Genomic solutions to sustainable development

Week 4 — Gender & Health

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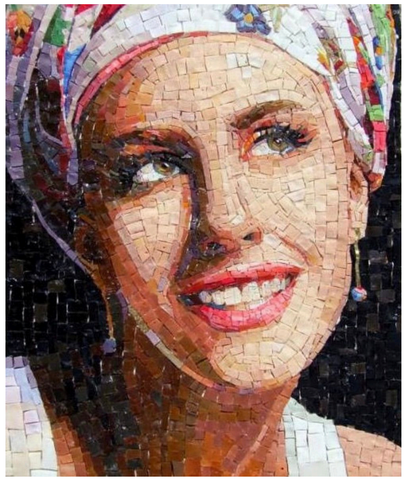
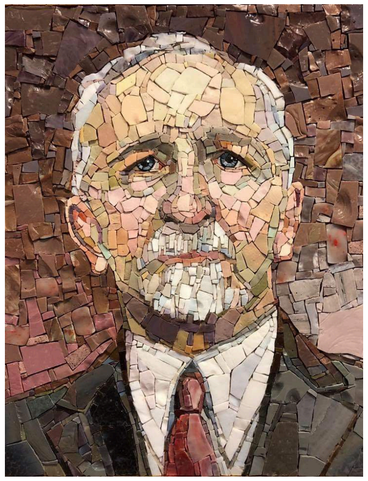
Outline

- Overview of mechanisms behind de novo germline mutations
- Overview of mechanisms behind somatic mutations
- Genetic predisposition to somatic mutagenesis

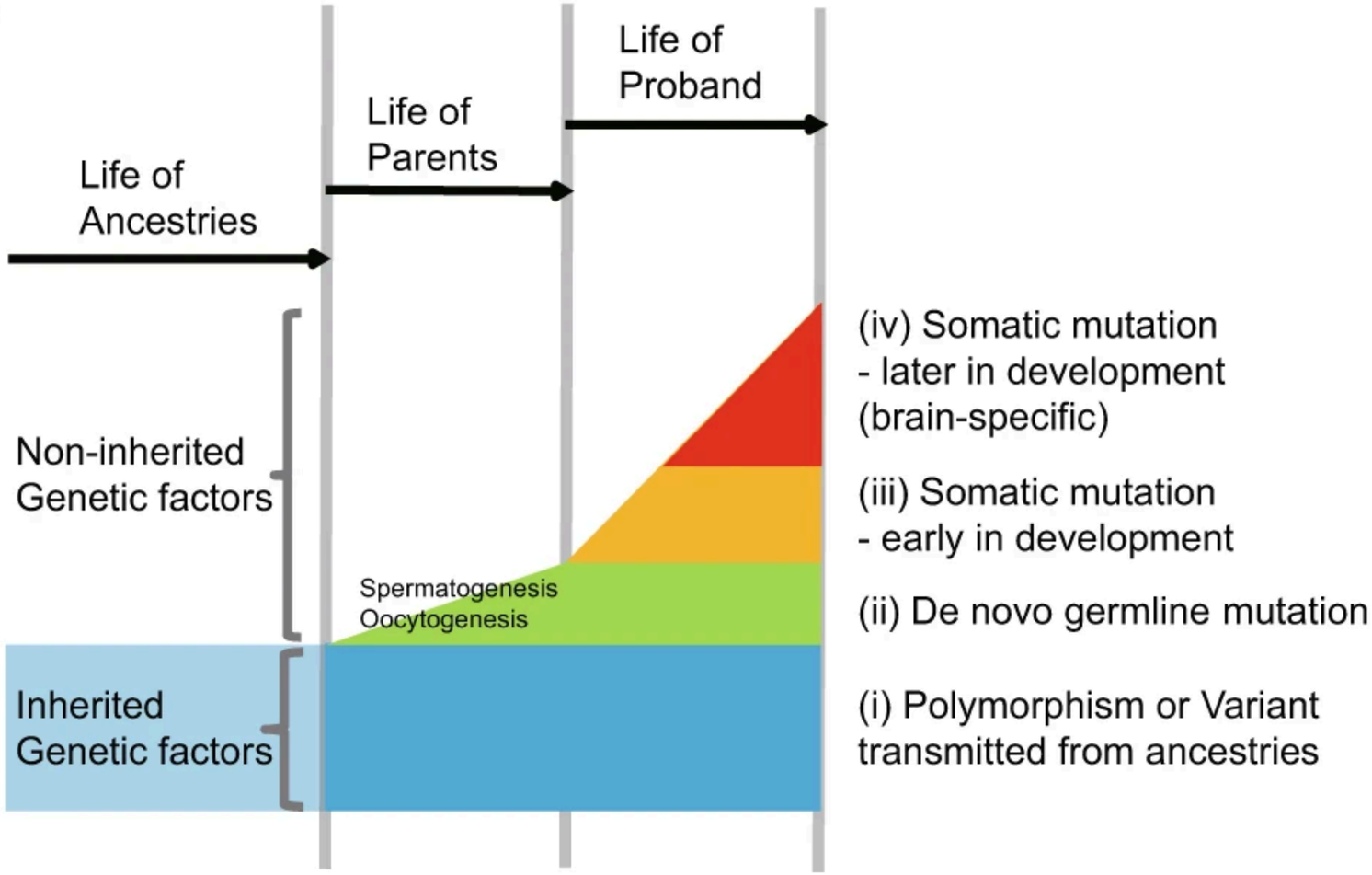
The human body is a mosaic of many genomes

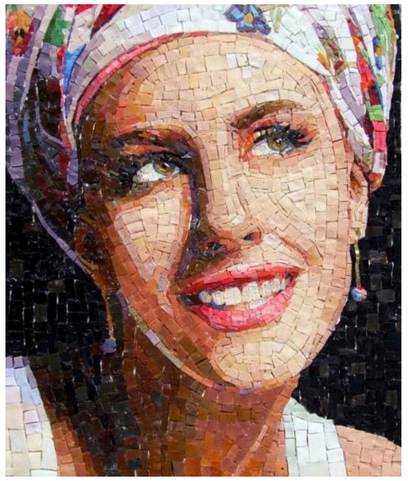
Images: Yulia Hanansen, Andjelka Radojevic, Nancie Mills Pipgras, Yury Malkov, Maria Vud

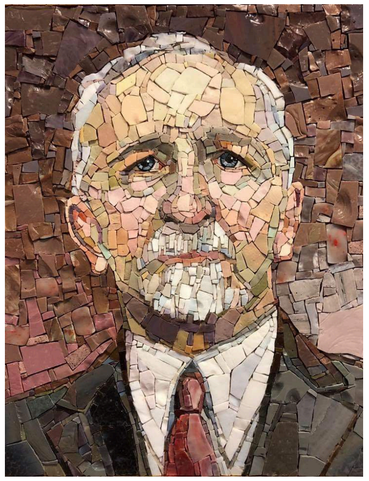
The human body is a mosaic of many genomes



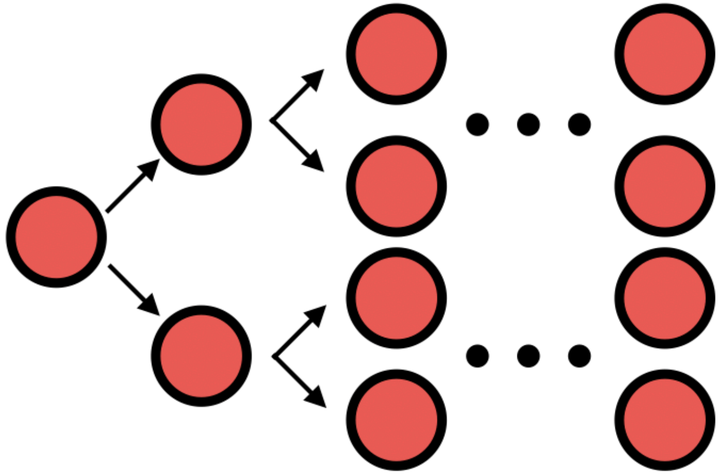
Nishioka et al *Mol Psychiatry* 2018

The human body is a mosaic of many genomes

Germline polymorphisms
De novo germline mutations

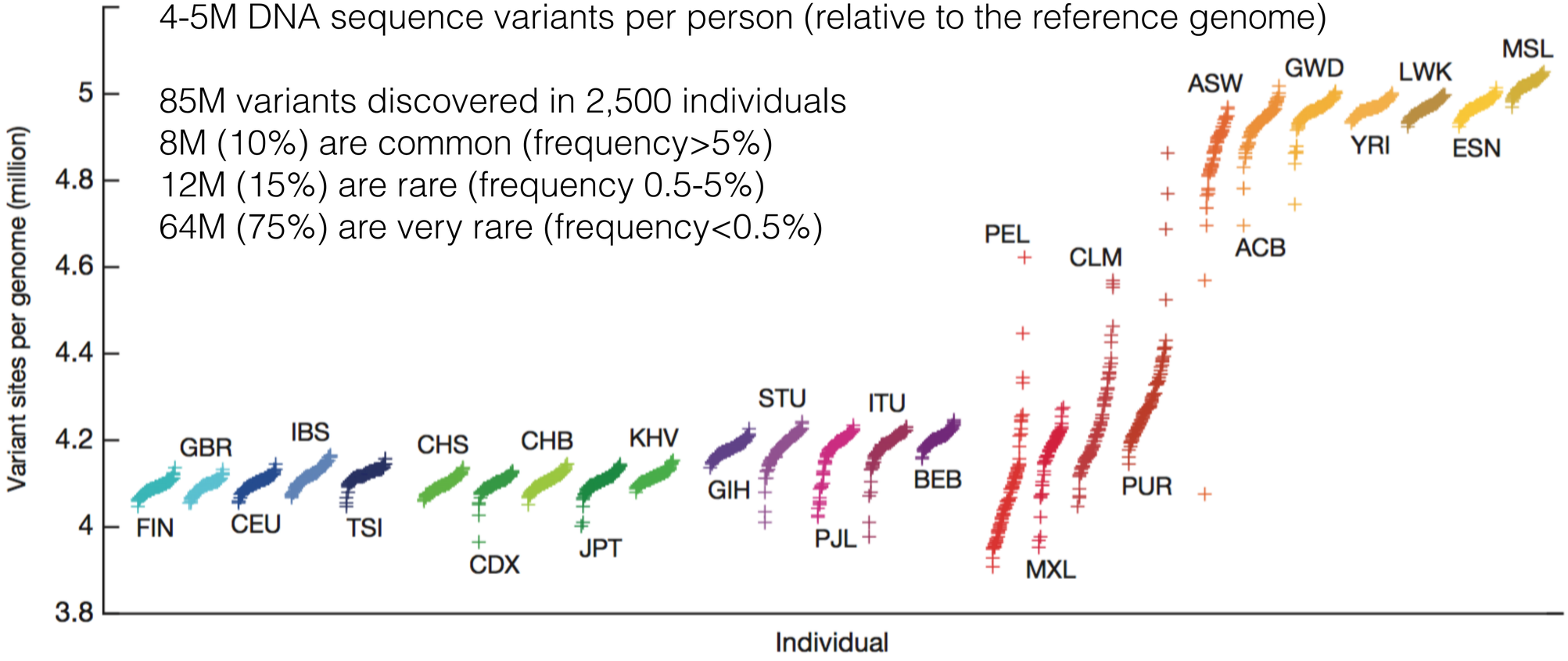


All somatic cells

A typical human genome in numbers

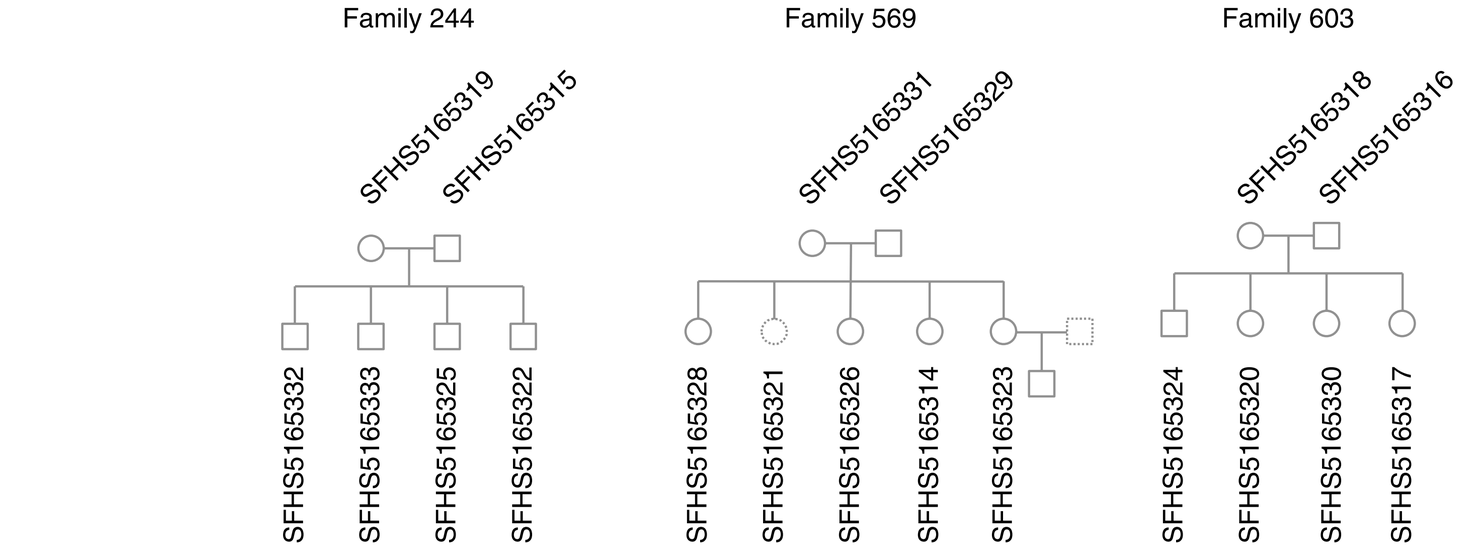
4-5M DNA sequence variants per person (relative to the reference genome)

85M variants discovered in 2,500 individuals
8M (10%) are common (frequency>5%)
12M (15%) are rare (frequency 0.5-5%)
64M (75%) are very rare (frequency<0.5%)



1000 Genomes Project, Nature (2015)

Genome-wide *de novo* germline mutations



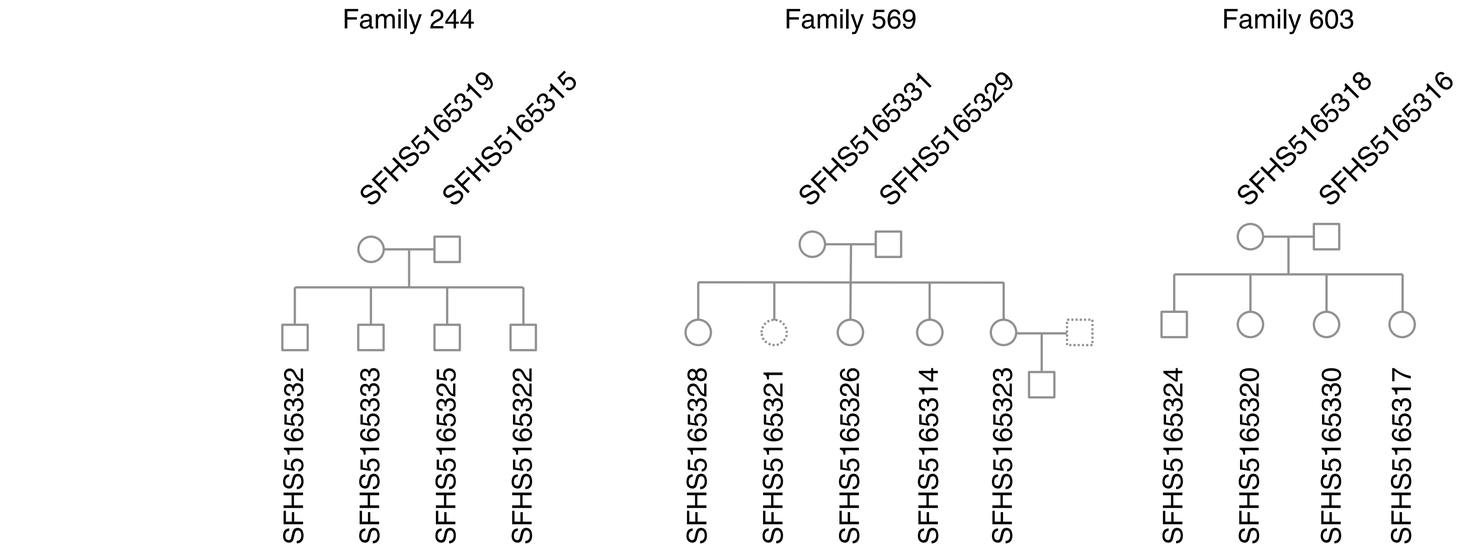
Age (years)					
	Mother	23	25	27	35
	Father	25	27	29	37

