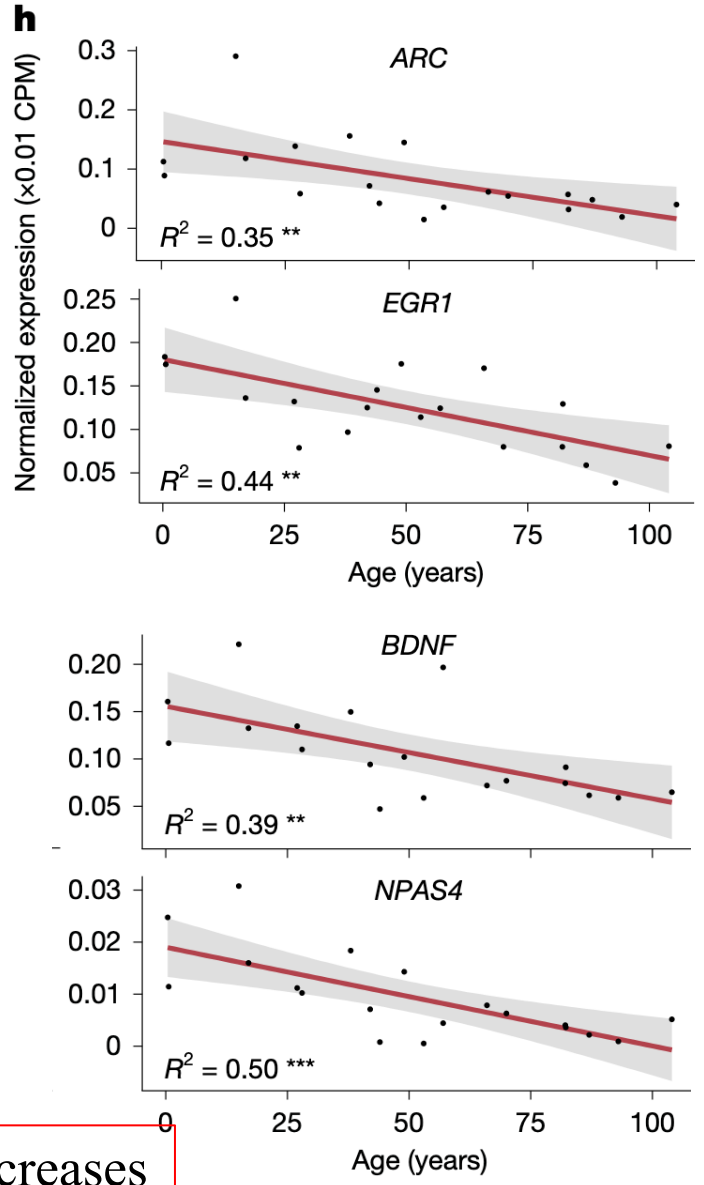
2. Housekeeping genes decrease in ageing

ribosomal genes





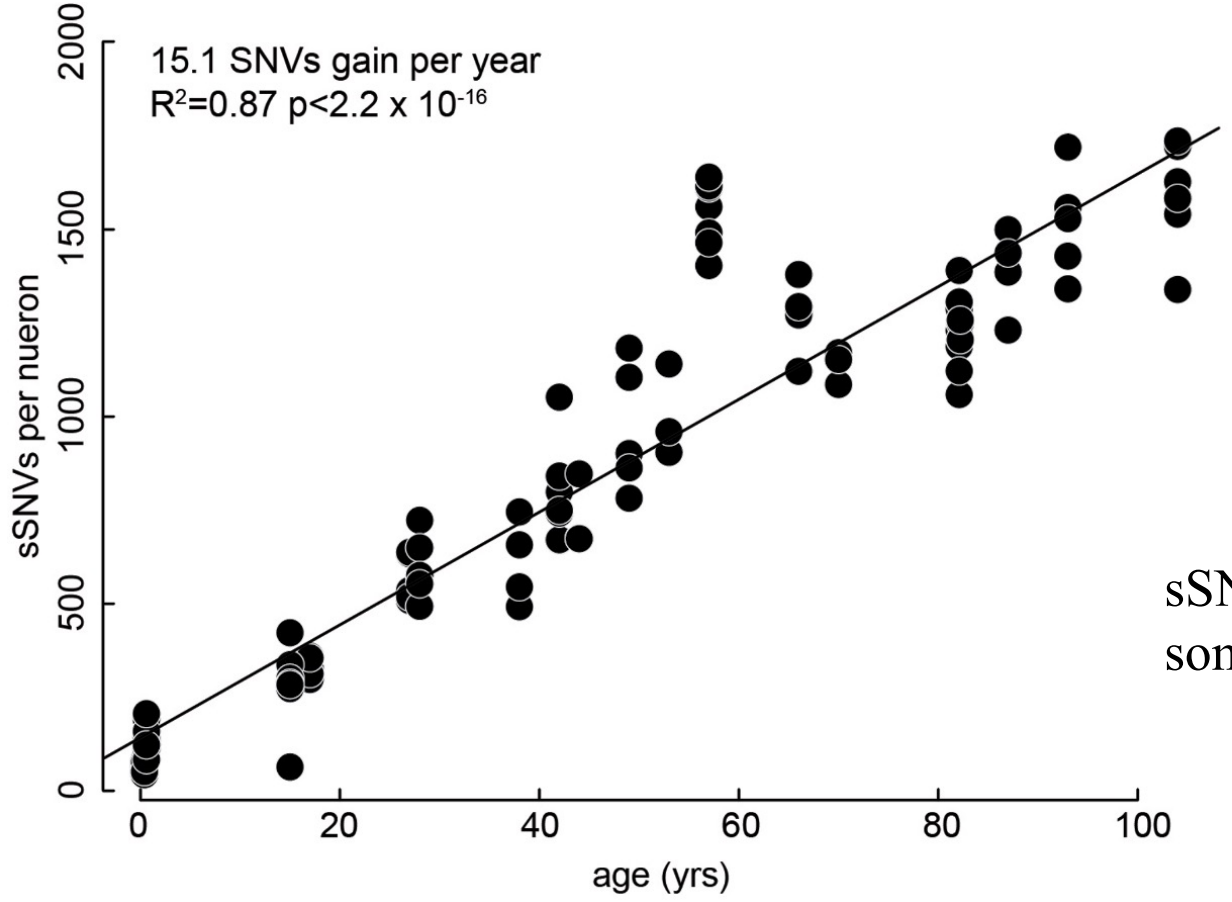
immediate early genes.



