Sperm sequencing reveals extensive positive selection in the male germline

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Sperm sequencing reveals extensive positive selection in the male germline

Matthew D. C. Neville, Andrew R. J. Lawson, Rashesh Sanghvi, Federico Abascal, My H. Pham, Alex Cagan, Pantelis A. Nicola, Tetyana Bayzetinova, Adrian Baez-Ortega, Kirsty Roberts, Stefanie V. Lensing, Sara Widaa, Raul E. Alcantara, María Paz García, Sam Wadge, Michael R. Stratton, Peter J. Campbell, Kerrin Small, Iñigo Martincorena, Matthew E. Hurles & Raheleh Rahbari

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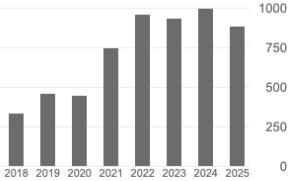

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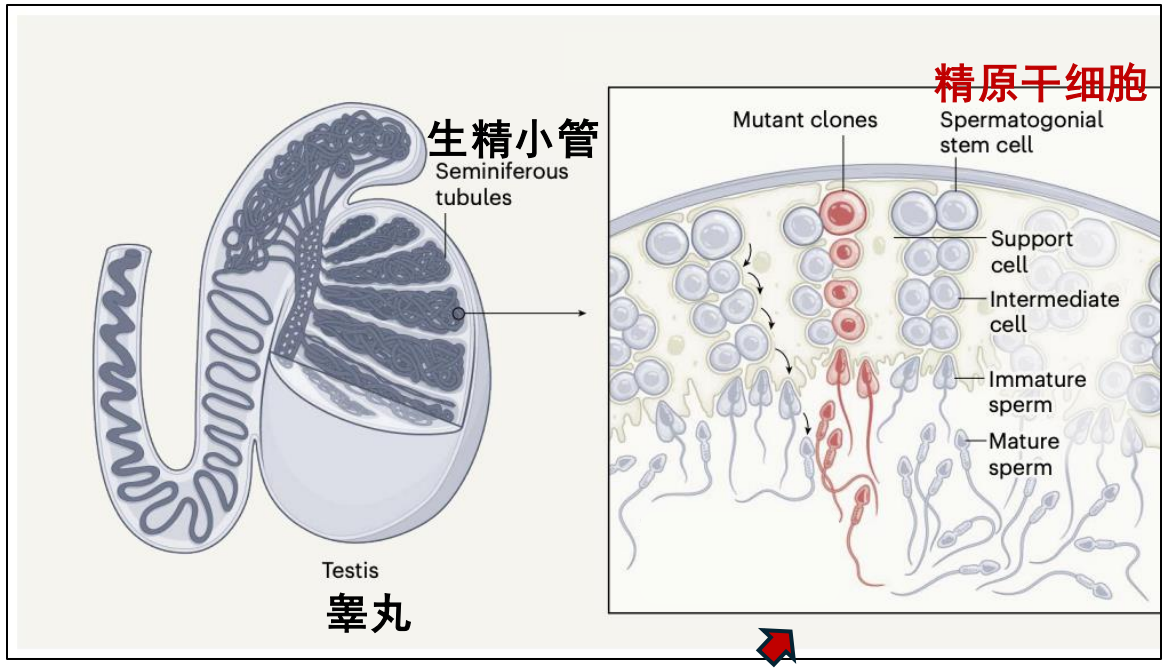
Background



"Selfish" Clonal Expansion

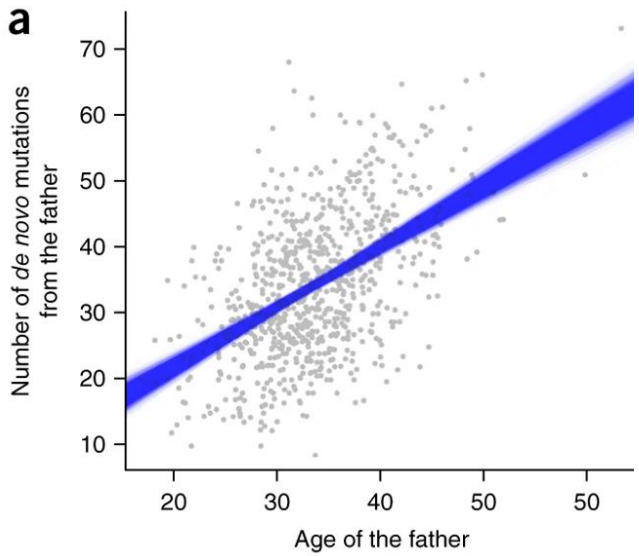
- **Unique niche of spermatogonial stem cells**

a. The only adult proliferating cells transmitting genetic info to offspring.

b. Lowest mutation rate (5-20x lower than somatic cells).

c. High proliferation pressure: Produce 150–275 million sperm/day.

