

Discovering somatic mutations during aging

Xiao Dong, Ph.D.

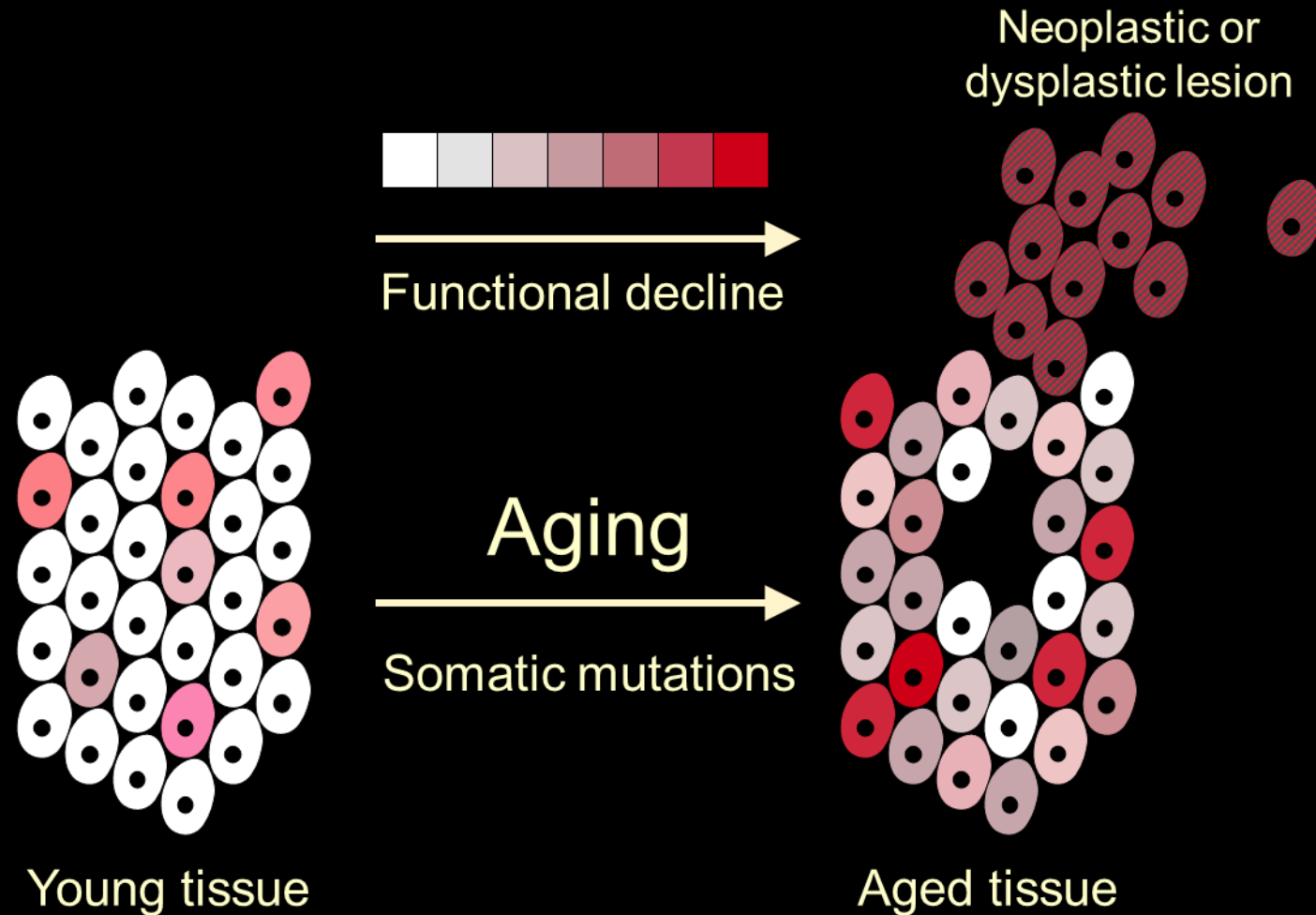
Assistant Professor

Institute on the Biology of Aging and Metabolism

Department of Genetics, Cell Biology and Development

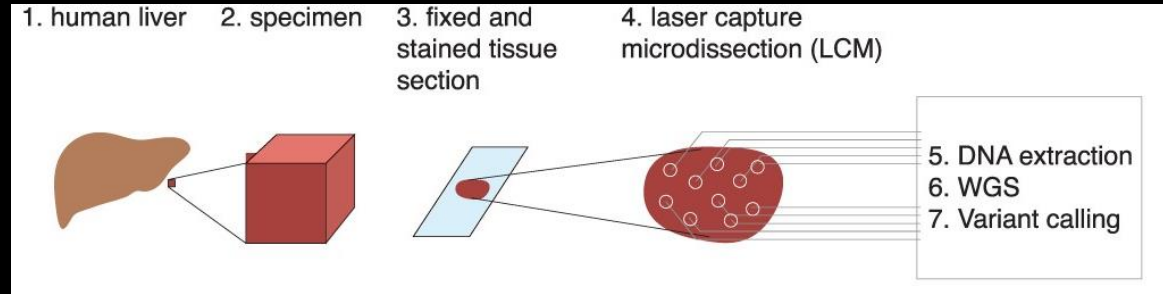
University of Minnesota, Twin Cities

Somatic mutation, aging and cancer



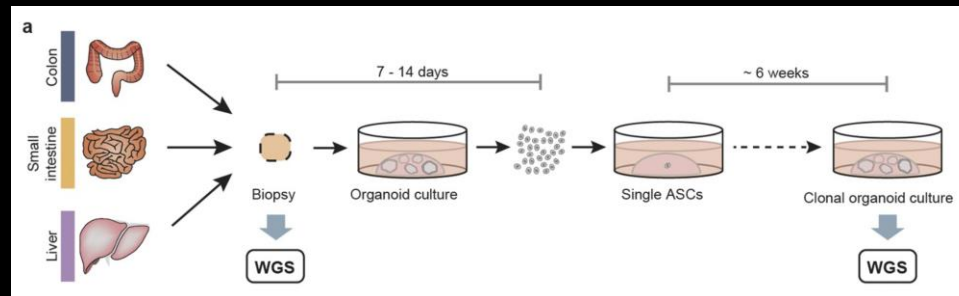
Measure mutations as single-cell expansions