neuronal metabolic activity decreases

3. Mutation patterns reflect transcription

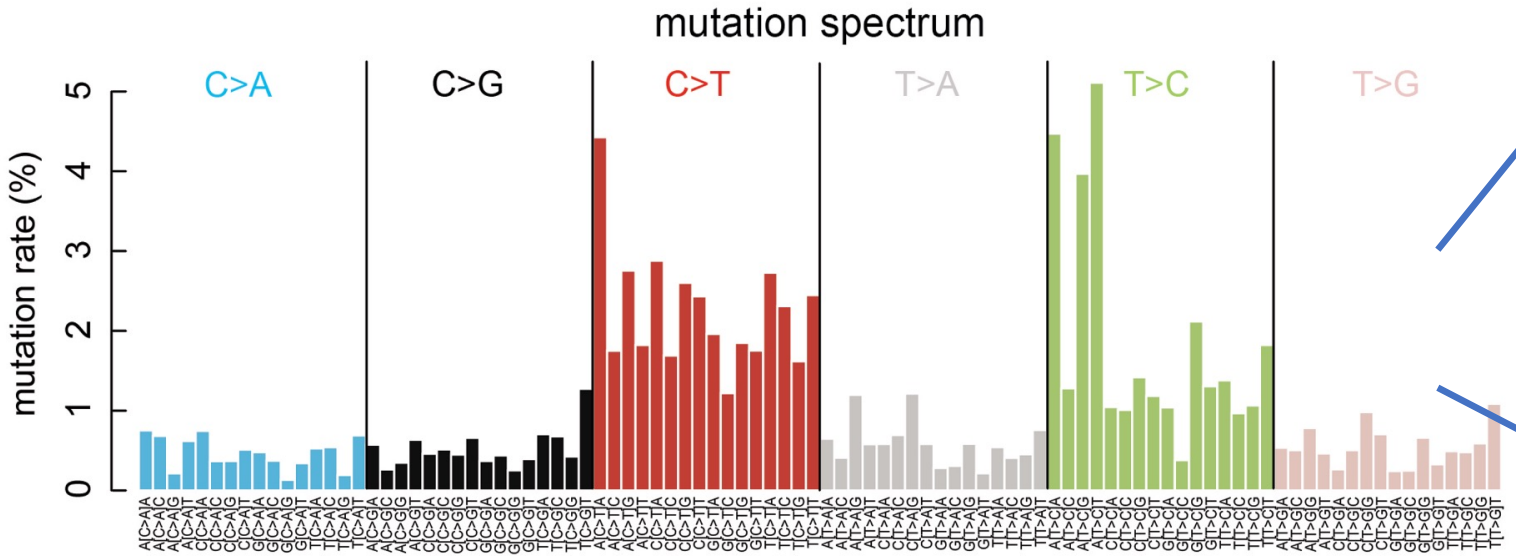
whether these gene expression changes are related to somatic mutations?



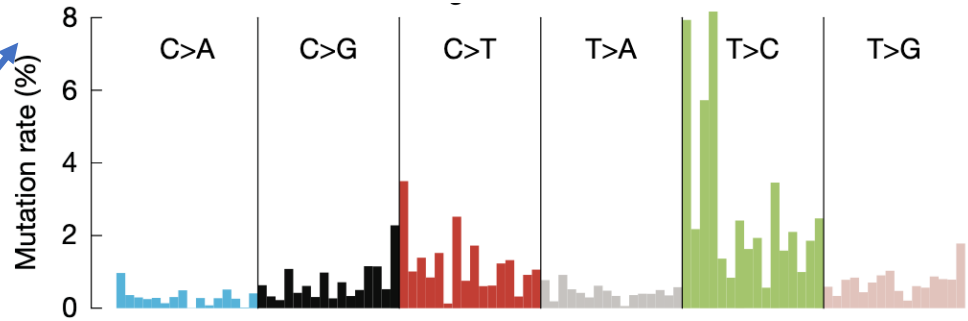
sSNVs：
somatic single-nucleotide variants

neuronal somatic SNVs accumulate with age

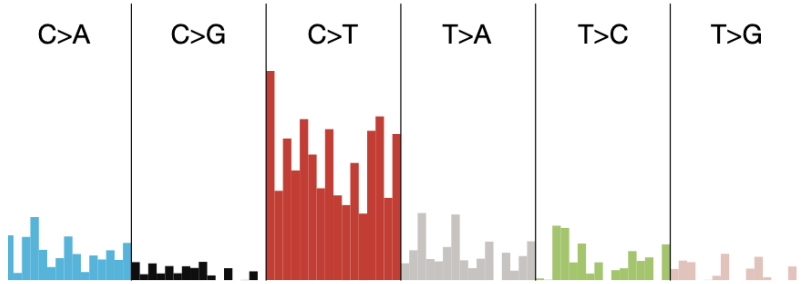
3. Mutation patterns reflect transcription