24	27	31	34	37
24	27	31	34	37

26	28	34	38
23	25	31	35

Rahbari et al. Nature Genetics 2015

Genome-wide *de novo* germline mutations

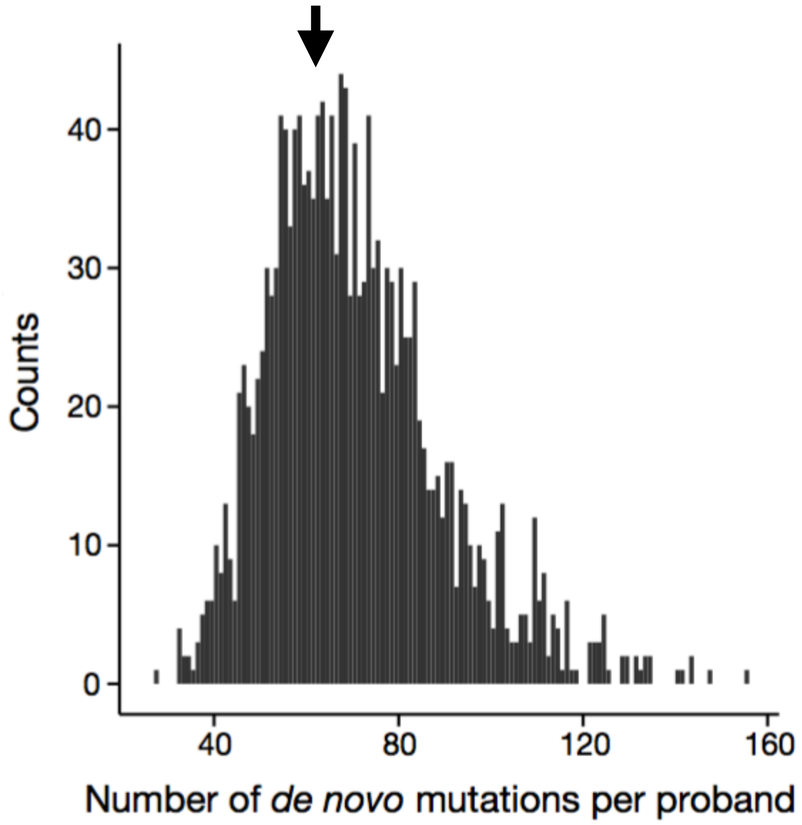


Age (years)	Mother	23	25	27	35	24	27	31	34	37	26	28	34	38
	Father	25	27	29	37	24	27	31	34	37	23	25	31	35
De novo SNVs		59	62	65	74	45	–	63	81	84	43	49	68	75

Rahbari et al. Nature Genetics 2015

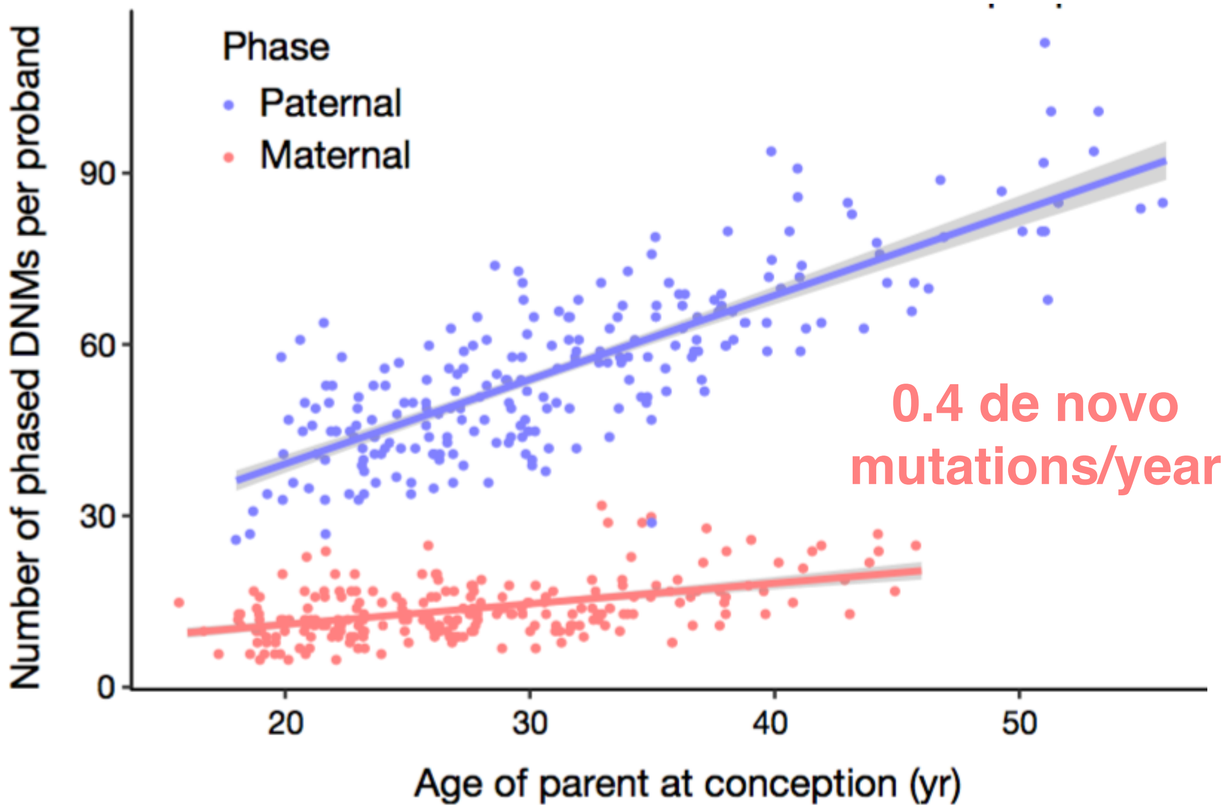
Sex and parental age affect the number of *de novo* germline mutations

70 *de novo* germline mutations



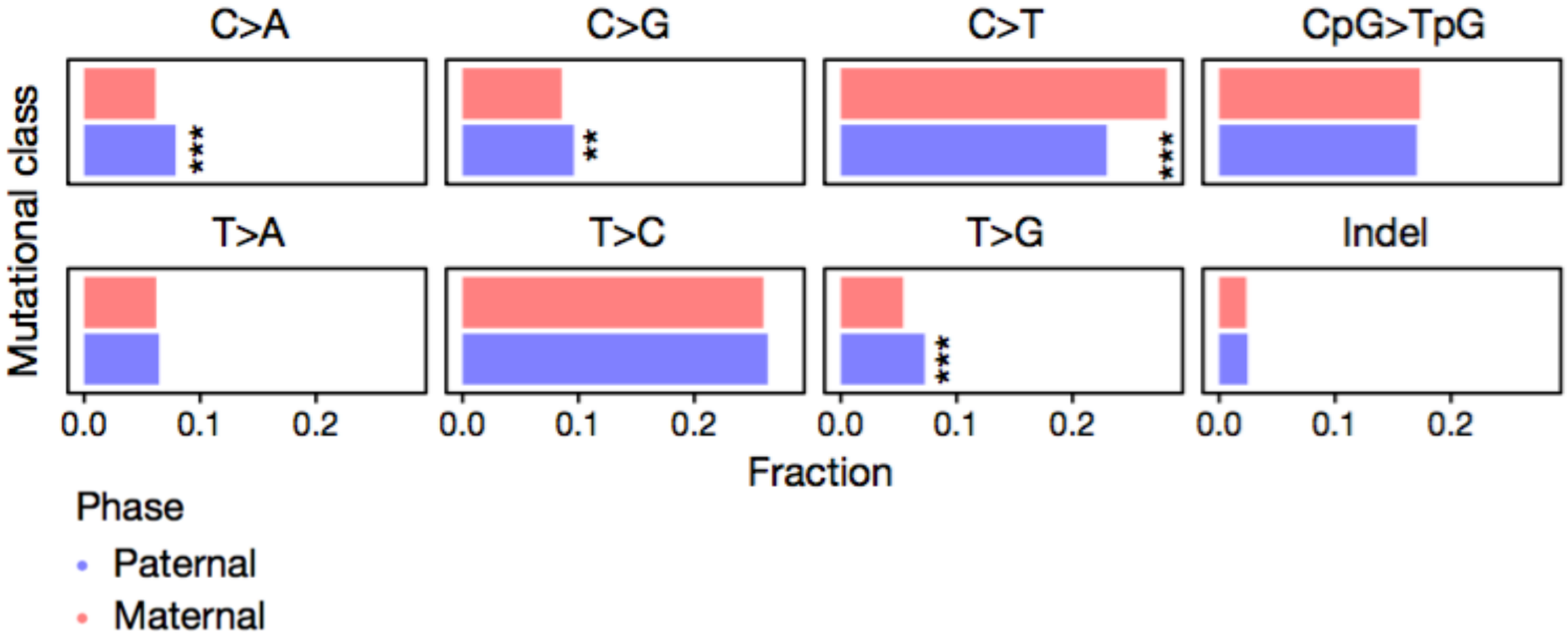
1.5 de novo mutations/year
(80% of all de novo mutations)