Deep sequencing of natural single cell expansions from micro-biopsies



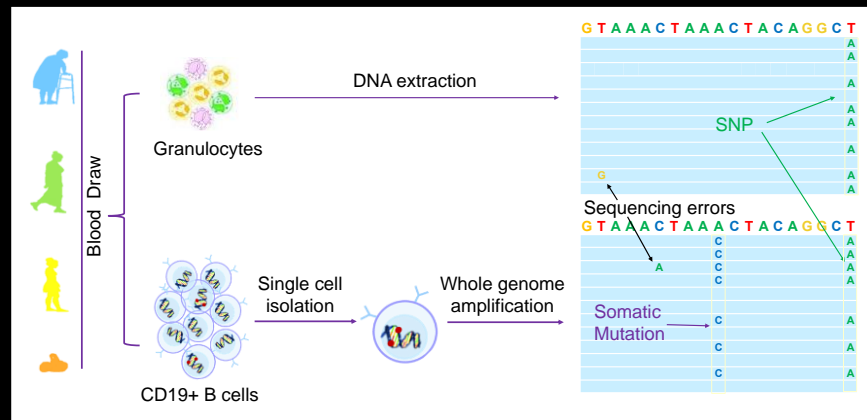
Brunner SF, et al. *Nature*, 2019.

Expand stem cells *in vitro*



Blokzijl F, et al. *Nature*, 2016.

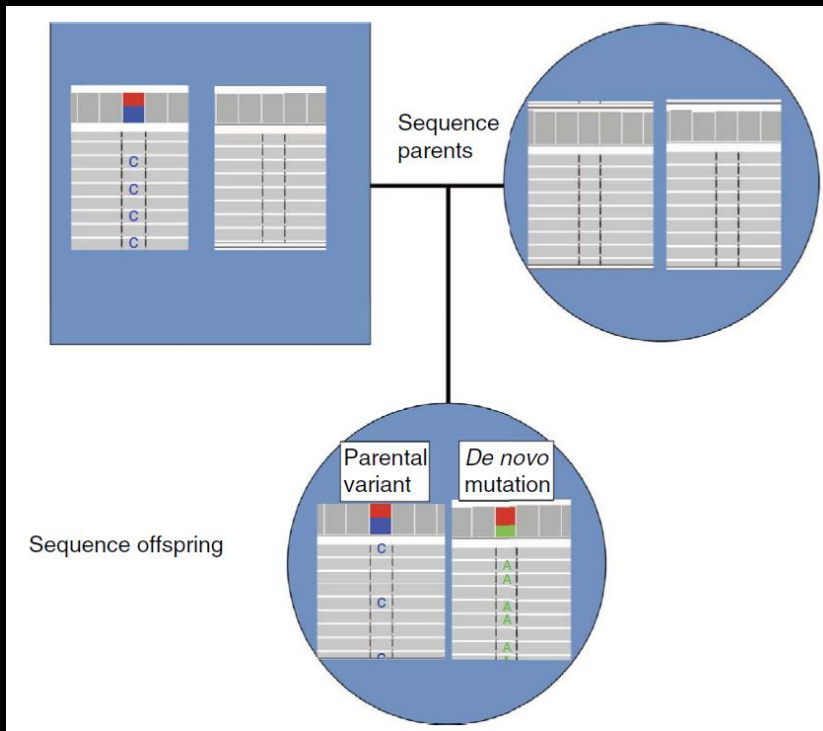
Whole genome amplification on single cells



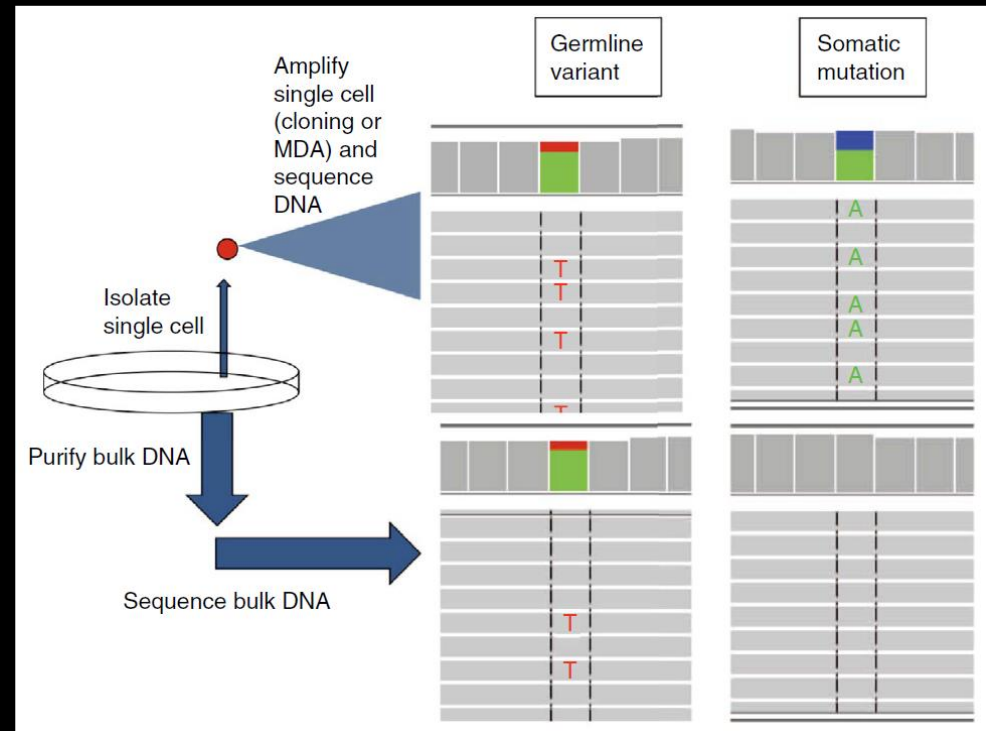
Revised from:
Dong X, et al. *Nat Methods*, 2017.
Zhang L, et al. *PNAS*, 2019.