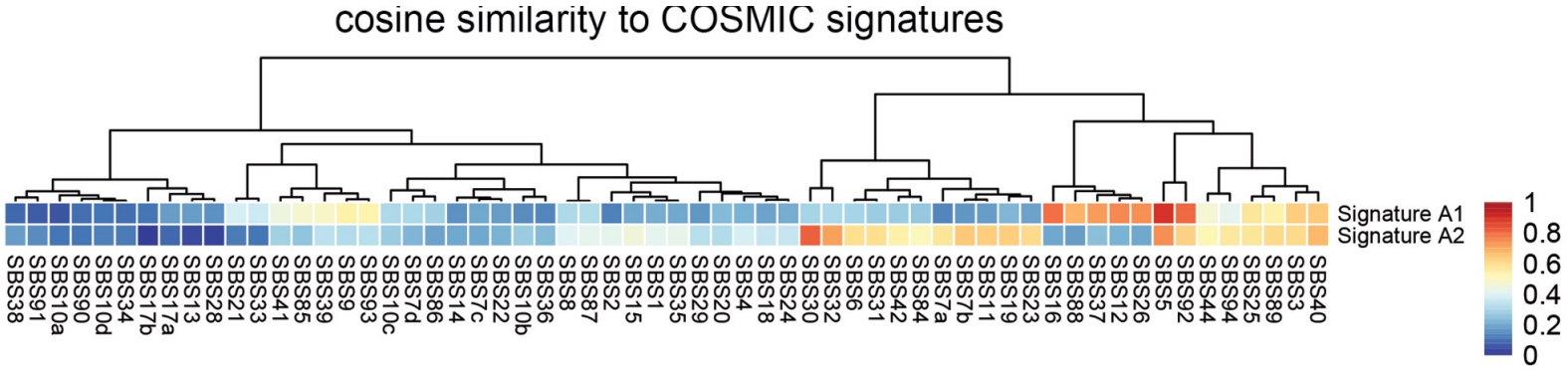


Signature A1 ~ SBS5



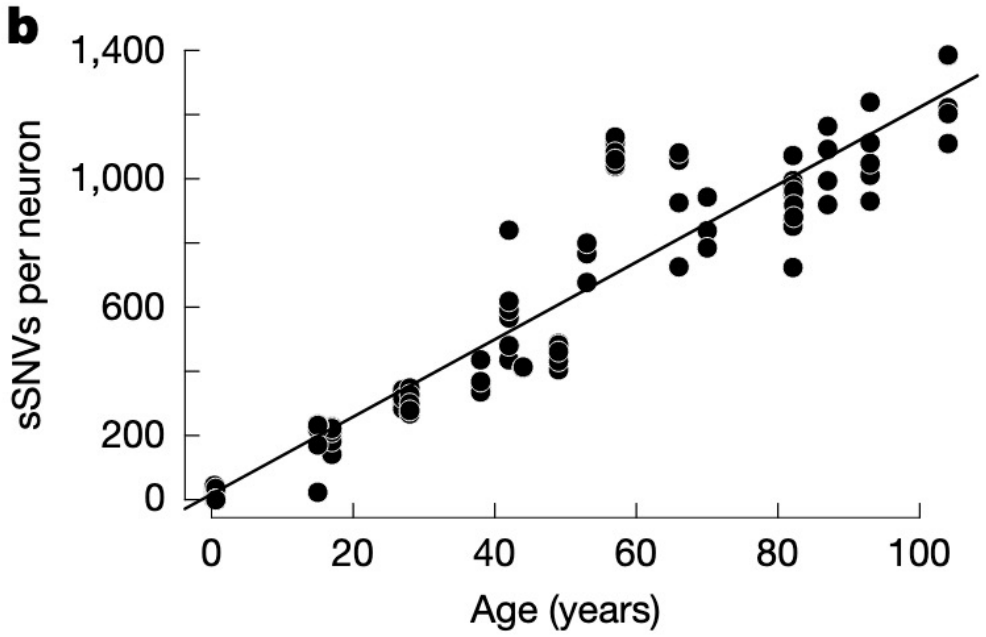
Signature A2 ~ SBS30



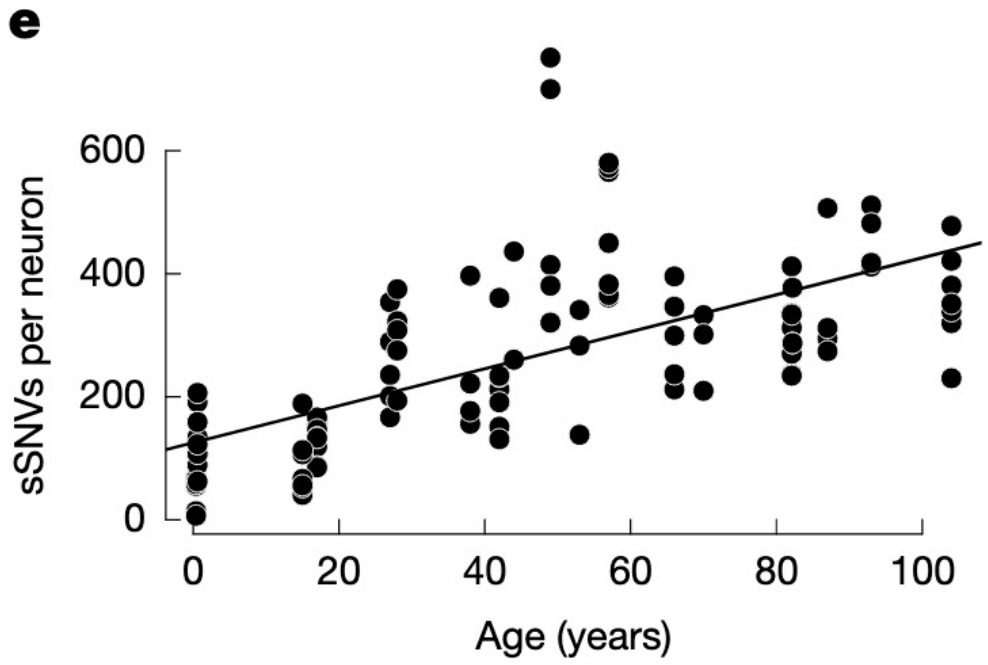


3. Mutation patterns reflect transcription

Signature A1



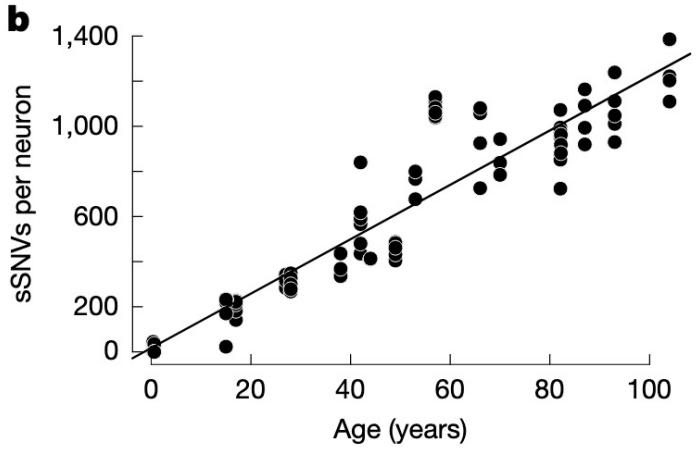
Signature A2



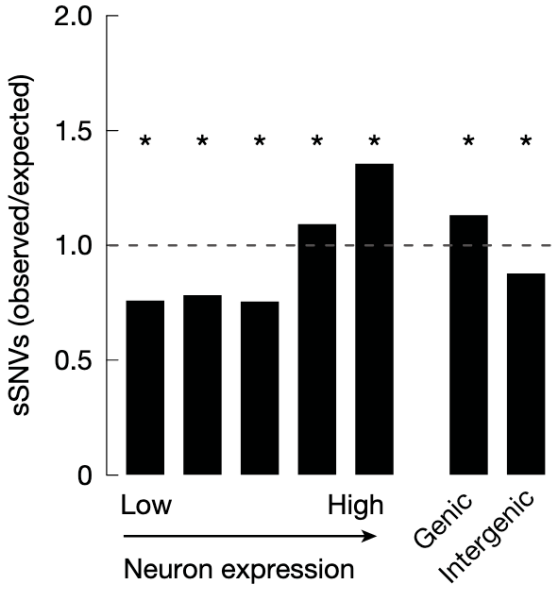
A1: strongly correlates with age