0.4 de novo mutations/year



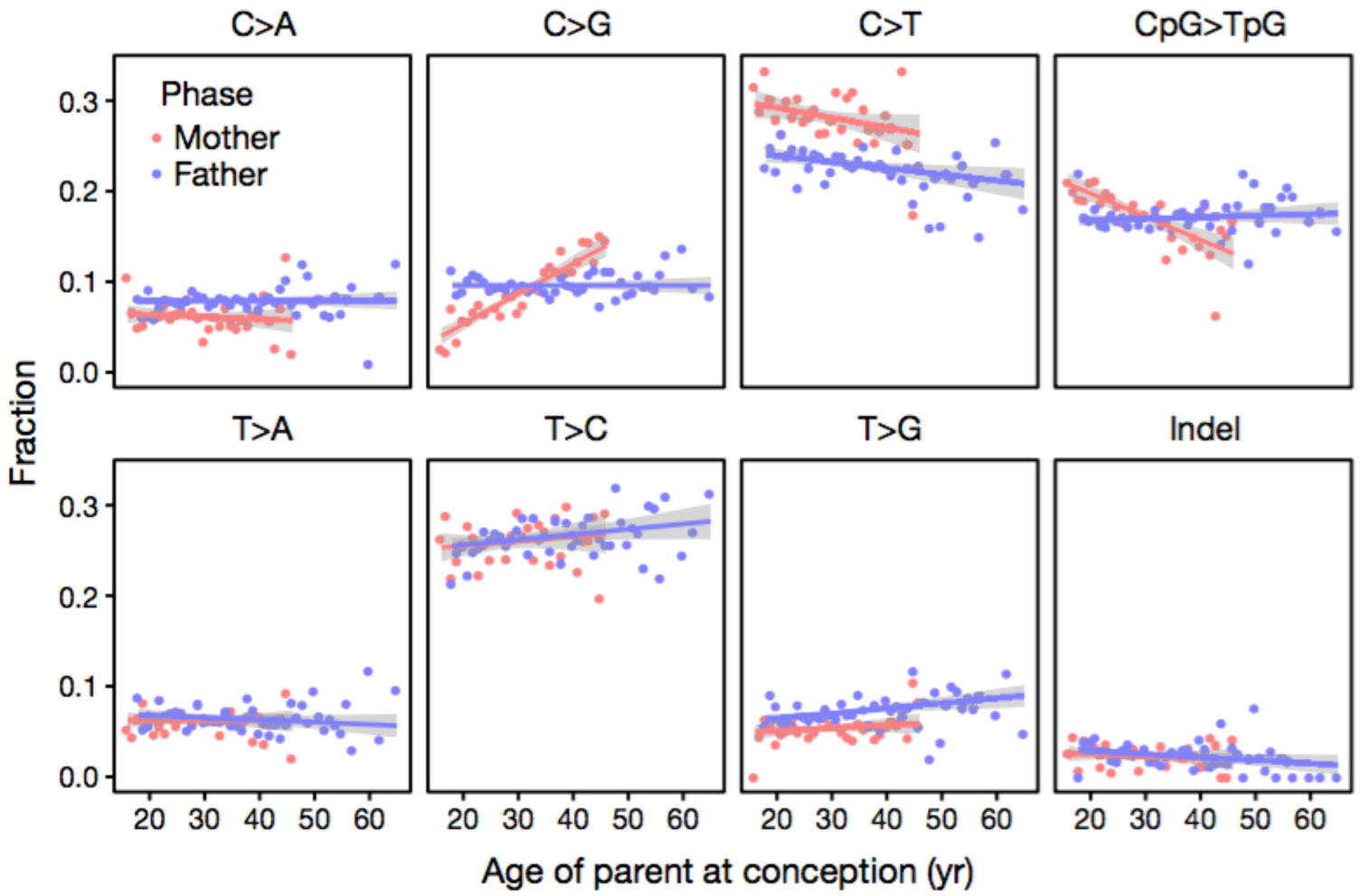
Jónsson et al. Nature 2017

Sex and parental age affect the type of *de novo* germline mutations



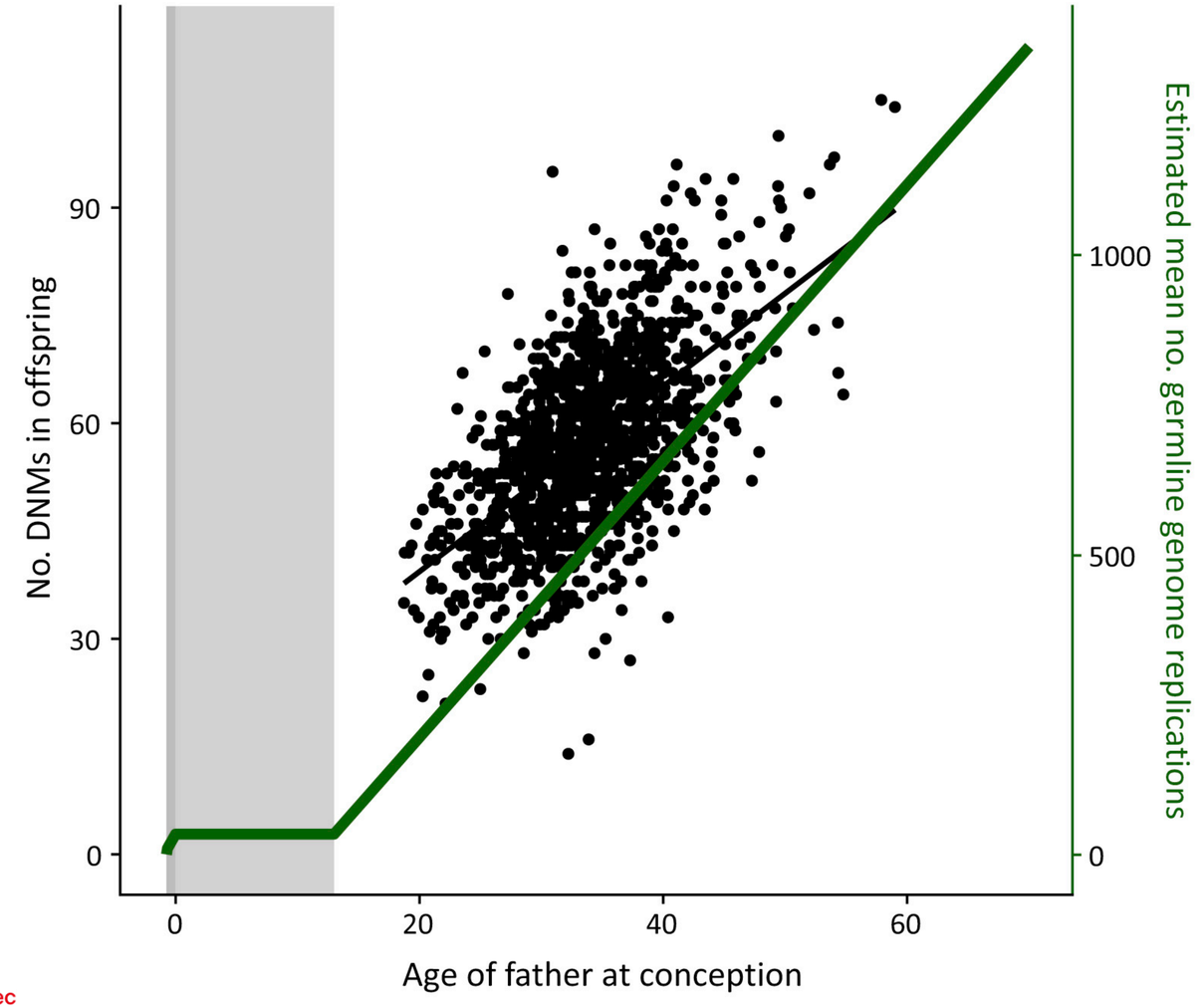
Jónsson et al. Nature 2017

Sex and parental age affect dynamics of *de novo* germline mutation types



Jónsson et al. Nature 2017

The spermatogonium division model and genome-replication hypothesis



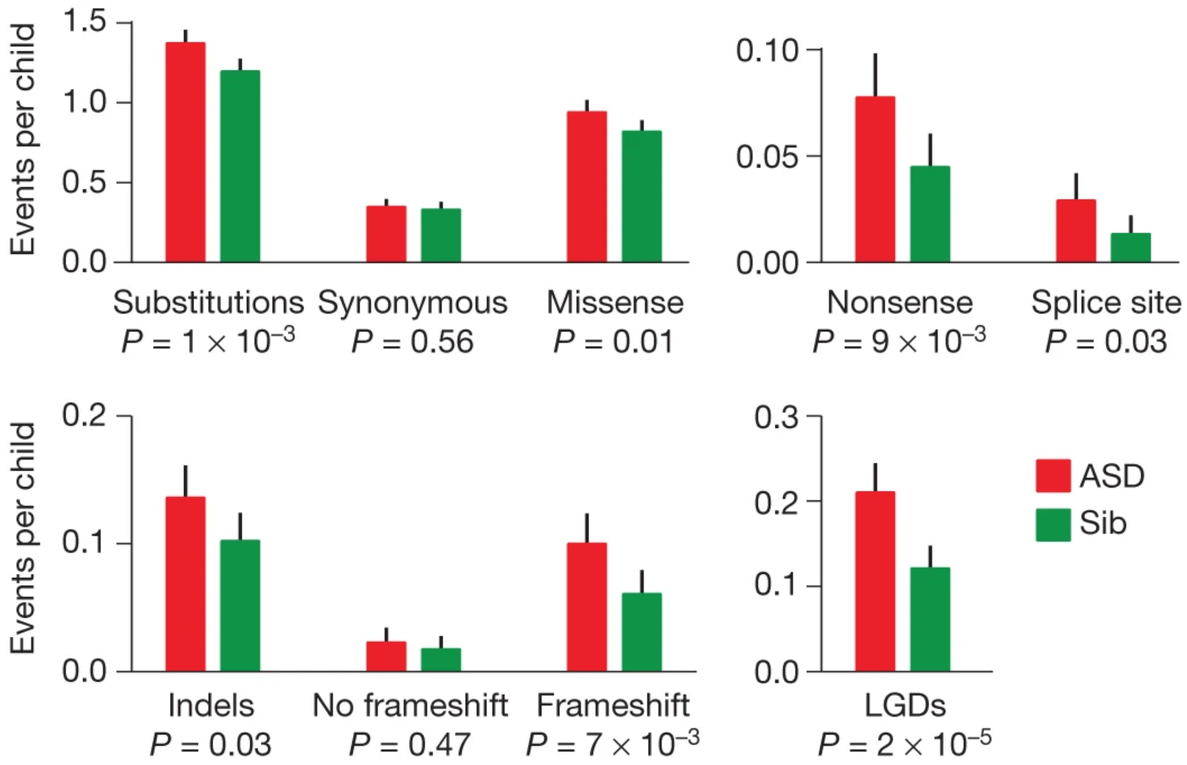
- **Very early embryogenesis and germline cell specification:** 10 cell divisions
- **Sex organ development:** 24 cell divisions
- **Spermatogonia divide and produce spermatocyte starting from onset* of puberty:** 23 divisions/year/spermatogonium
- **Spermatocyte to sperm cell:** 4 cell divisions
- **Total number of cell divisions to produce sperm:**
  - 20 year-old male: 10+24+7x23+4=199 divisions
  - 30 year-old male: 10+24+17x23+4=429 divisions
  - 40 year-old male: 10+24+17x23+4=659 divisions

Goldmann et al. Trends in Genetics 2019

*approx. 13 years old

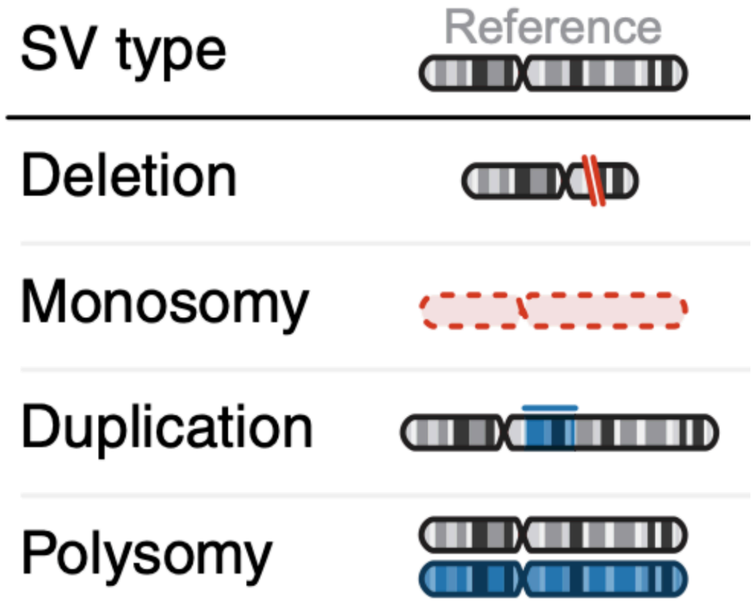
Functional impact of *de novo* germline gene mutations

- 1-2 de *novo* germline gene mutations per child
- 75% *de novo* mutations cause functional protein changes
- Higher rates of functional *de novo* germline mutations in patients with cancer, ASD, structural birth defects

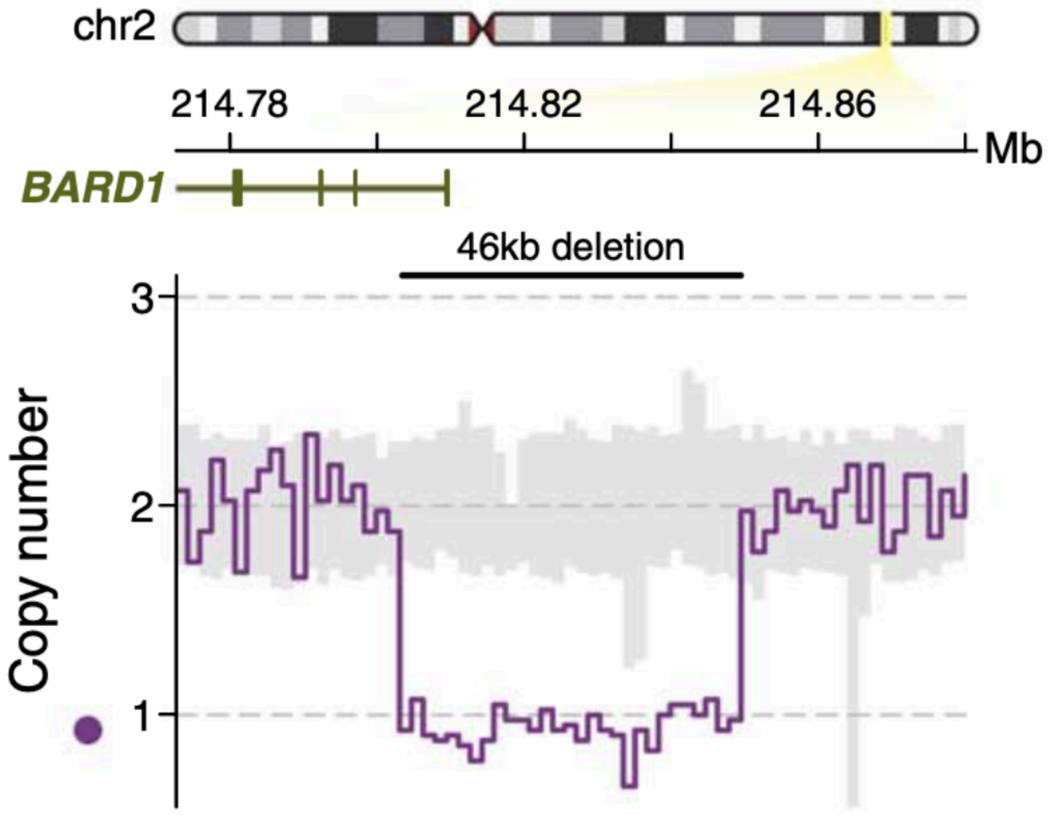


Iossifov et al. Nature 2014

Rare germline DNA copy number variants in childhood cancer patients



Gillani, et al. Science (2025)



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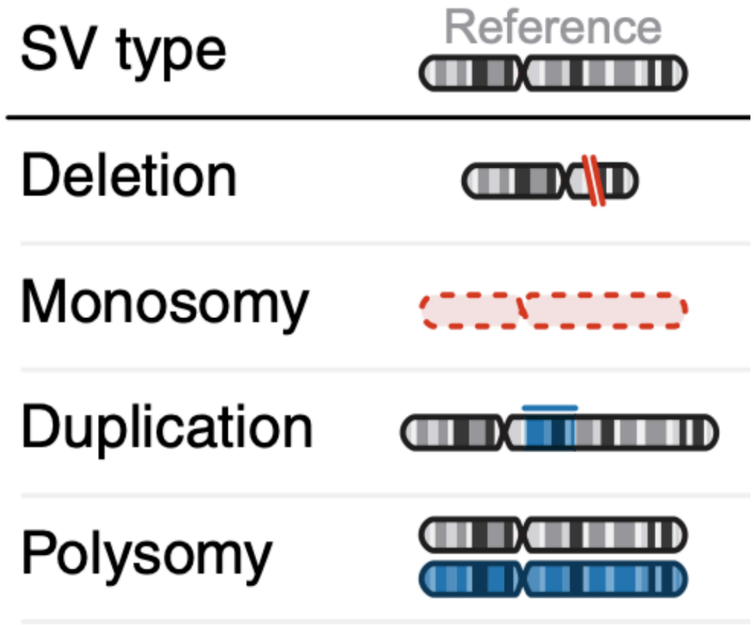

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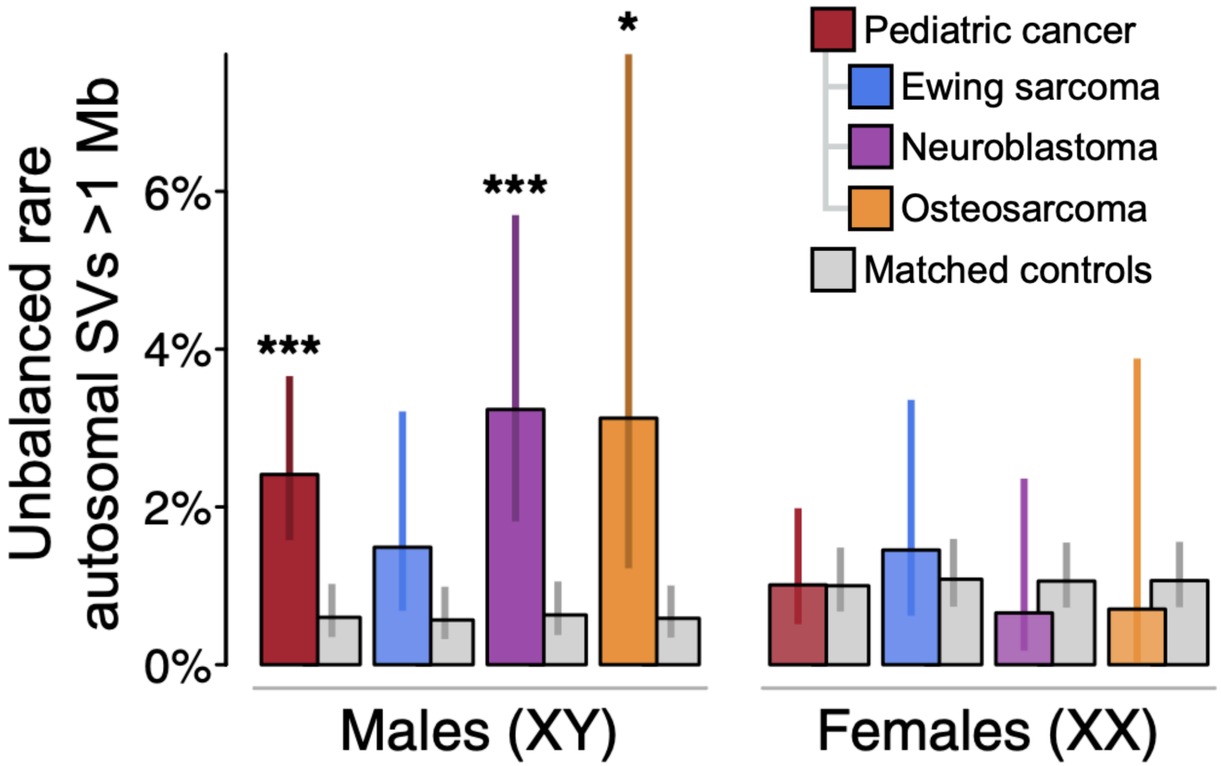
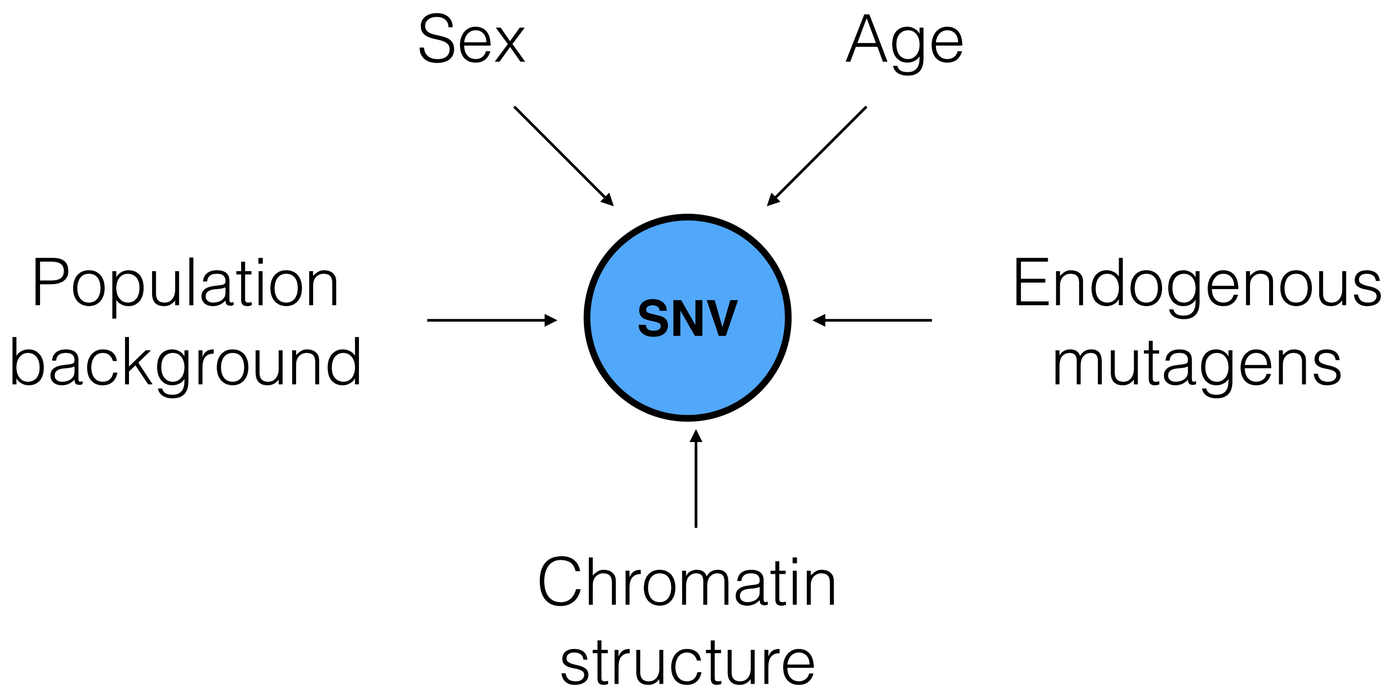
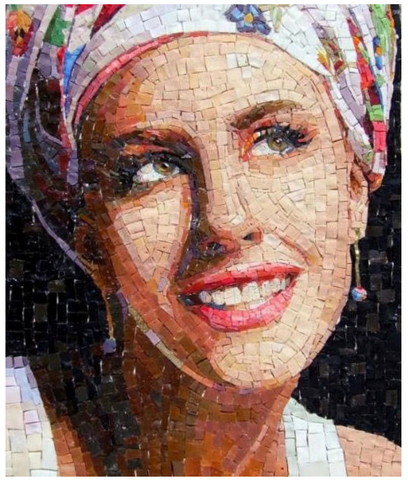