If mutations cause aging, is the germline protected?

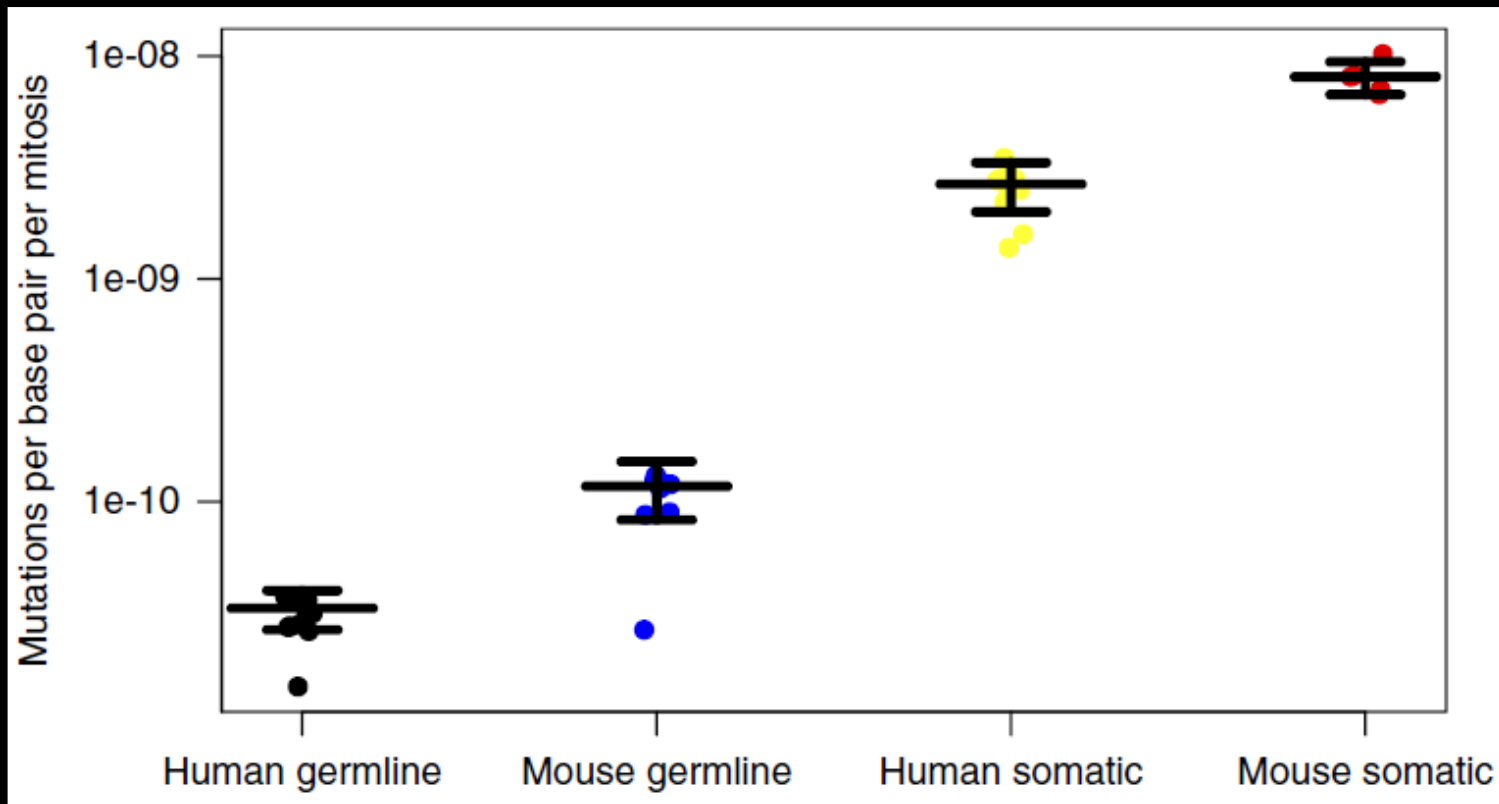
Germline *de novo* mutation



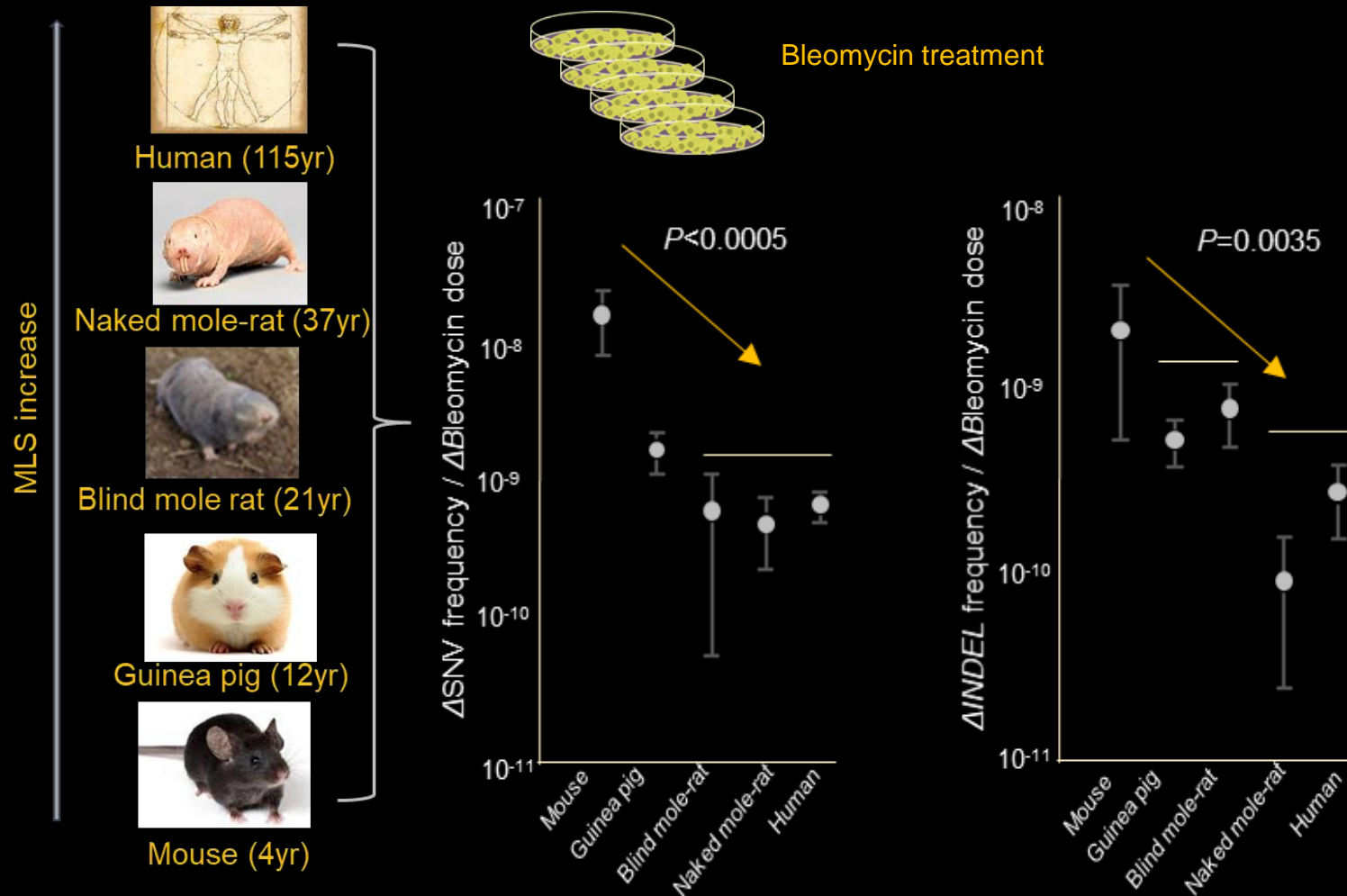