3. Mutation patterns reflect transcription

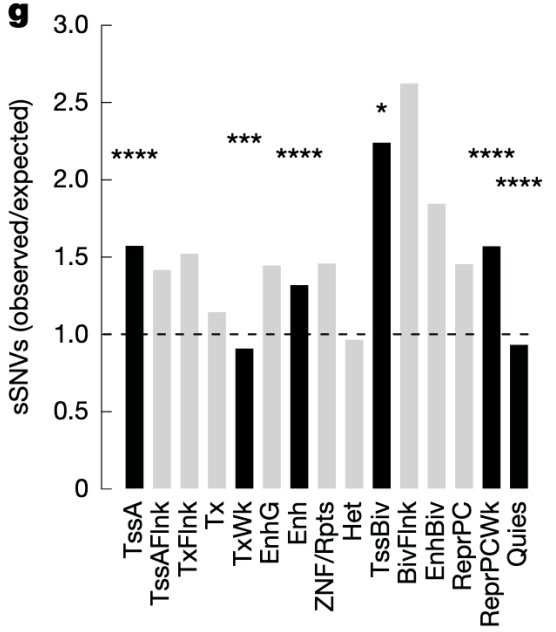
Signature A1



gene expression



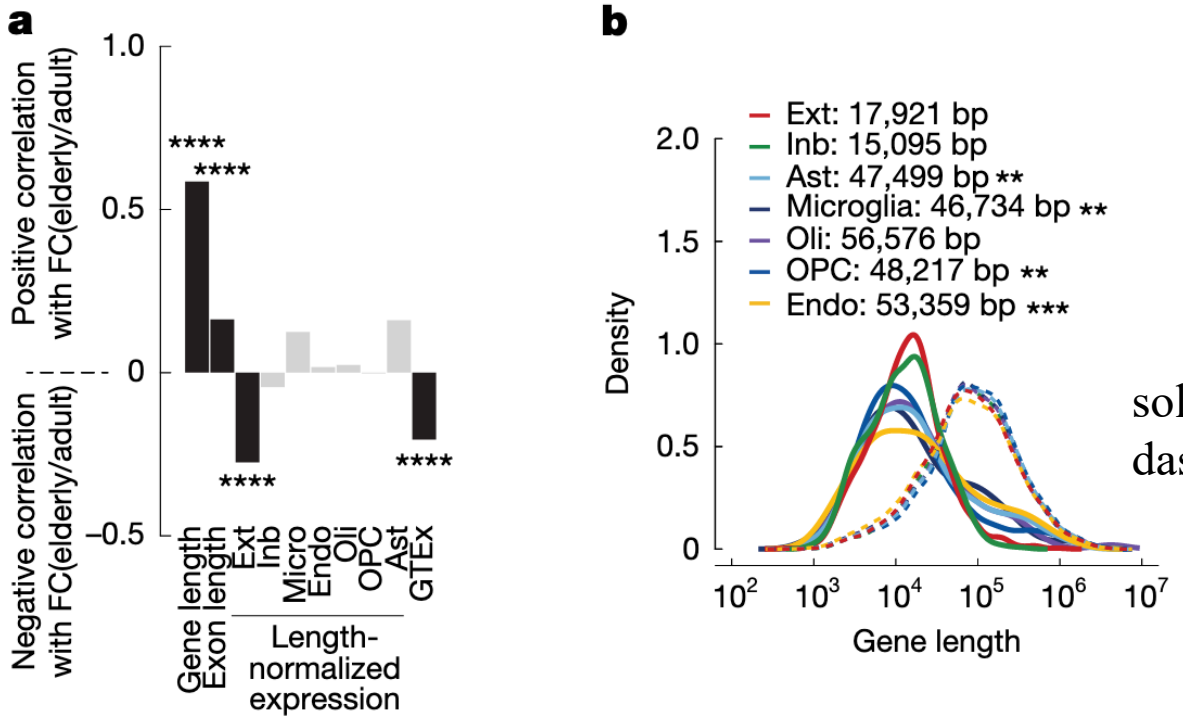
mutation location



mutations ~ gene expression: +

enrich in active chromatin regions

4. Gene length, transcription and mutation in ageing



solid lines: downregulated genes