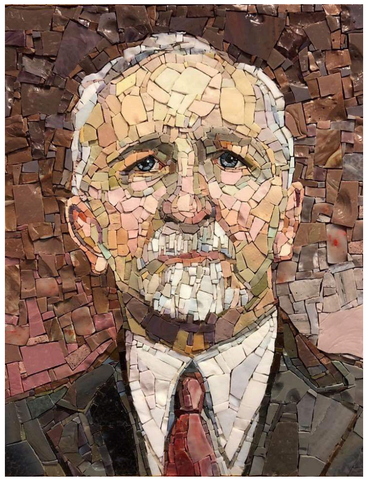
4-fold higher rate of rare and large copy number variants in males

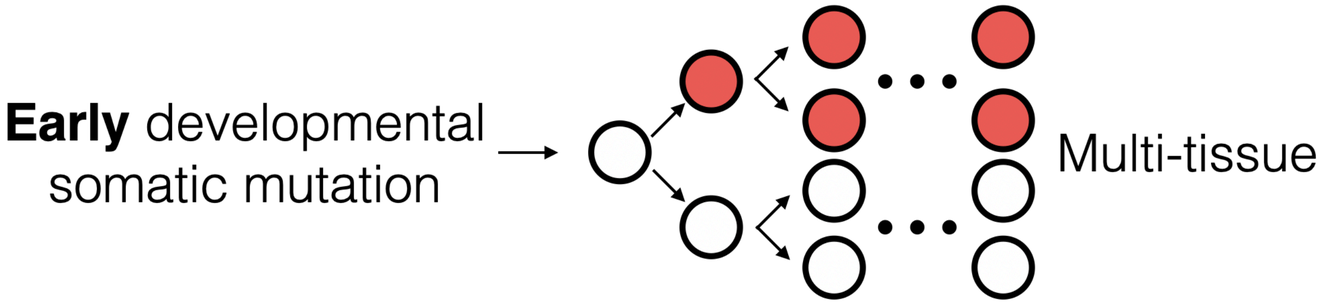
Endogenous factors that influence germline *de novo* mutation rates



The human body is a mosaic of many genomes



Images: Yulia Hanansen, Andjelka Radojevic, Nancie Mills Pipgras, Yury Malkov, Maria Vud

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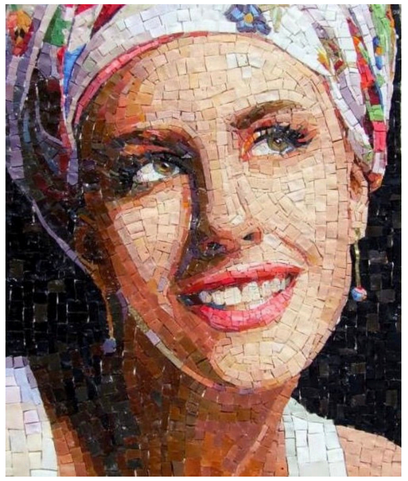
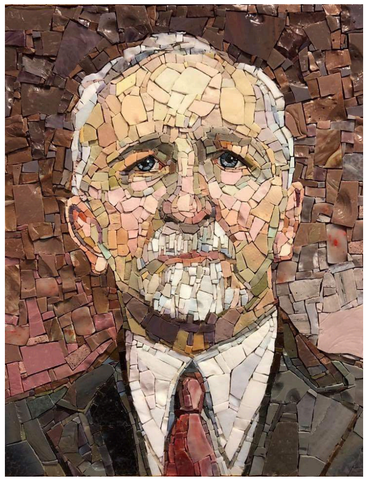
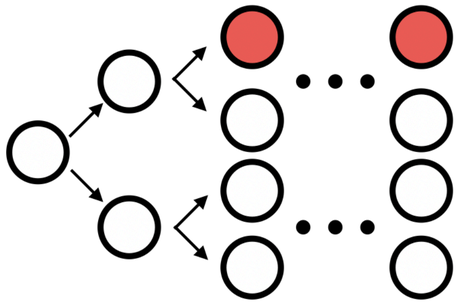


Early developmental somatic mutation



Cell type

Images: Yulia Hanansen, Andjelka Radojevic, Nancie Mills Pipgras, Yury Malkov, Maria Vud

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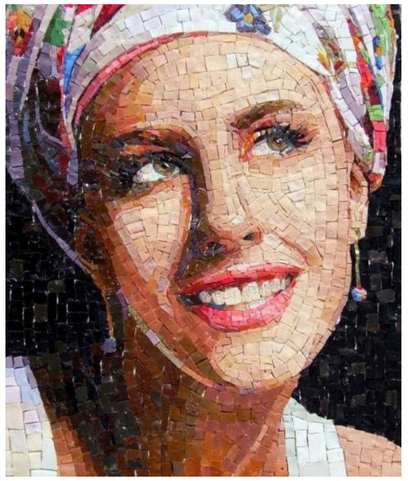
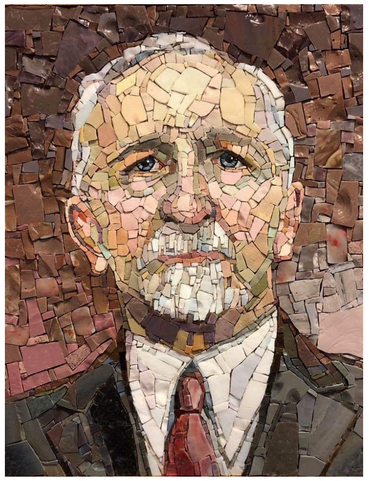
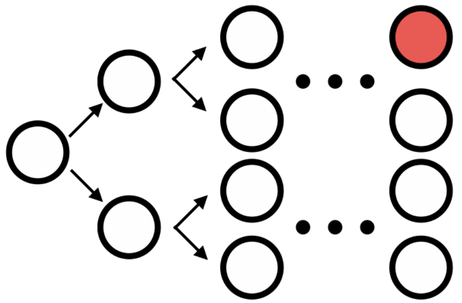


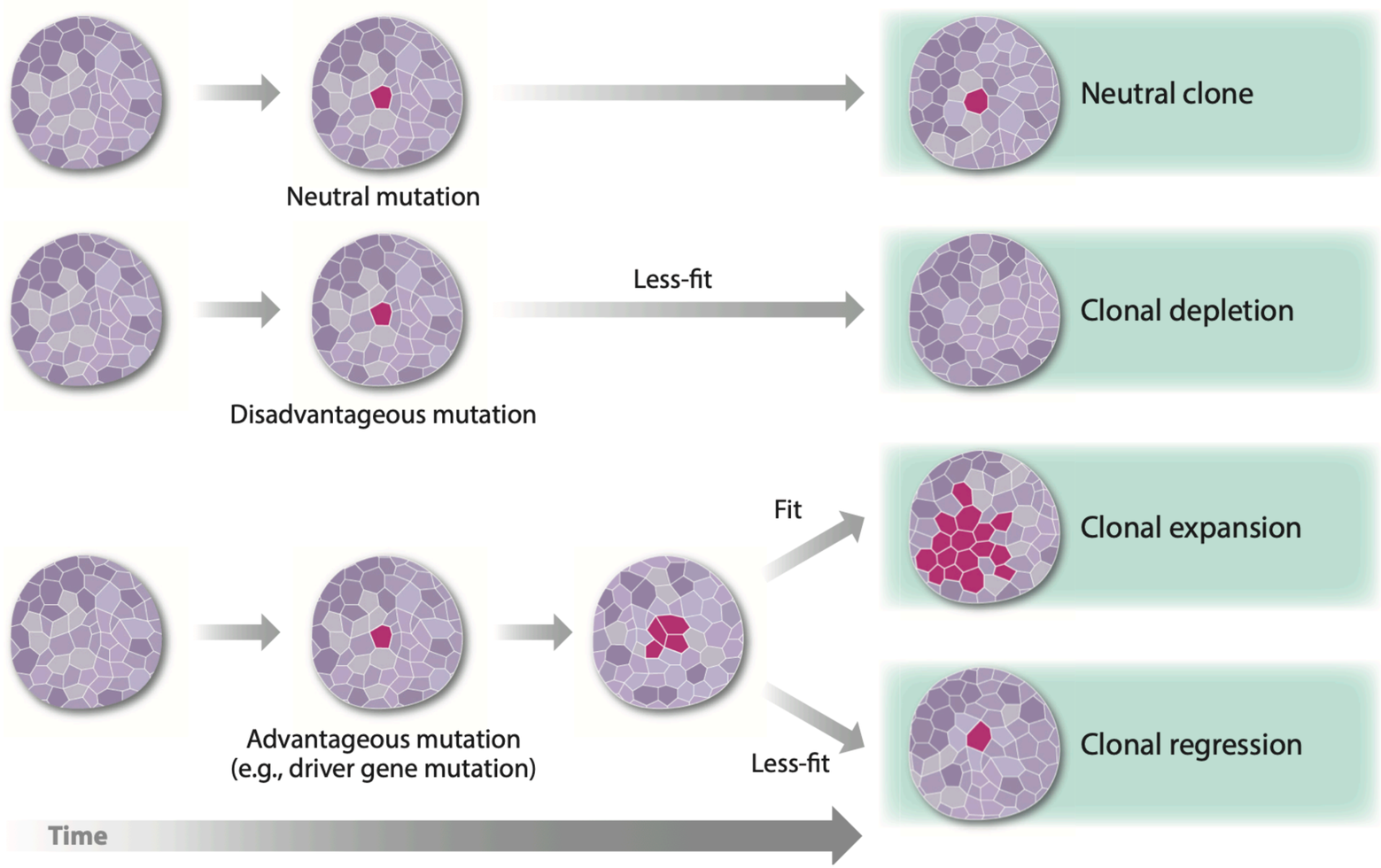
Ageing associated somatic mutations →



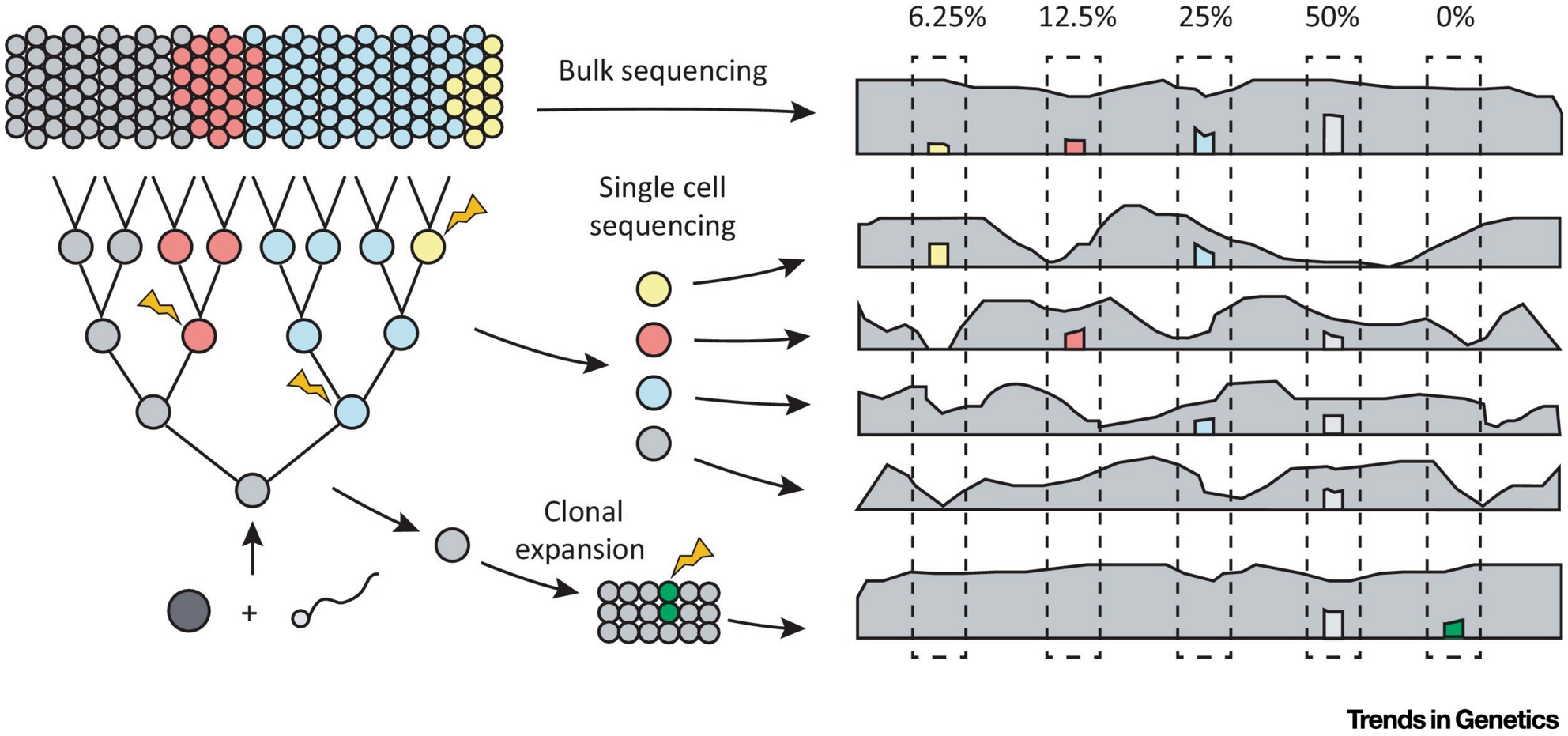
Single cell

Images: Yulia Hanansen, Andjelka Radojevic, Nancie Mills Pipgras, Yury Malkov, Maria Vud