Somatic *de novo* mutation



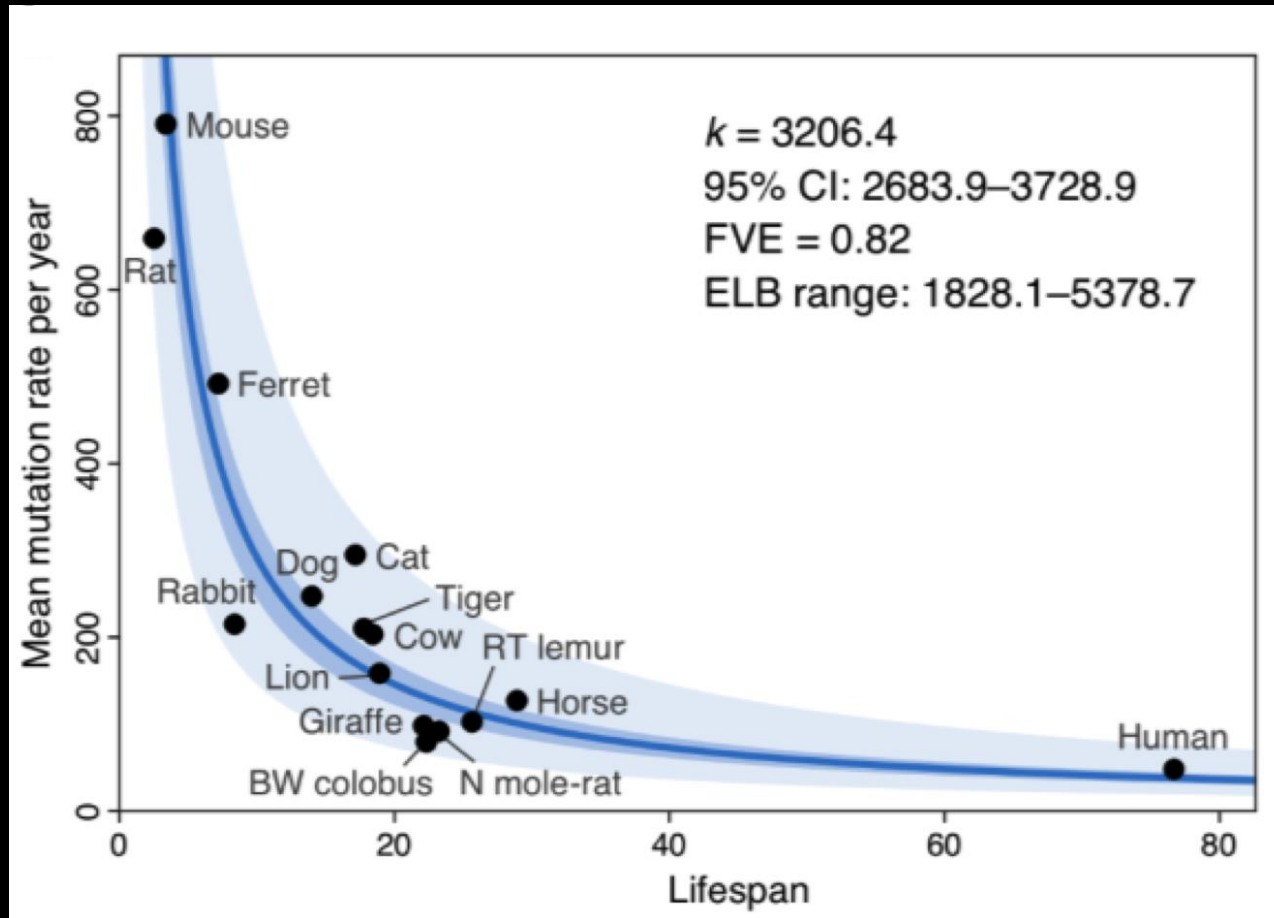
SNV frequency is significantly higher in soma than in germline: is the soma disposable?