dashed lines: all expressed genes

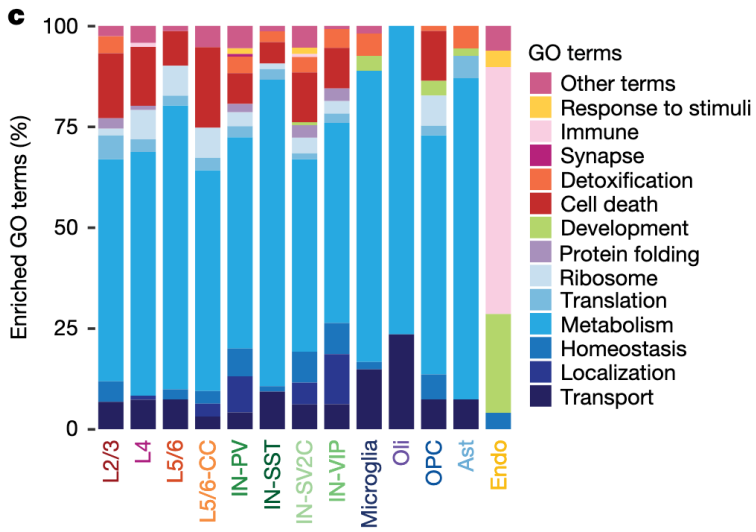
genes with higher baseline expression: downregulated

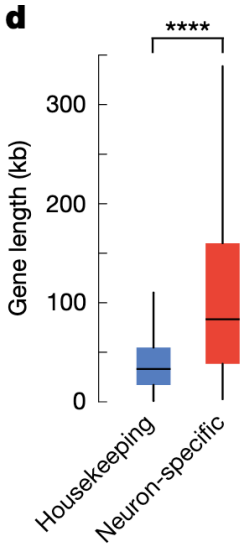
shorter genes : downregulated

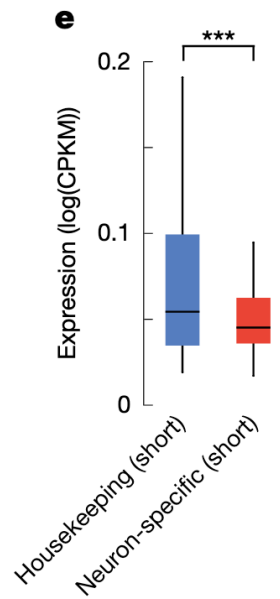
downregulated genes : short genes (neuron)

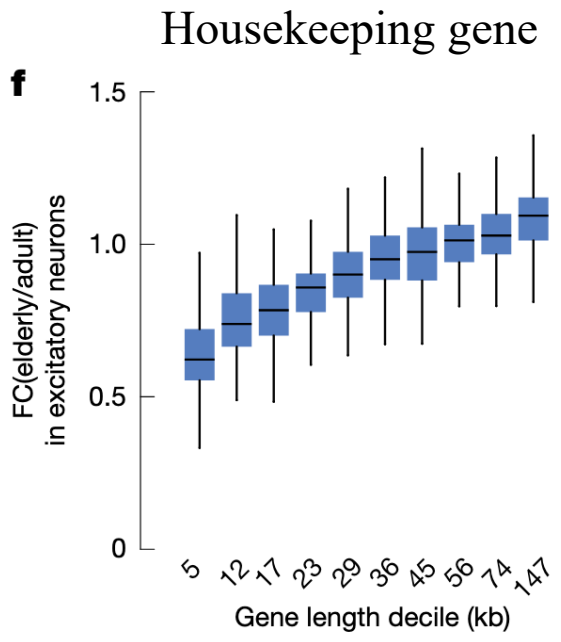
exon length / **gene length**?