Scenarios of clonal evolution

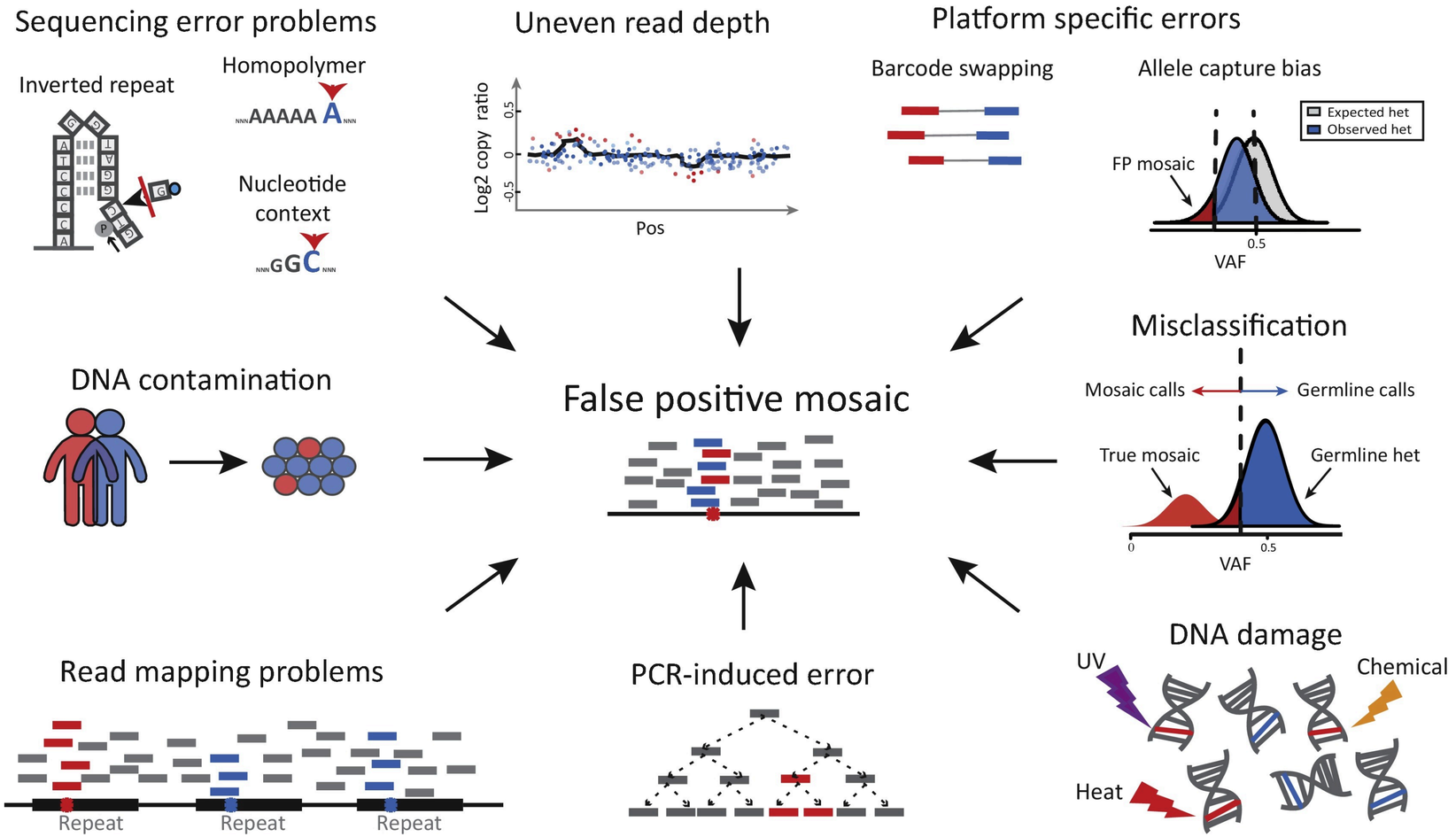


Detecting somatic mutations in normal cells



Dou et al. Trends Genet 2018

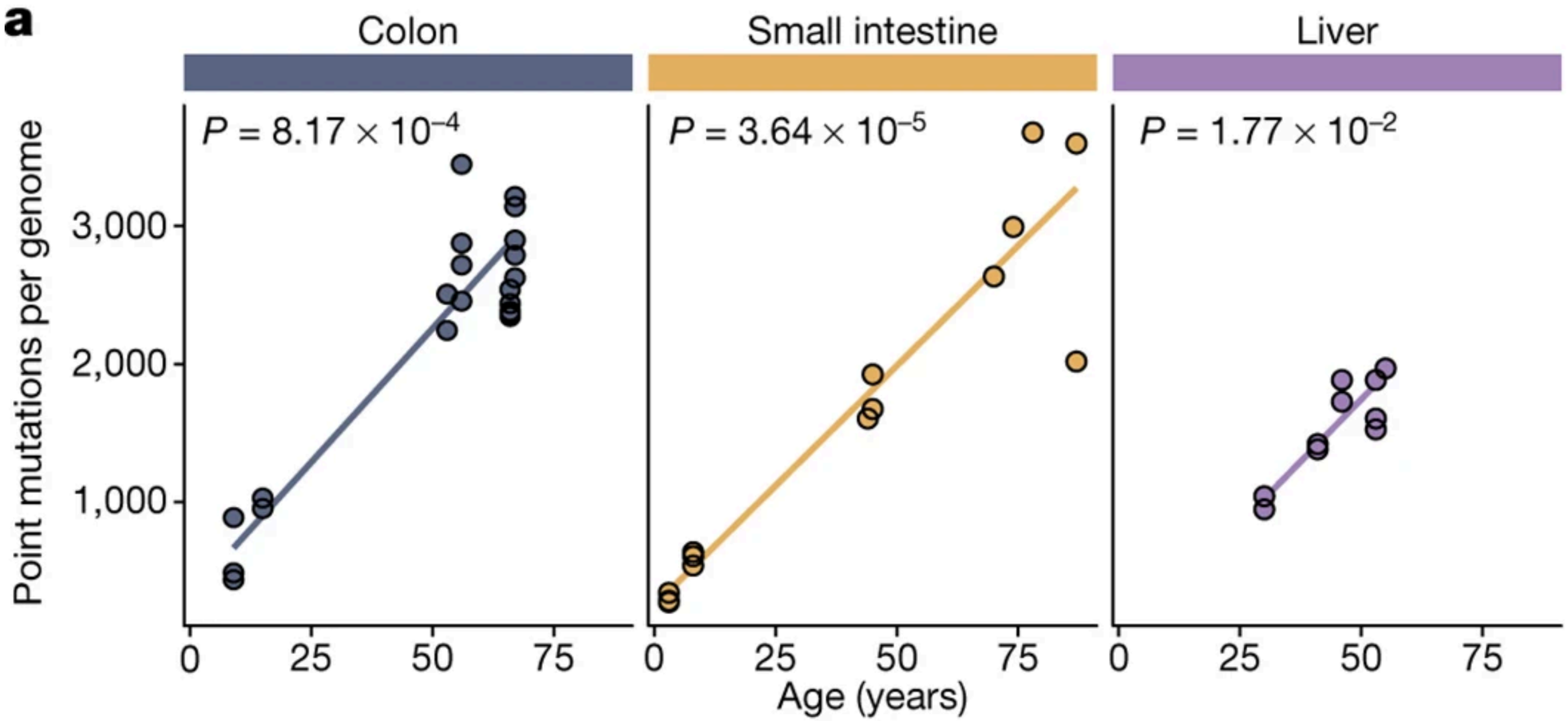
Sources of false positive somatic mutations in normal tissues



Trends in Genetics

Dou et al. Trends Genet 2018

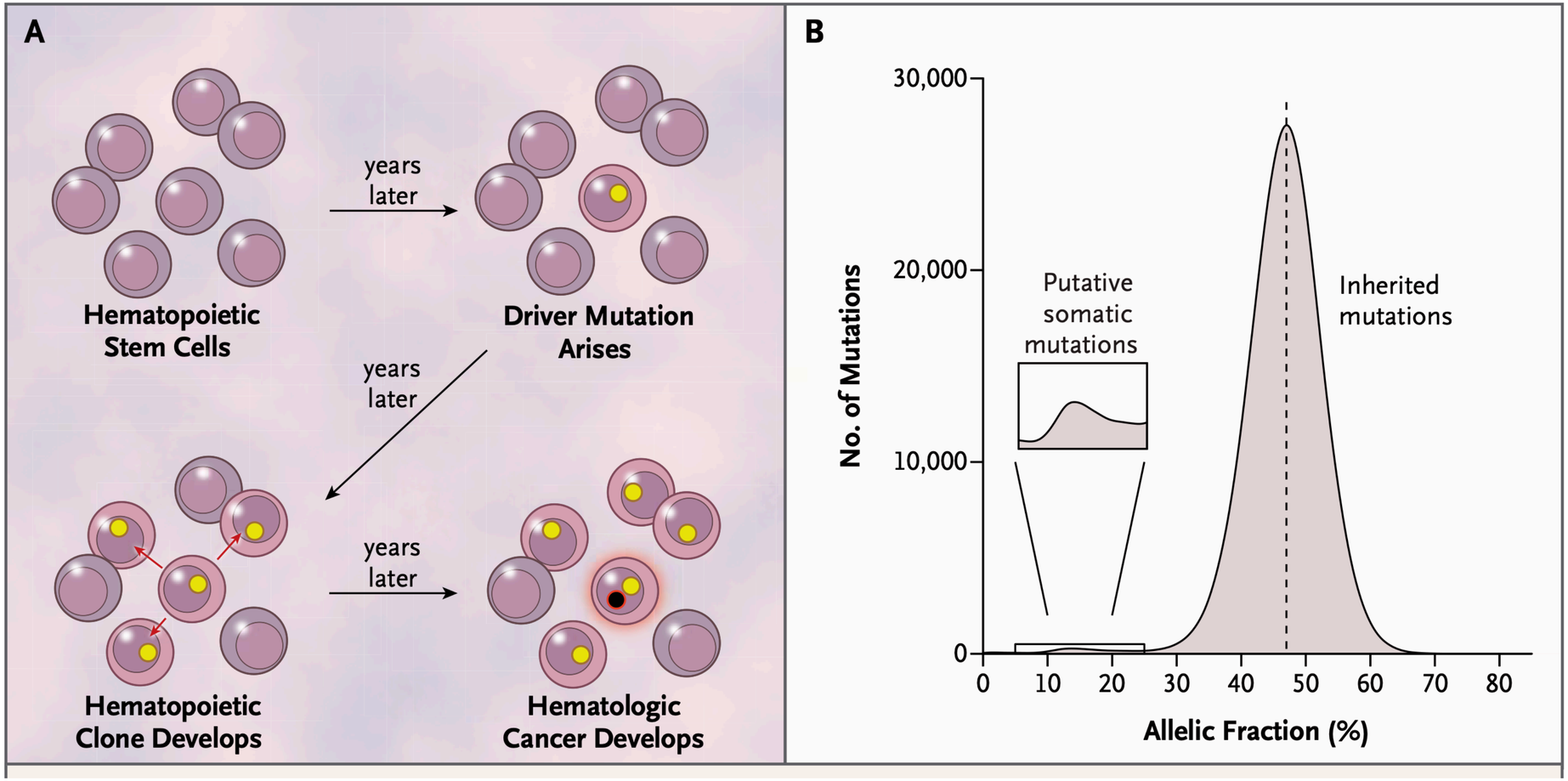
Clock-like accumulation of somatic mutations in adult stem cells



2,000-3,000 somatic mutations per stem cell at the age of 65 years

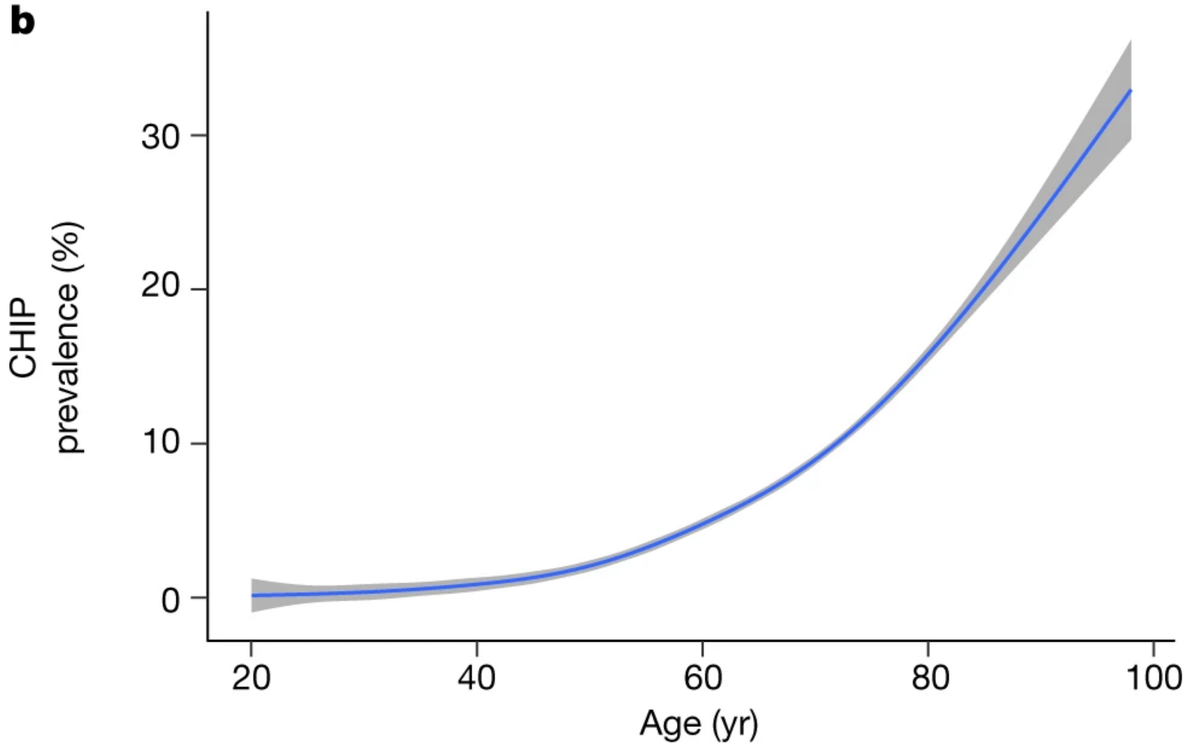
Blokzijl et al. *Nature* 2016

Clonal hematopoiesis
(blood cell production)