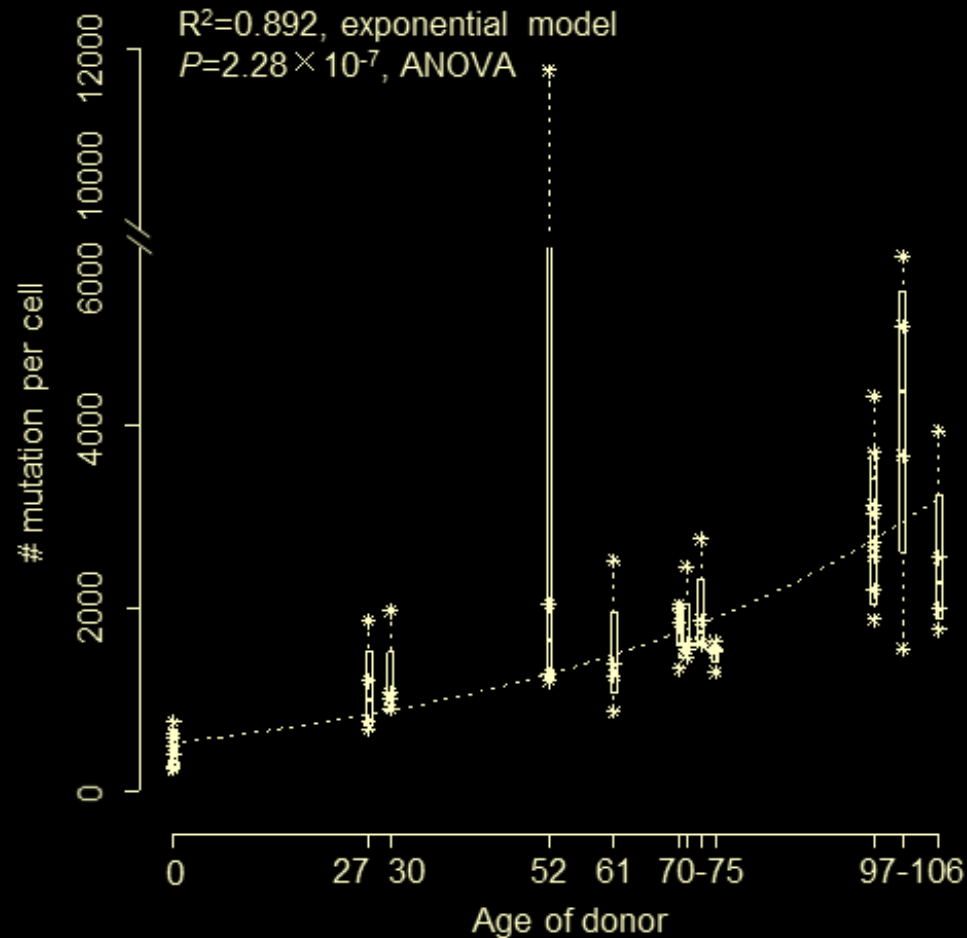
Somatic mutation rates are inversely correlated with species-specific lifespans