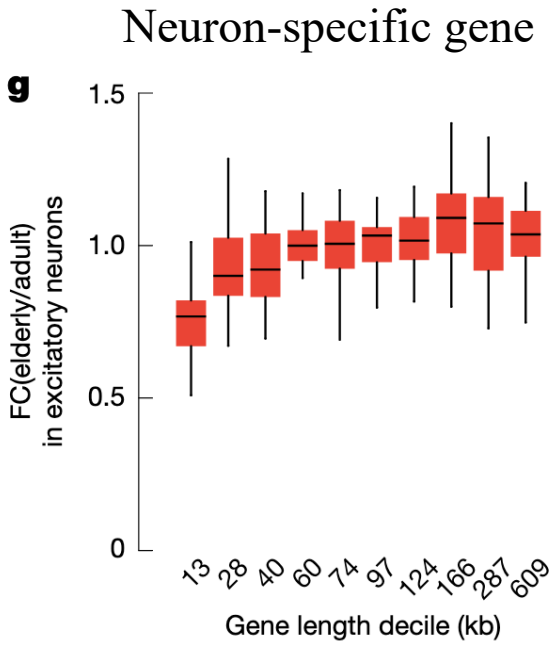
4. Gene length, transcription and mutation in ageing











Housekeeping genes : down

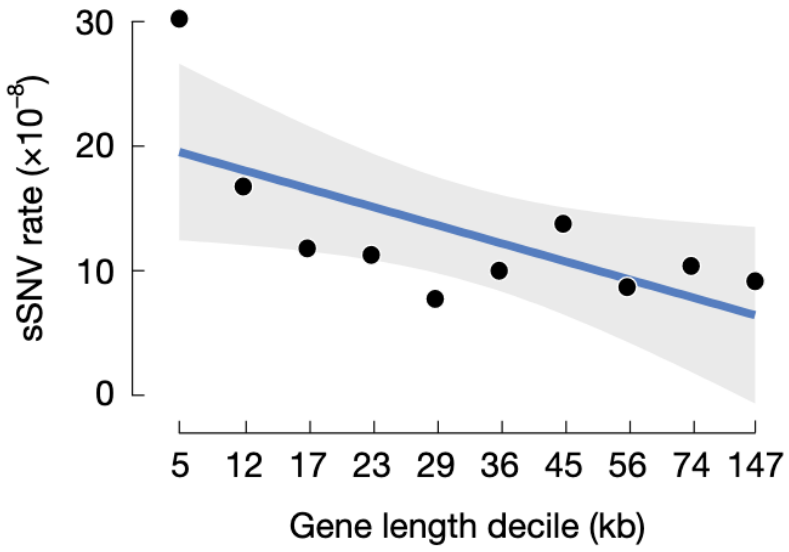
→ Short and highly expressed

Housekeeping genes :
shorter gene length ~ gene downregulated

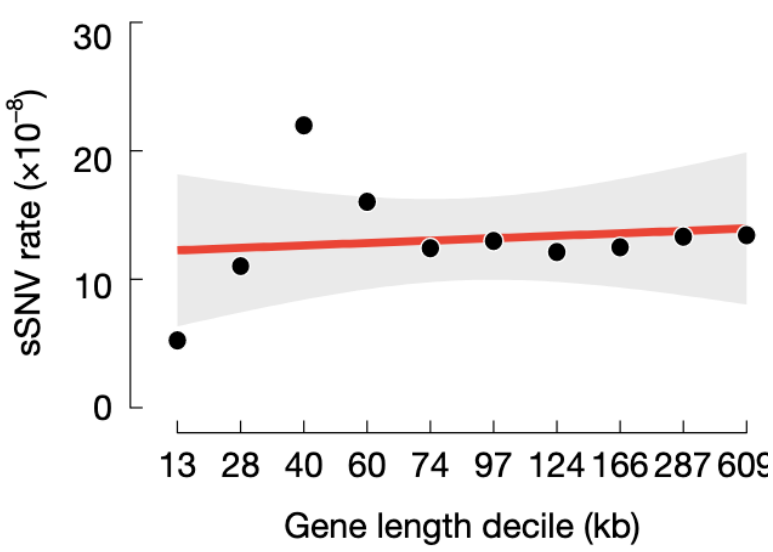
neuron-specific genes: ✗

4. Gene length, transcription and mutation in ageing

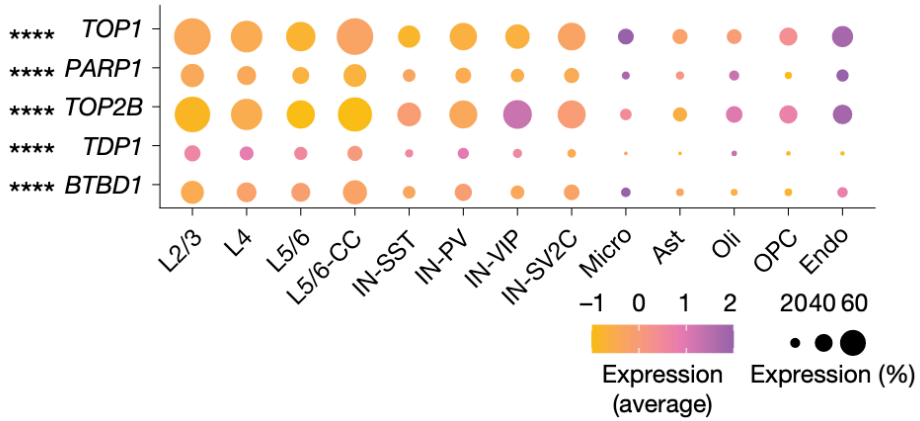
Housekeeping gene



Neuron-specific gene



topoisomerase complex genes



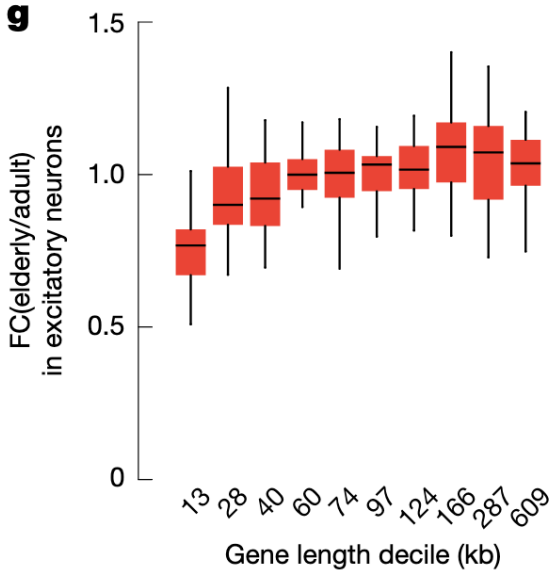
shorter housekeeping genes： more sSNVs

neuron-specific genes: ✗

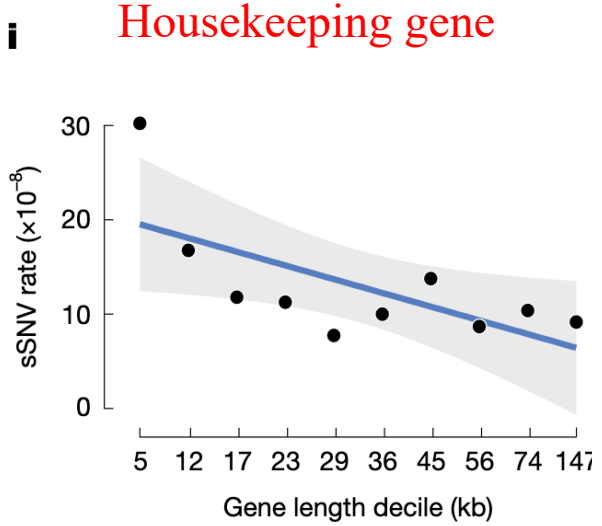
Take home messages

human prefrontal cortex (PFC):