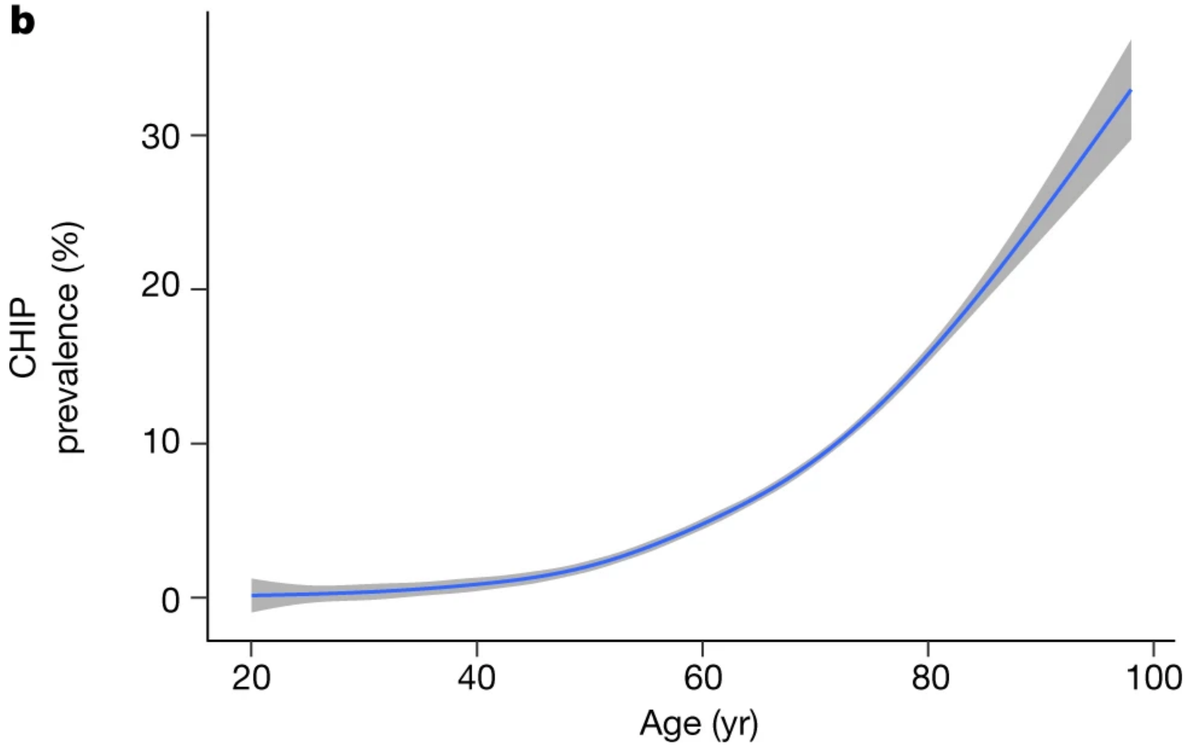
Genovese et al. NEJM 2014

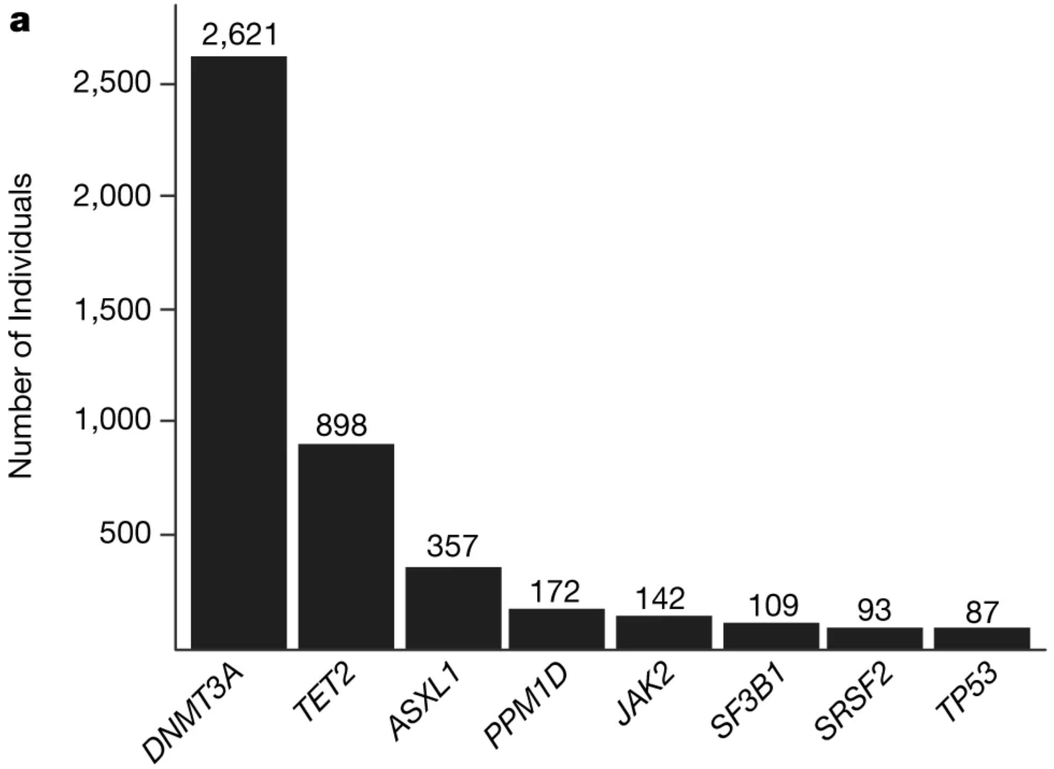
Age-associated clonal hematopoiesis



Bick et al. Nature 2020

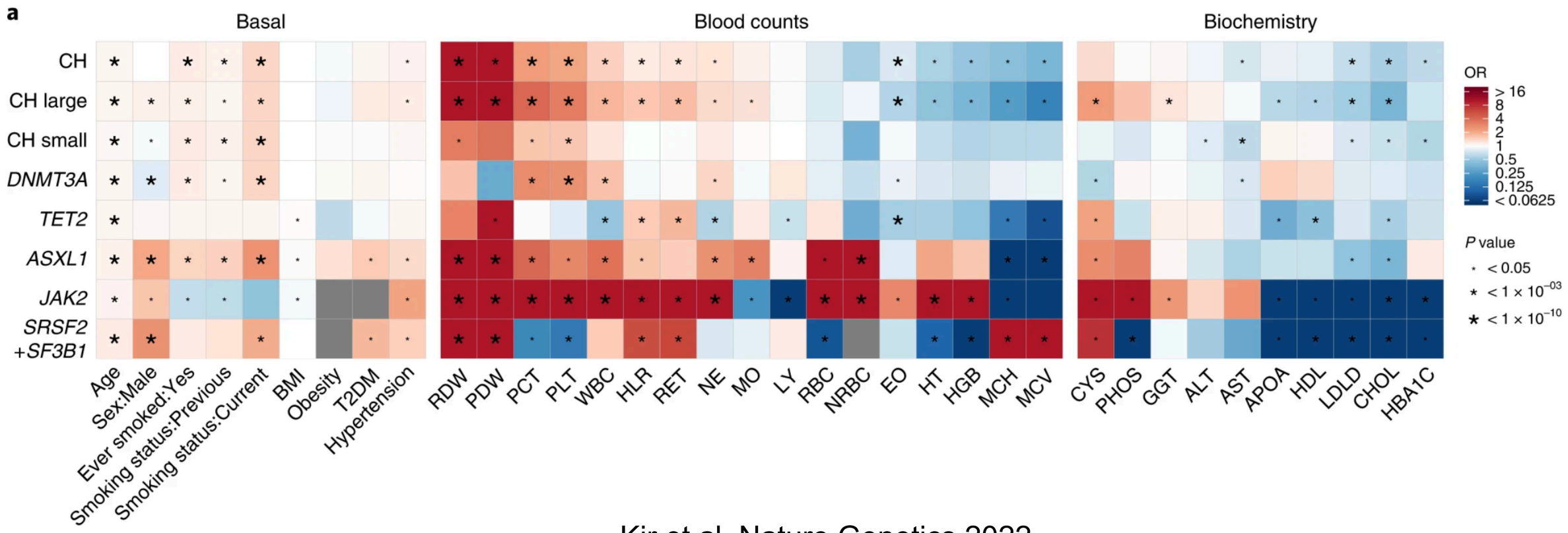
Age-associated clonal hematopoiesis





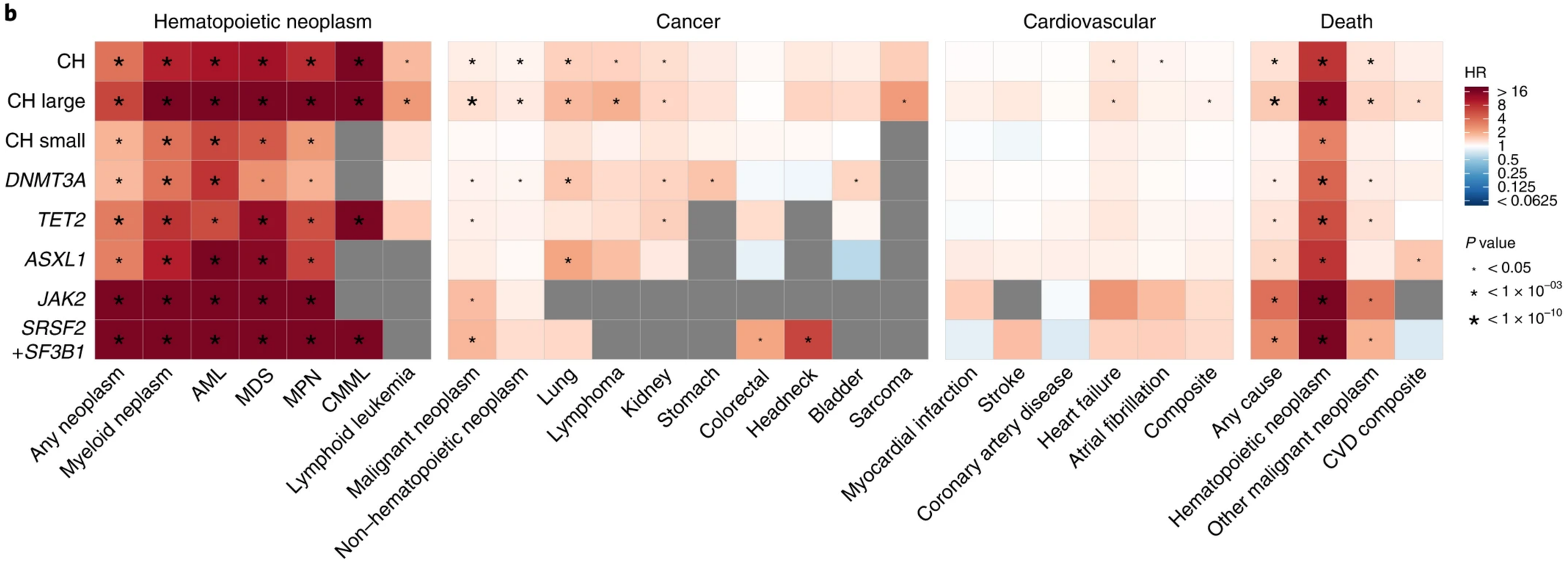
Bick et al. Nature 2020

Age-associated clonal hematopoiesis predisposes to hypertension and atypical blood counts



Kir et al. Nature Genetics 2022

Age-associated clonal hematopoiesis predisposes to blood and heart diseases



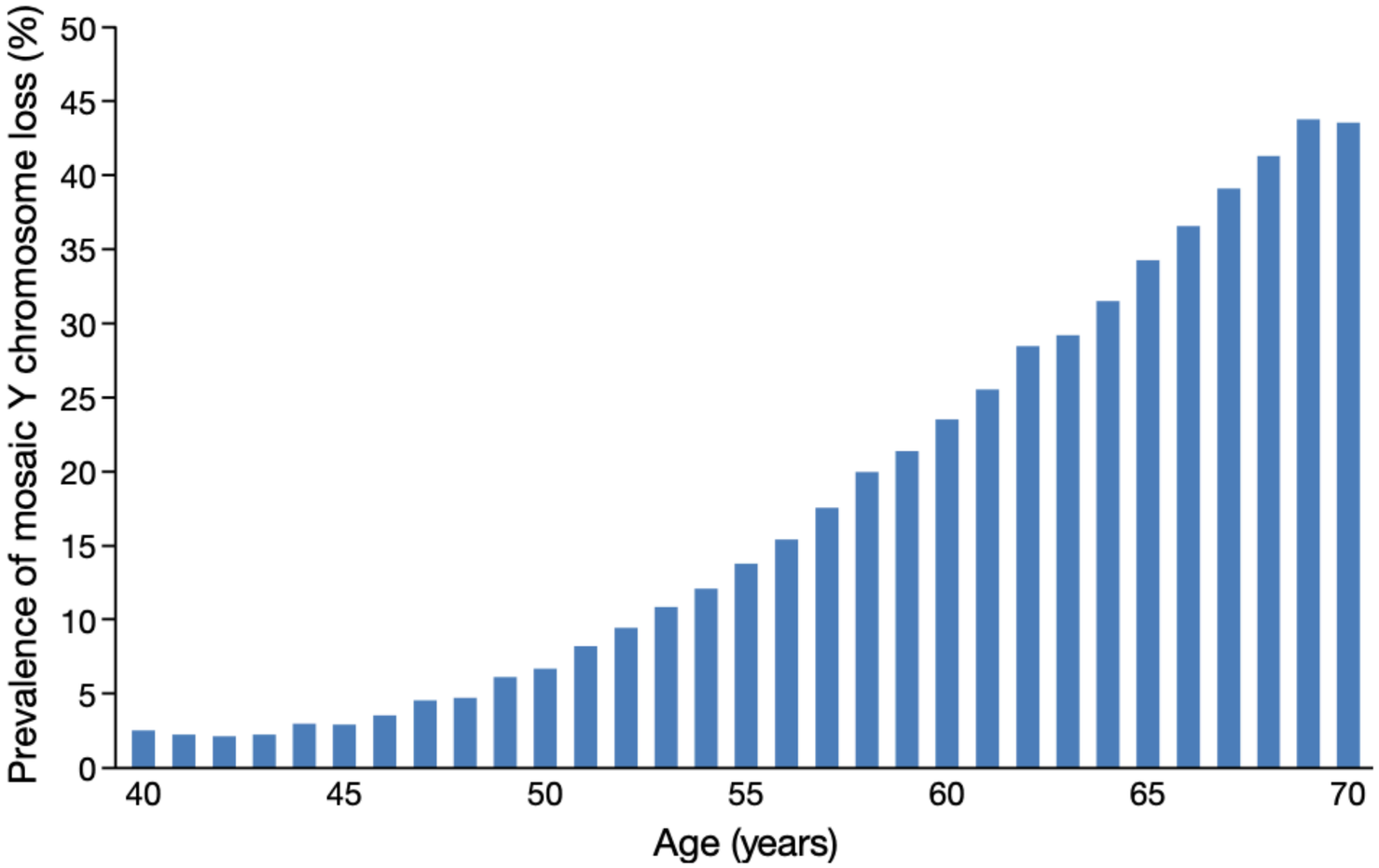
Kir et al. Nature Genetics 2022

Sex-biased clonal hematopoiesis

- Female-biased clonal hematopoiesis: DNMT3A- and GNB1-expanded HSCs
- Male-biased clonal hematopoiesis: PPM1D, TP53, JAK2, SF3B1, ASXL1, and SRSF2-expanded HSCs

Kir et al. Nature Genetics 2022

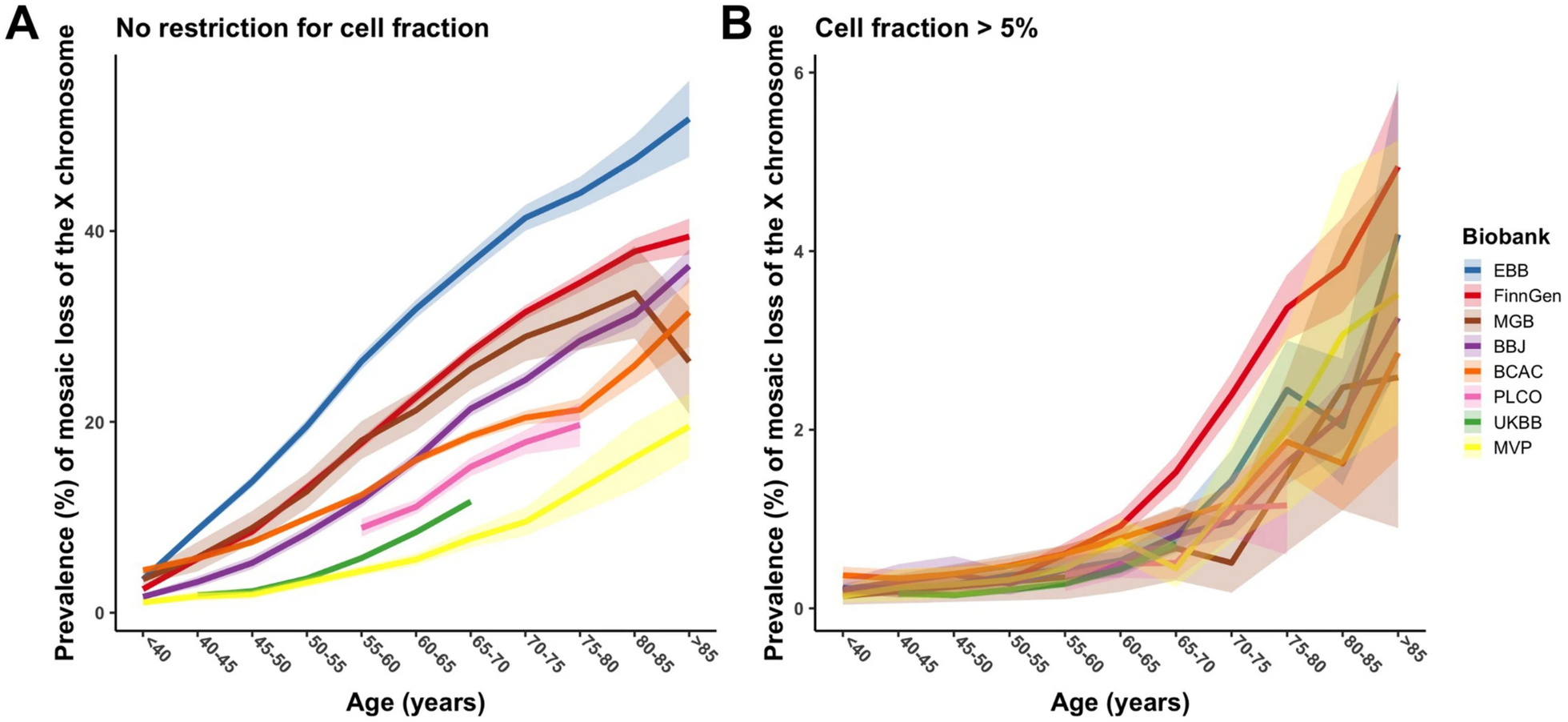
Ageing-associated loss of chromosome Y (LOY) in males



- **Known risk factors for mosaic LOY in blood cells in males**
  - Ageing
  - Smoking
- **Biomarker for diseases**
  - Cancer
  - Infections
  - Heart disease