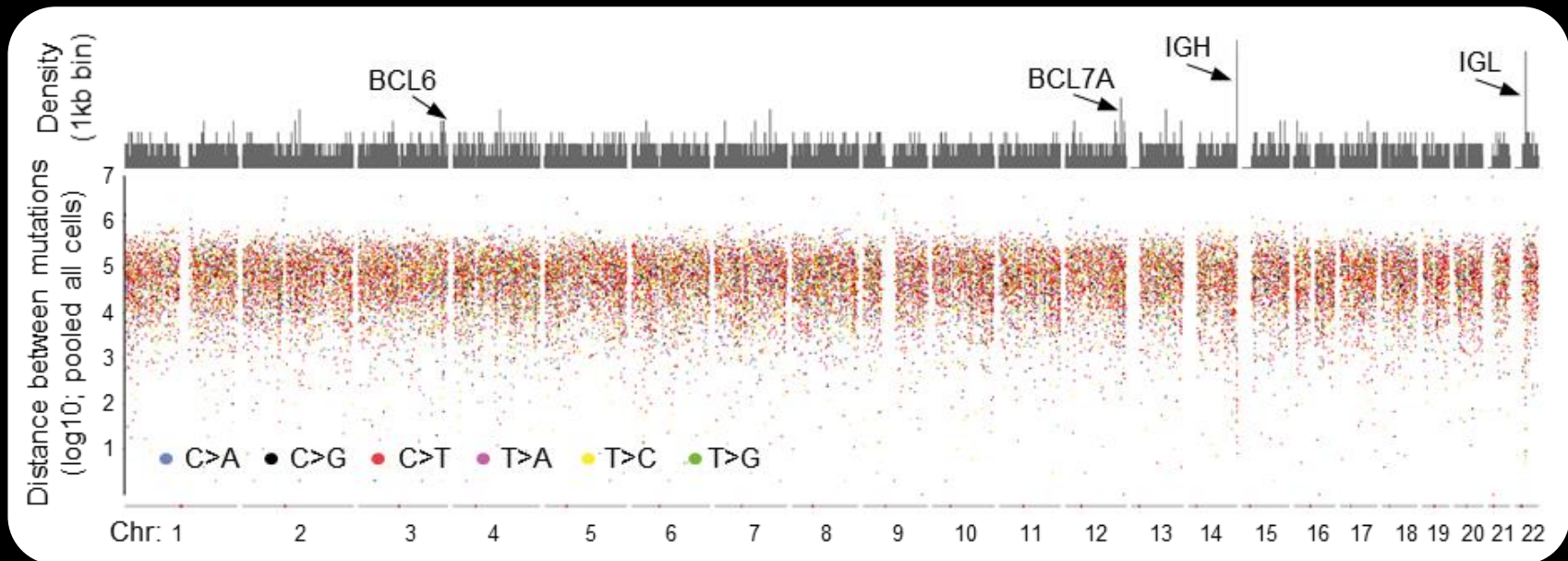
Somatic mutation rates scale with lifespan across mammals



Somatic SNVs accumulate with age in human B lymphocytes



Distribution of mutations and mutational hotspots in pooled 56 B cells

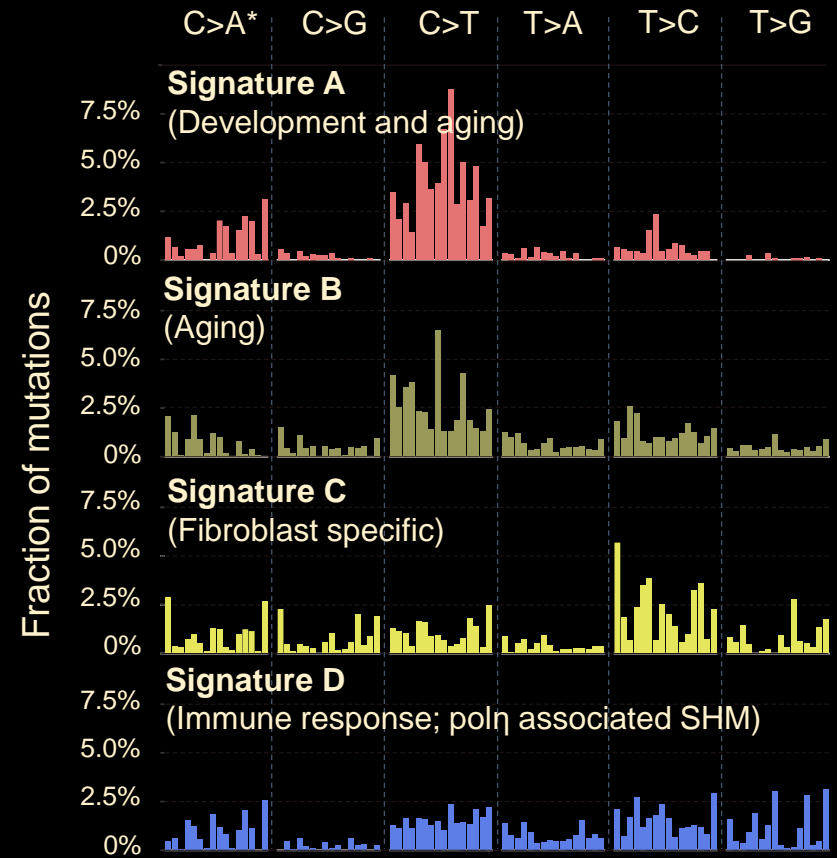
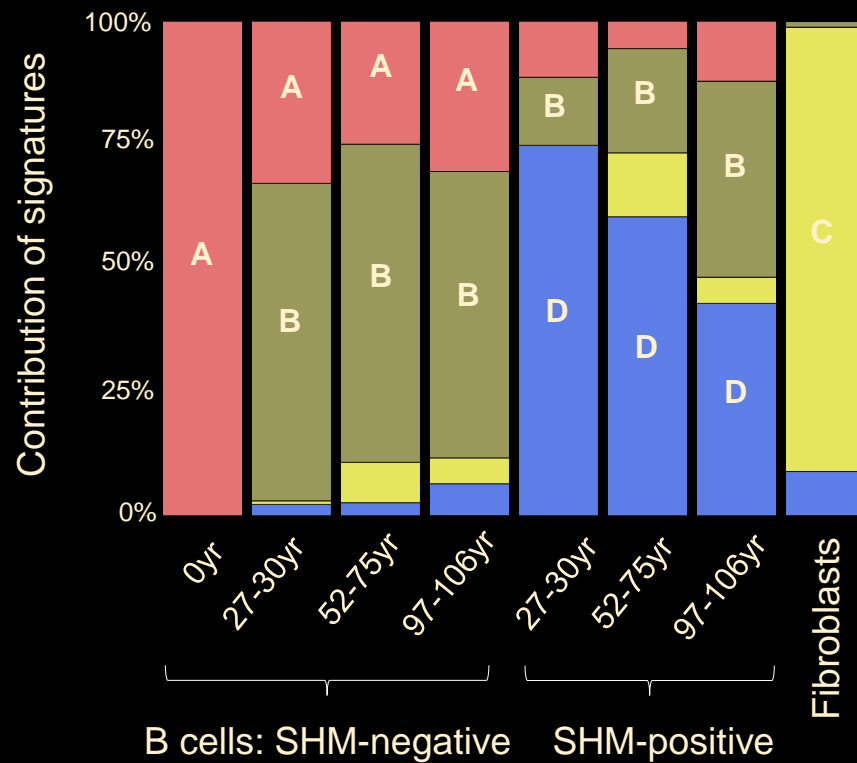