1. Neuron-specific genes : long upregulated during ageing

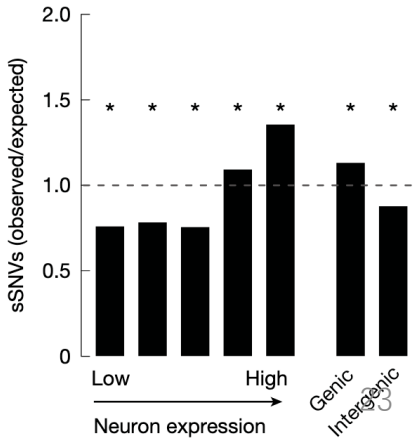


2. How are these mutations related to
- gene length,
- gene expression?



Housekeeping gene

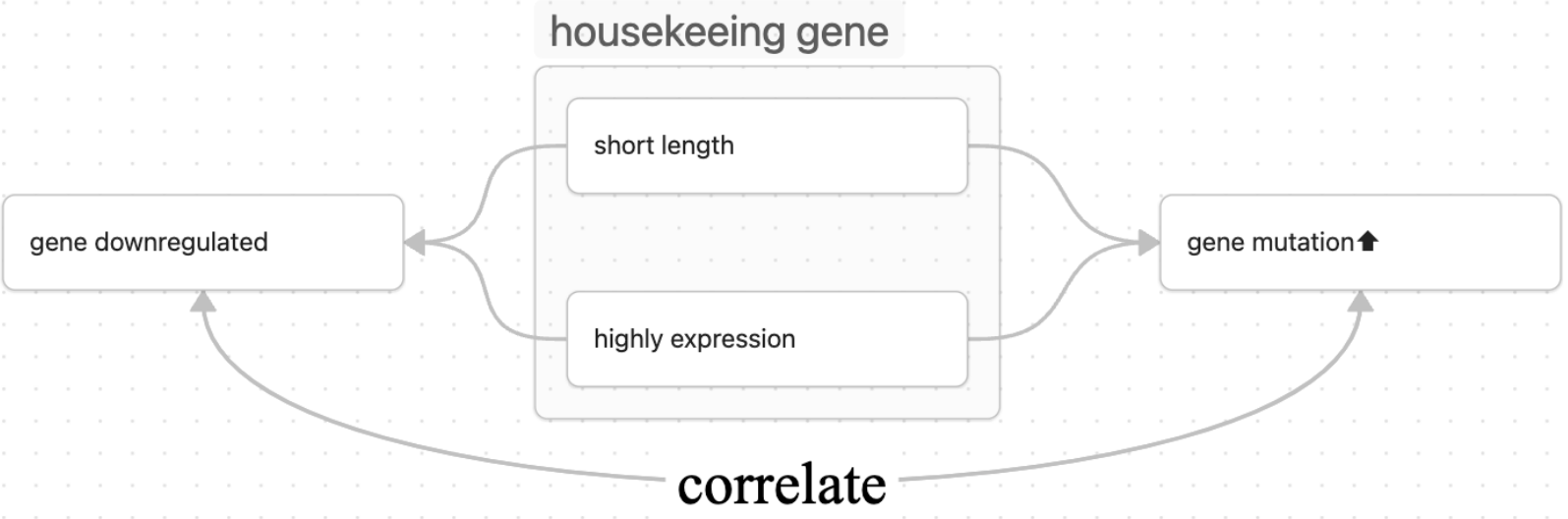
global gene



Summary

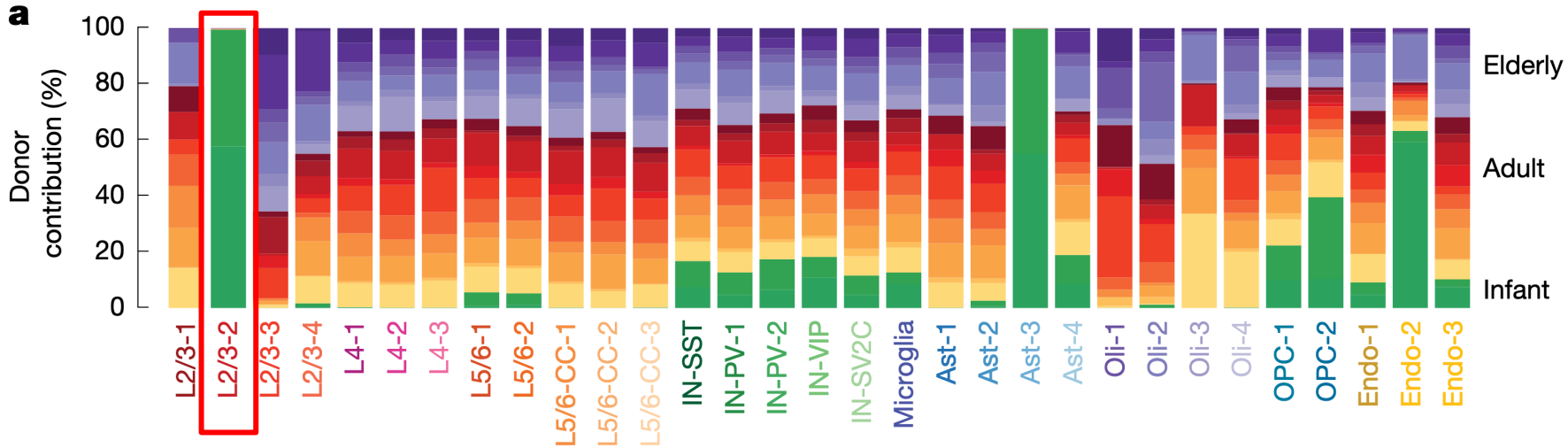
1. brain-cell development continues after birth.
In the infant brain, they identified populations of immature neurons and astrocytes

2. Short and highly expressed housekeeping genes :