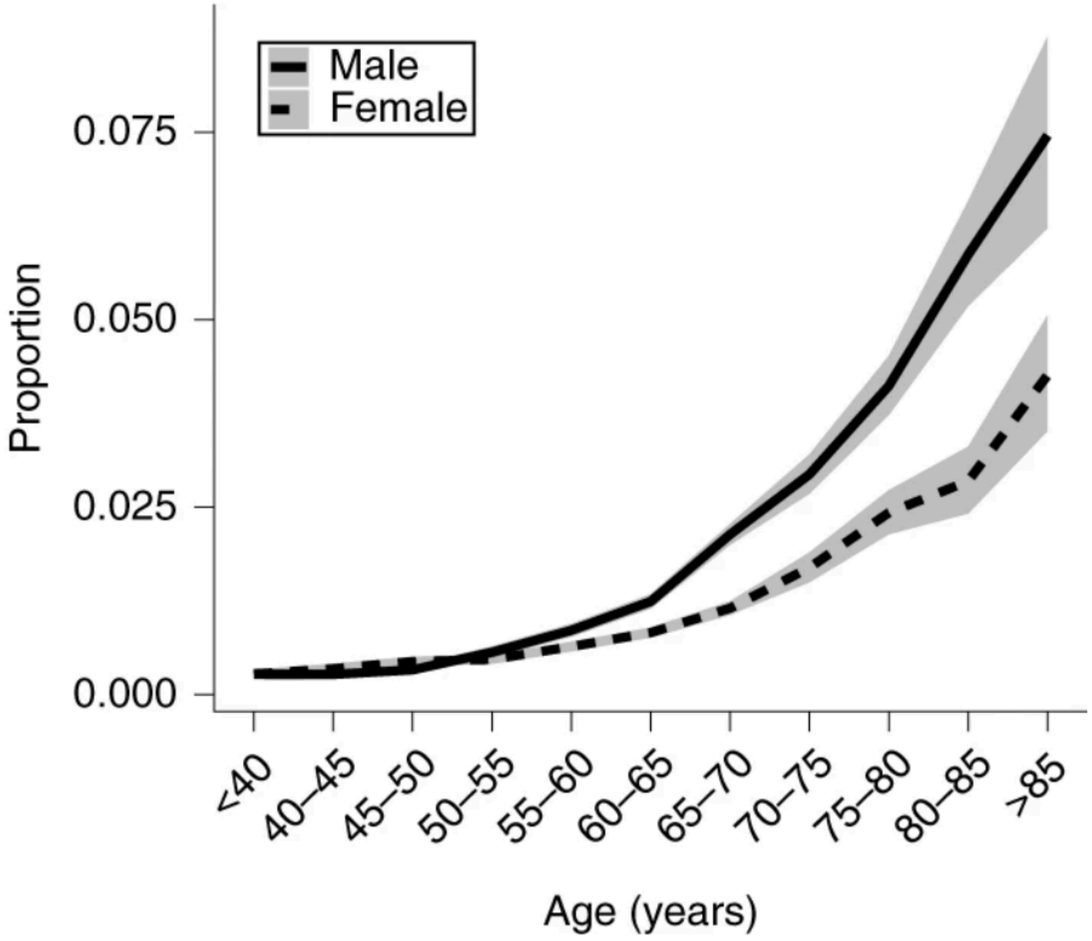
Thompson et al. Nature 2019

Ageing-associated loss of chromosome X (LOX) in females



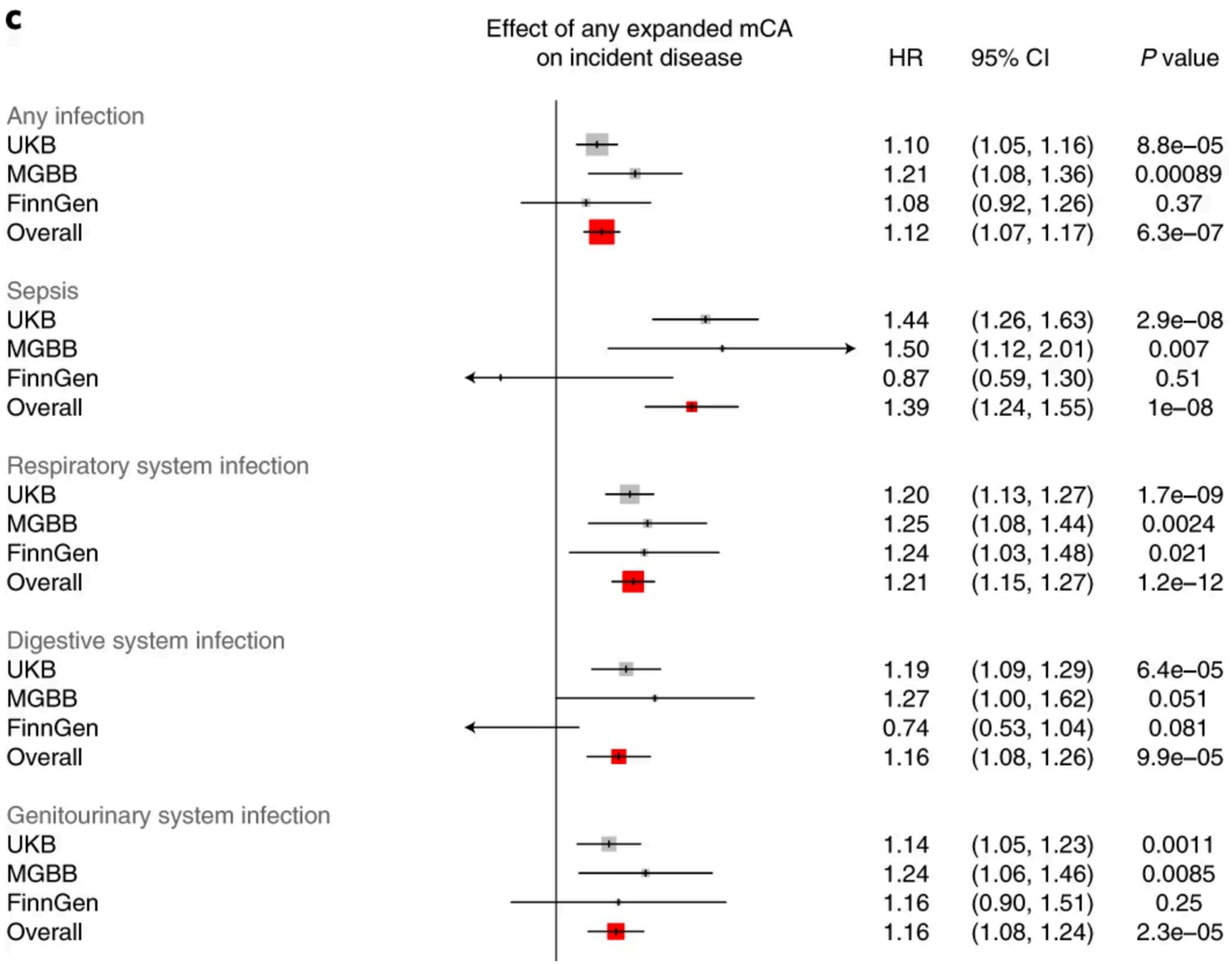
Liu et al. Nature 2024

Ageing- and sex-associated autosomal mosaic chromosomal alterations



Zekavat et al. Nature Medicine 2021

Mosaic chromosomal alterations and infections



Zekavat et al. Nature Medicine 2021

Mosaic chromosomal alterations and COVID-19 hospitalisation

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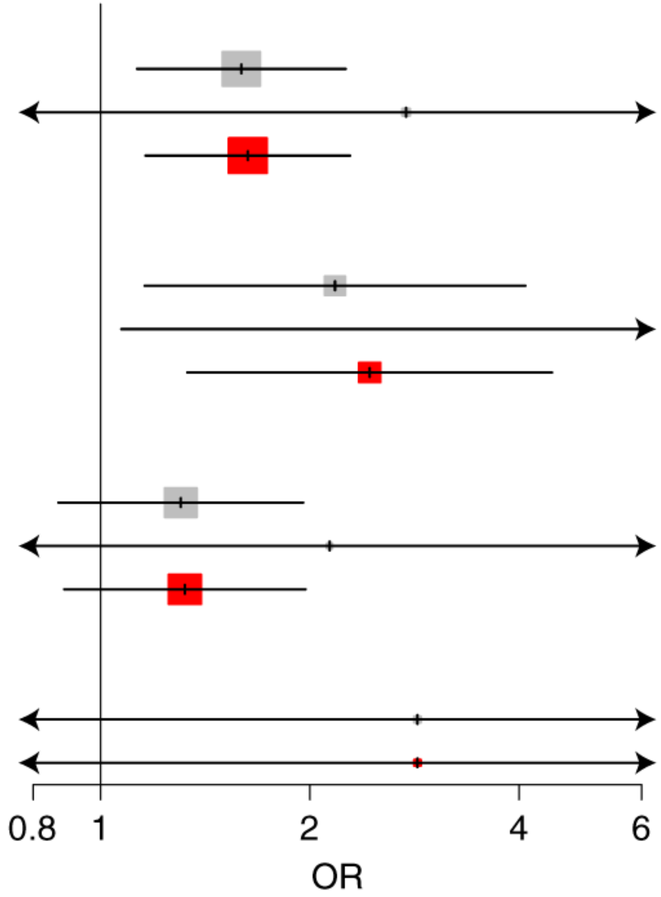
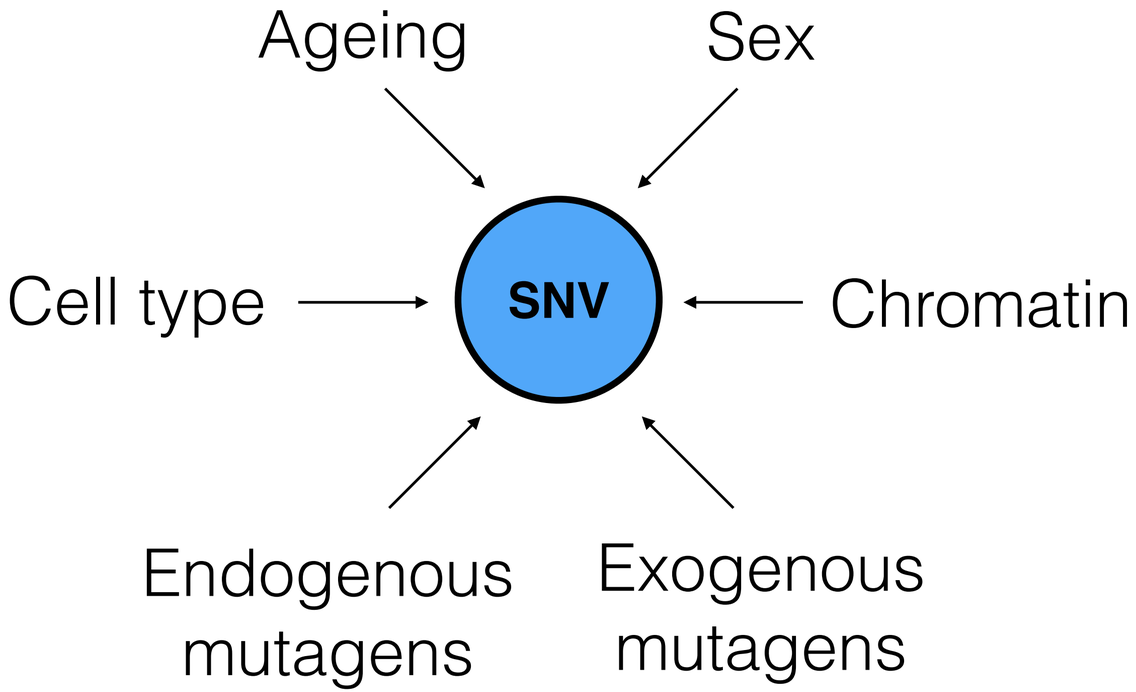


Effect of expanded mCAs on COVID-19 hospitalization	OR	95% CI	*P* value	Cases (*n*)	Controls (*n*)
All					
UKB	1.59	(1.13, 2.25)	0.0082	719	337,877
FinnGen	2.75	(0.50, 15.21)	0.25	14	66,584
Overall	1.63	(1.16, 2.28)	0.0048		
Autosomal					
UKB	2.17	(1.16, 4.08)	0.016	686	329,961
FinnGen	8.80	(1.07, 72.28)	0.043	13	63,934
Overall	2.44	(1.33, 4.46)	0.0038		
ChrY					
UKB	1.30	(0.87, 1.96)	0.2	385	143,825
FinnGen	2.14	(0.19, 23.54)	0.54	7	28,874
Overall	1.32	(0.89, 1.97)	0.17		
ChrX					
UKB	2.86	(0.40, 20.48)	0.3	324	191,661
Overall	2.86	(0.40, 20.48)	0.3		

Key contributors to somatic mutagenesis

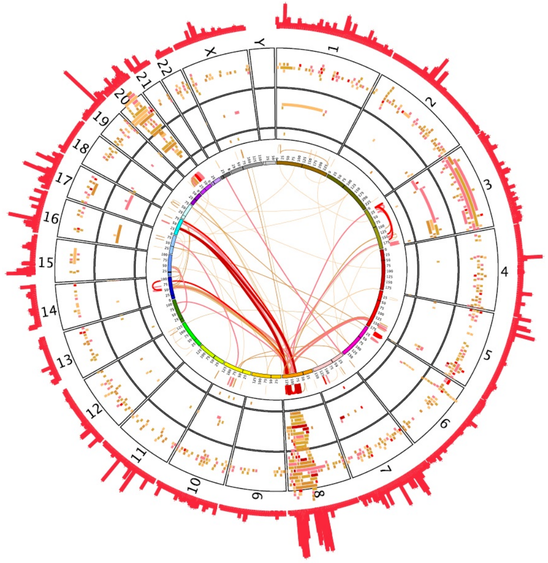


Genome-to-genome association studies to identify mechanisms of somatic mutagenesis

Population variation
(eg, SNPs)

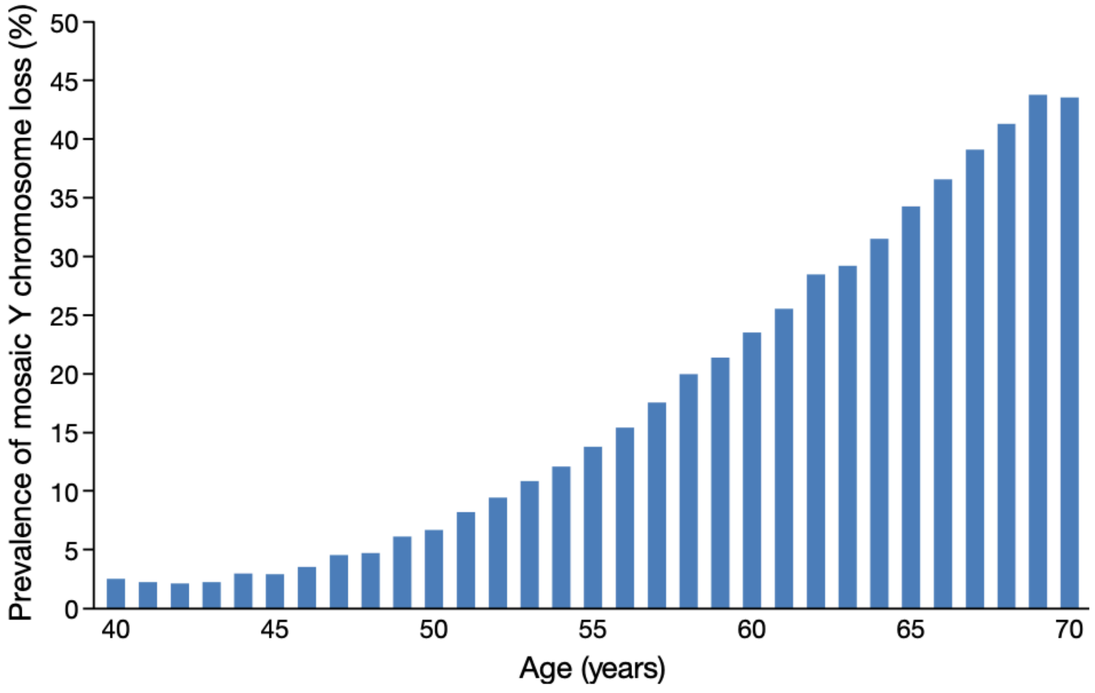
Genome-wide association study (GWAS) based on logistic or linear regression

Mutational phenotypes
(eg, loss of Y in blood cells)



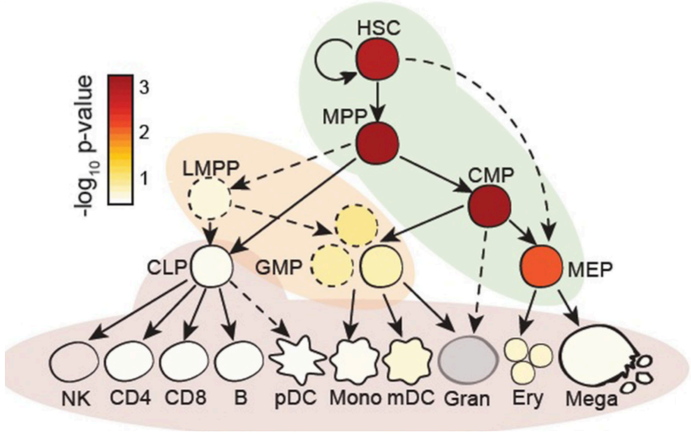
Genetic predisposition to loss of Y in males