24 hotspots observed

Hotspots: >4 SNVs in a ~5kb region

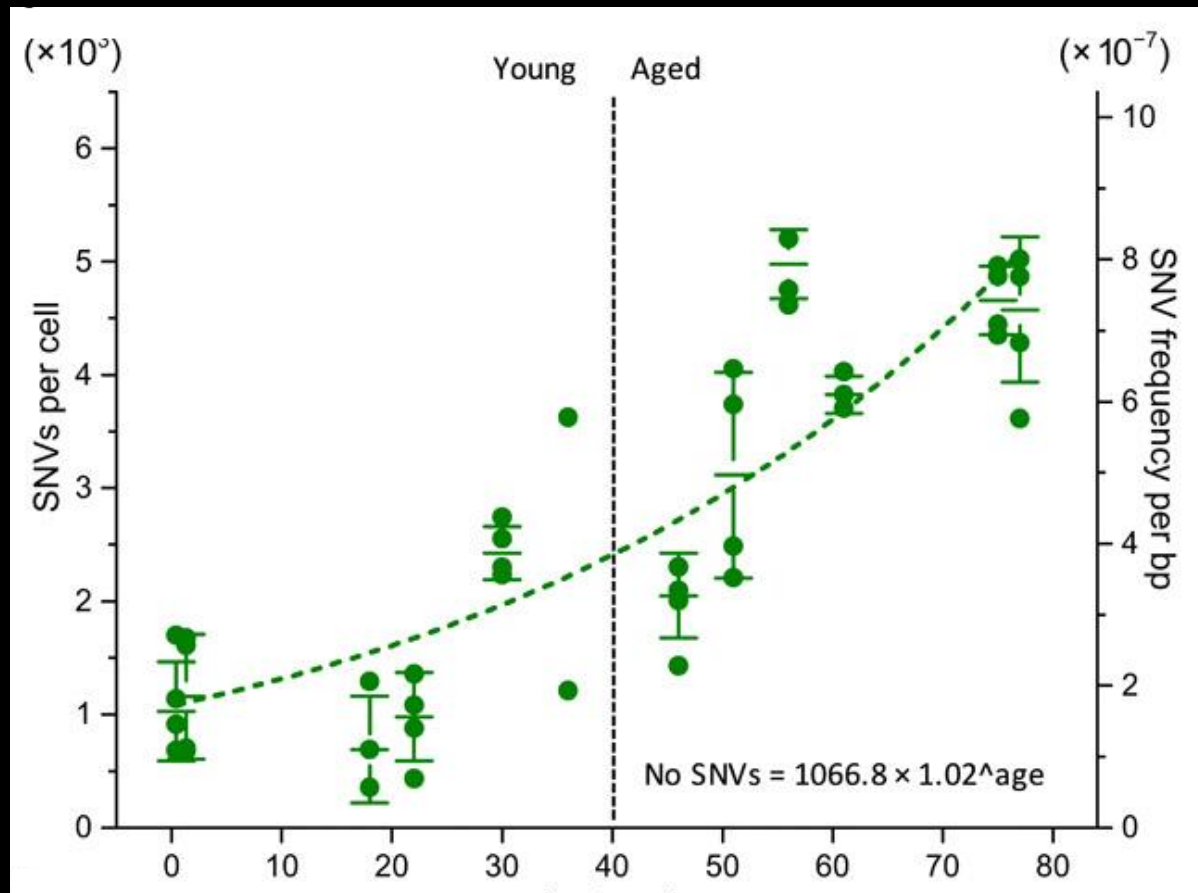
Genome average: 0.05 SNV in a 5kb region

Mutational signatures in normal B lymphocytes during aging



* From ACA -> AAA to TCT -> TAT

Somatic SNVs accumulate with age in human hepatocytes and other cell types



SomaMutDB: a database of 2.5 million discovered mutations in normal somatic human tissues

Welcome to SomaMutDB!