show high rates of sSNV accumulation during life
that correlate with reduced expression.

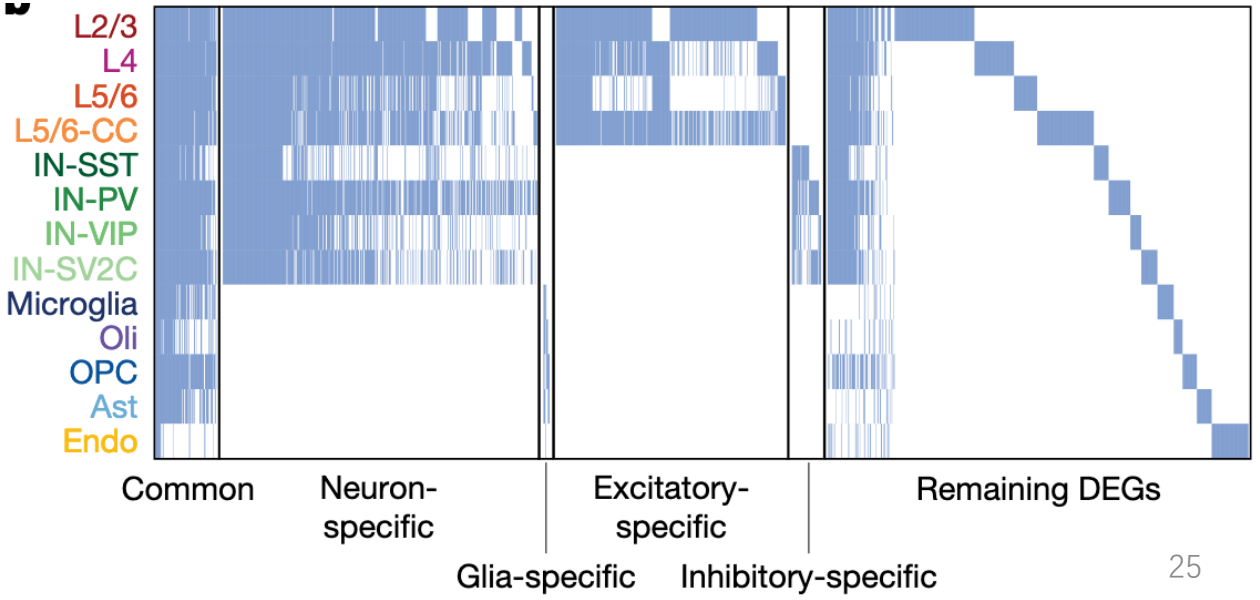


Limitations

1.the infant-specific immature neuron :
without direct validation using proliferation or cell-cycle markers.



2. housekeeping genes: downregulated
But many downregulated genes are cell-type–specific,
their relationship to the housekeeping,
neuron-specific gene classification
remains incompletely resolved.



Thank you for your attention!

Q & A