GWAS of LOY with 85,000 male participants
156 common variants predispose to LOY
LOY heritability is estimated at 32%

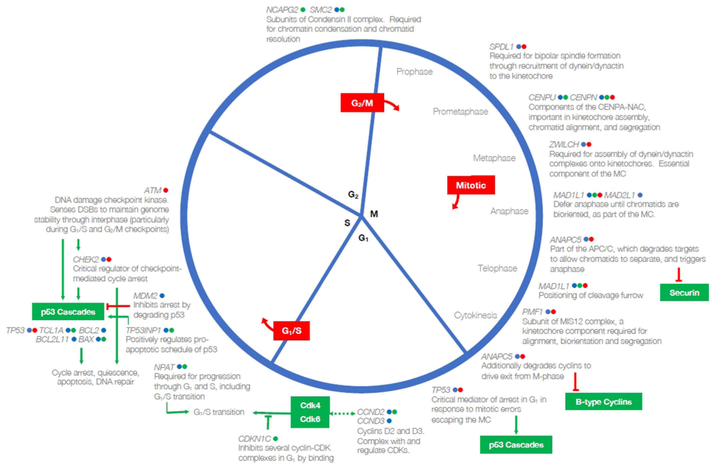


Thompson et al. *Nature* 2019

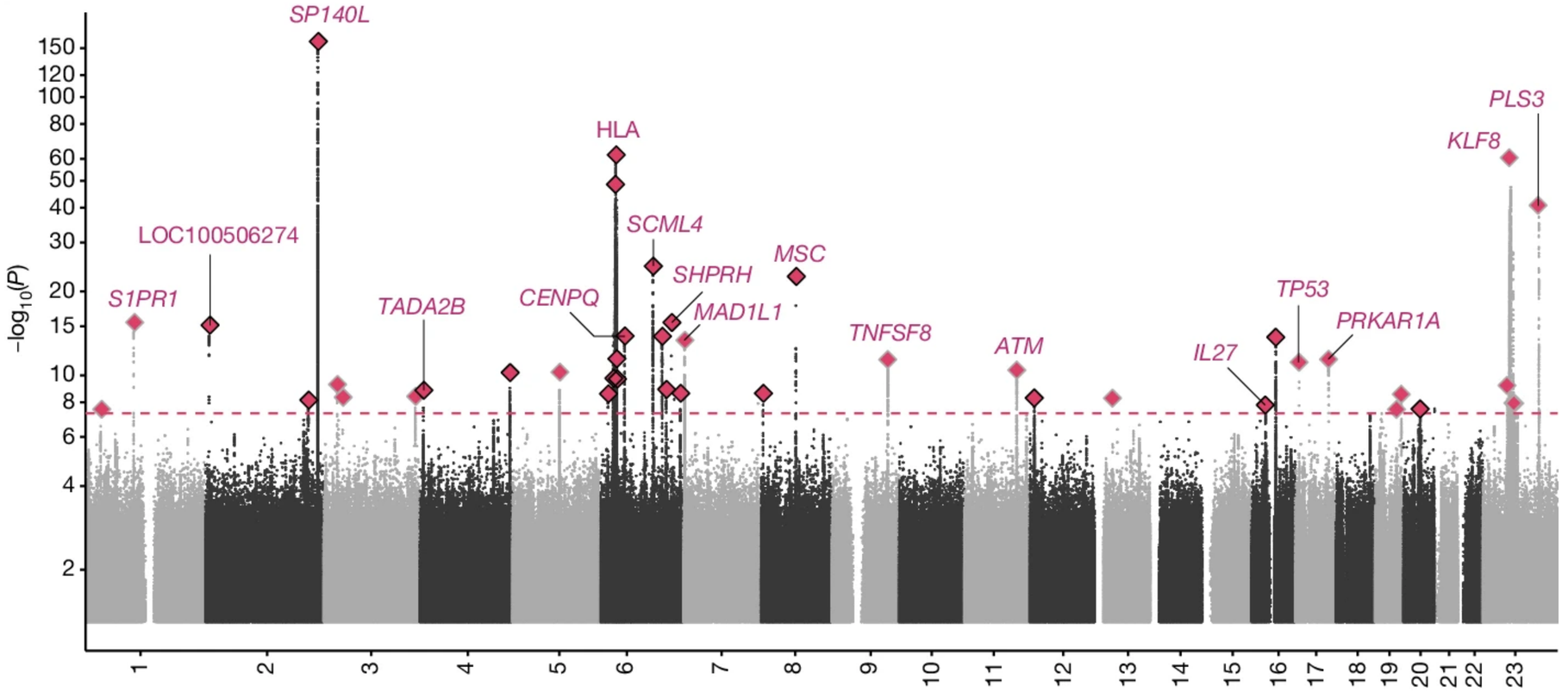
LOY risk variants affect HSC/HPCs



LOY risk are close to cell cycle genes



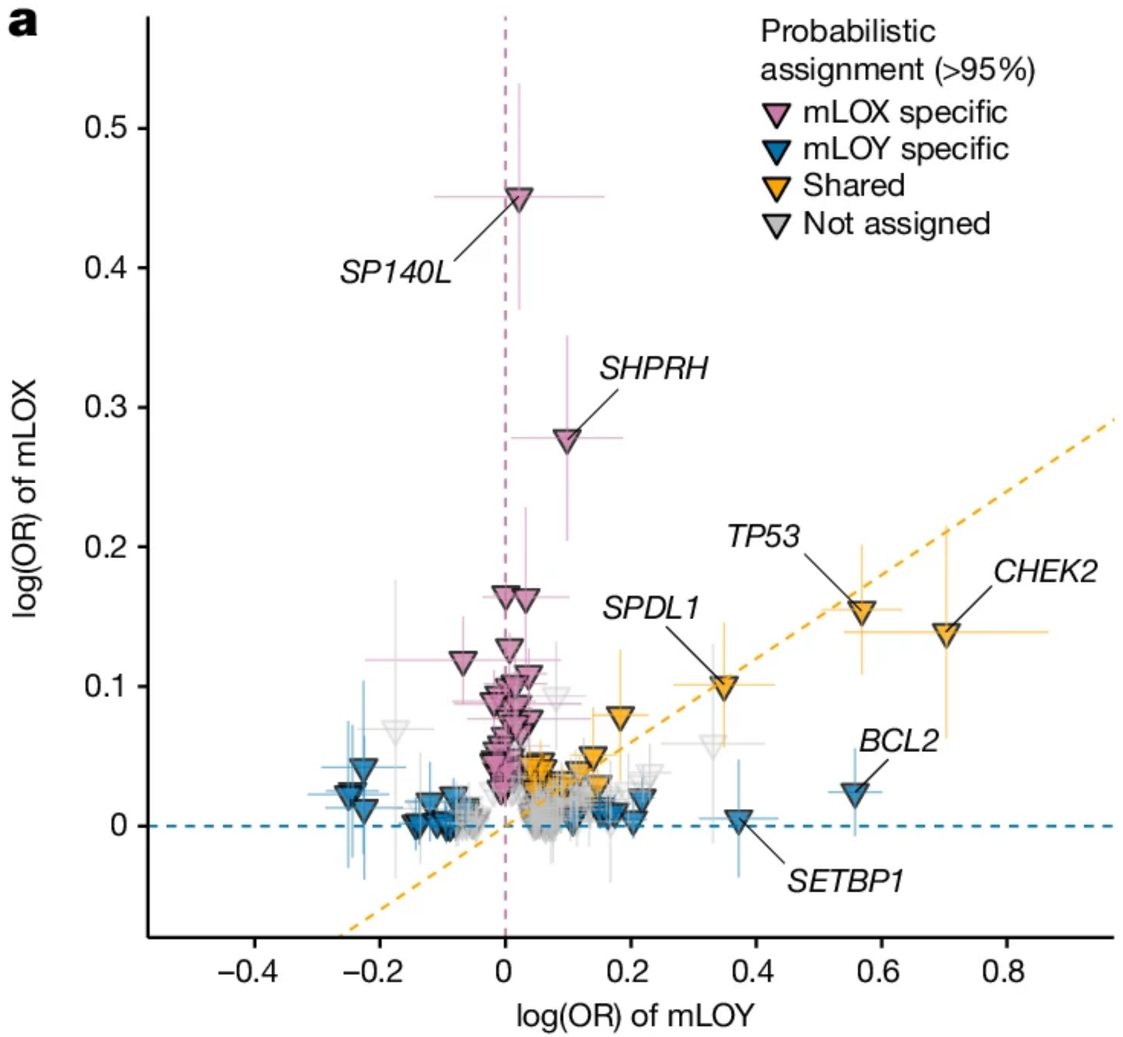
Genetic predisposition to loss of X in females



GWAS for LOX with >800,000 female study participants
56 common variants predispose to loss of X in females
Association with cancer predisposition and autoimmune disease

Liu et al. *Nature* 2024

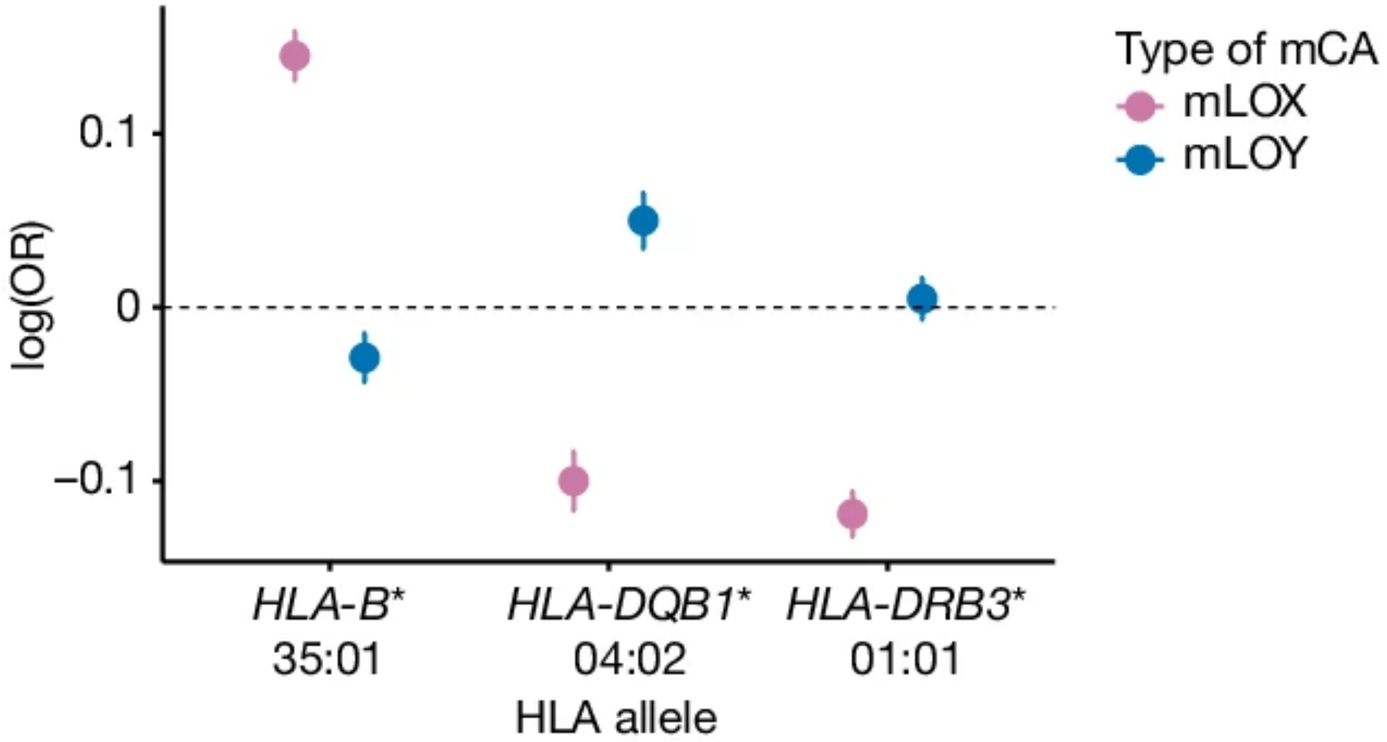
Shared and distinct genetic architecture of loss of X (LOX) and loss of Y (LOY)



OR = SNP effect size

Liu et al. *Nature* 2024

Shared and distinct genetic architecture of loss of X (LOX) and loss of Y (LOY)

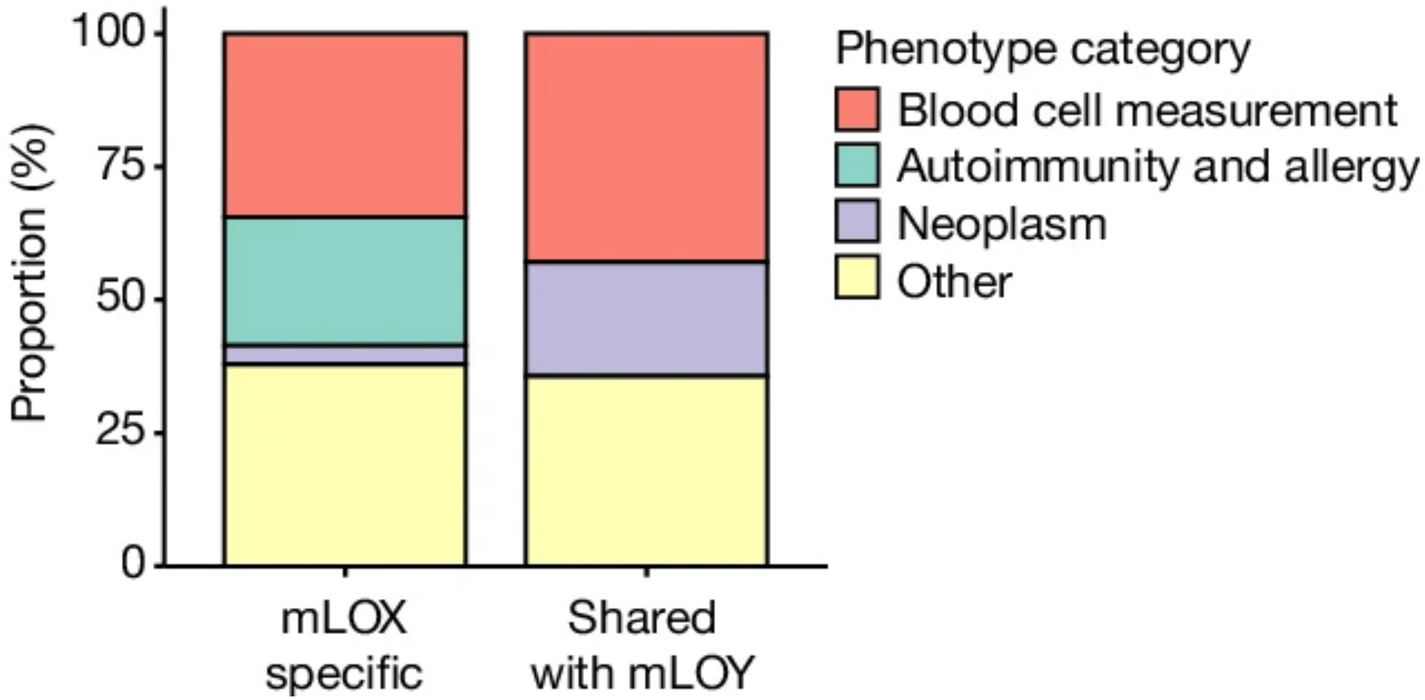


HLA-B*35:01 —> higher risk of mLOX in females, yet not risk for mLOY in males

HLA-B*35:01 —> higher risk of chronic thyroiditis (Hashimoto disease)

Liu et al. *Nature* 2024

Shared and distinct genetic architecture of loss of X (LOX) and loss of Y (LOY)



mLOX-specific genetic variants —> increased risk of autoimmunity and allergy

SmLOX/mLOY genetic variants —> increased risk of cancer

OR = SNP effect size

Liu et al. *Nature* 2024