A database of somatic mutations in normal human tissues

Home Browse Search Analysis Download Documentation V1.0 (June 2021)

Overview

The mission of SomaMutDB is to provide a resource of somatic mutations in normal human tissues to help improving our understanding of the impact of somatic postzygotic mutagenesis on human healthy aging and disease. The current version of SomaMutDB contains a comprehensive catalogue of somatic SNVs (single nucleotide variants) and small INDELs (insertions and deletions) from twenty normal human tissues and cell types. Currently, the database has a total number of 2.53 million somatic variants. For browse and search, we incorporate the annotations of gene and regulatory elements from EMBL and GENCODE, and median expression level for each tissue in GTEx. SomaMutDB also provides six useful tools for mutational signature analysis.

Cite SomaSC:
Shixiang Sun, Yujue Wang, Alexander Y. Maslov, Xiao Dong and Jan Vijg. SomaMutDB: a database of somatic mutations in normal human tissues. Under revision.

Variant type

Variant Type	Count
SNV	2417518
INDEL	116591

Age

Age Group	Count
Embryo	98
0-9	257
10-19	91
20-29	117
30-39	265
40-49	203
50-59	549
60-69	635
70-79	532
80-89	77
90-99	9

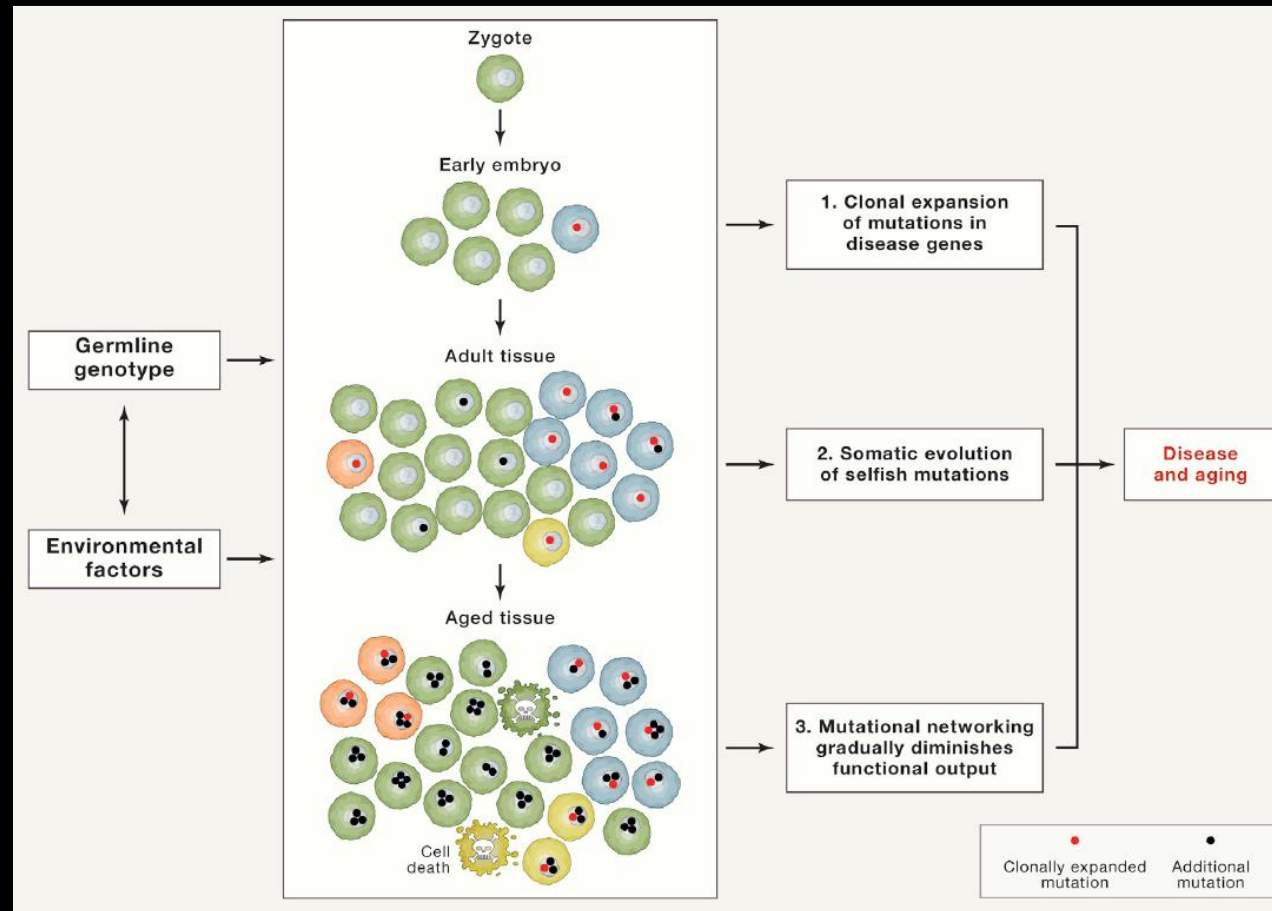
Sex

Sex	Count
Male	1427
Female	1339
Unknown	76

Conclusions and prospects

- Using the single-cell approaches we can now characterize the landscapes of somatic mutations in humans in relation to aging
- Is the accumulation of somatic mutations a direct cause to functional decline during aging?

Is the accumulation of somatic mutations a direct cause to functional decline during aging?



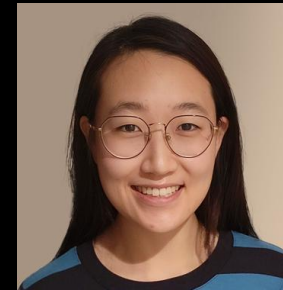
Acknowledgement



Jan Vijg



Lei Zhang



Hannim Jung



Josh Bartz



NIH K99/R00: Pathway to Independence Award (K99/R00 AG056656)