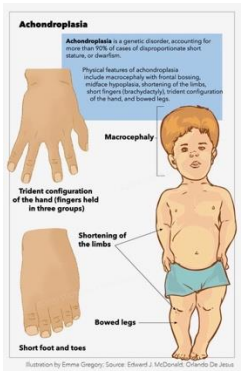
- **Mutation burden increases with age**



(Goldmann et al., 2016) *Nature genetics*

- **"Paternal age effect" (PAE) disorders** more common in the children of older fathers

Apert syndrome



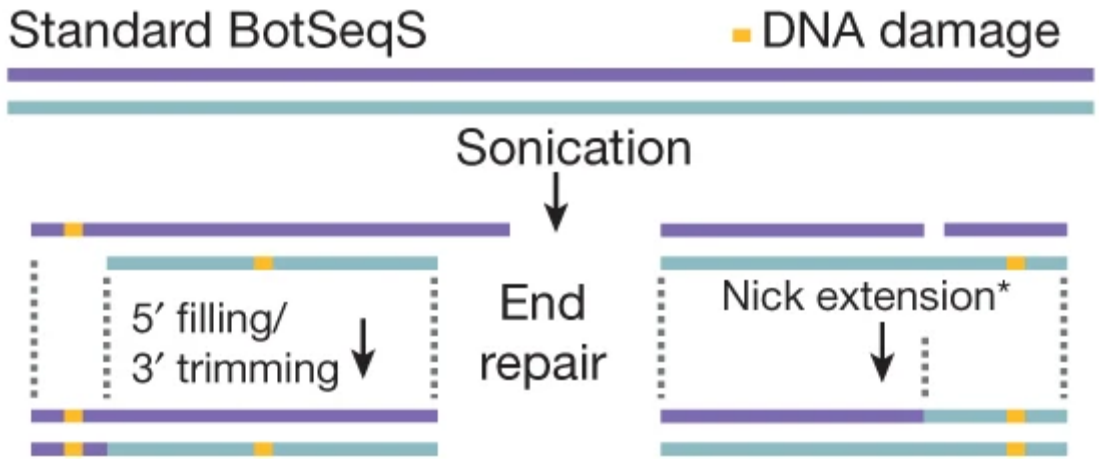
Achondroplasia

Crouzon syndrome

Background

■ Technical limitations

- low mutation rate of testis and sperm
- polyclonality 多克隆性

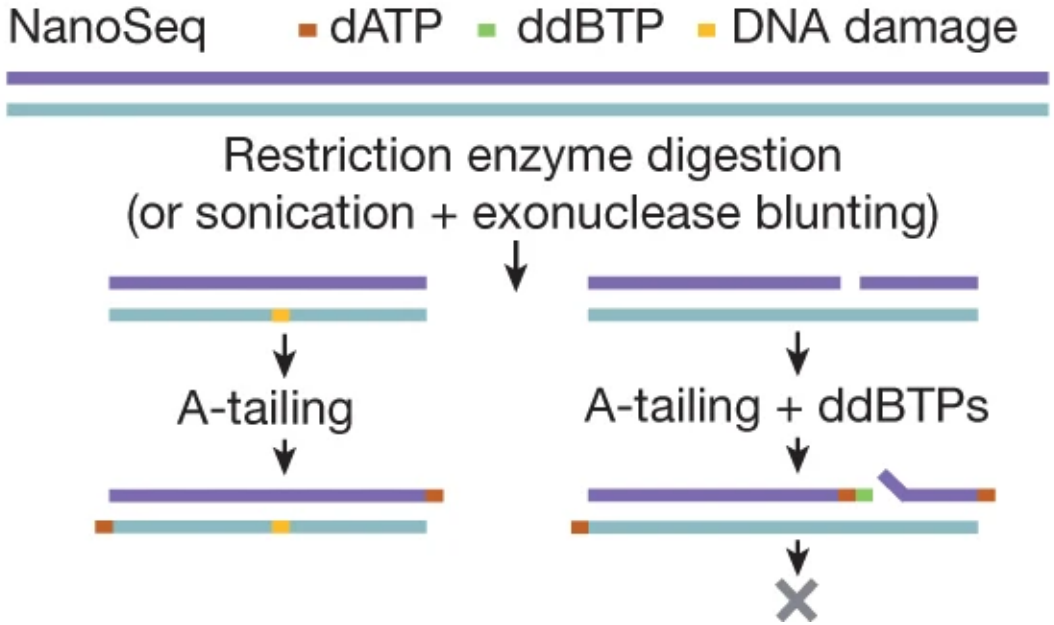


Errors introduced and NOT corrected

■ Error-corrected duplex DNA sequencing

- detect mutations at single-molecule resolution
- an error rate of <5 × 10^{-9} per base pair

Accurate estimation of mutation burden in sperm



Both strands sequenced → Errors filtered out

(Abascal et al., 2021) *Nature*

Main questions

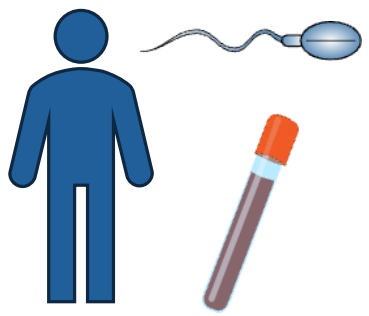
- **1. The scope:**

  How extensive is positive selection in the male germline beyond known hotspots?

- **2. The impact:**

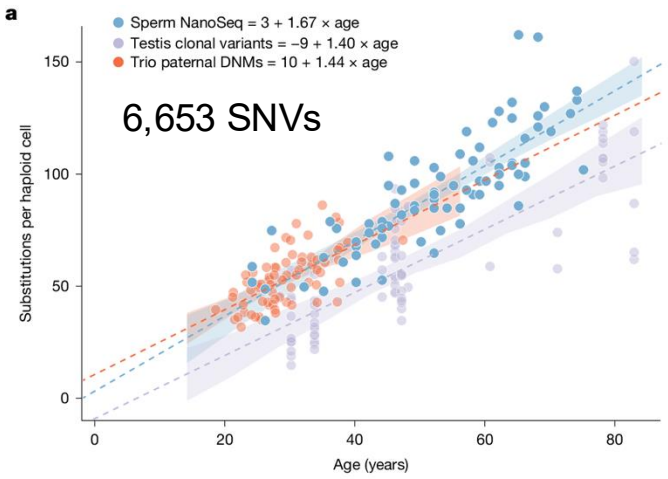
  How does this selection impact human health?

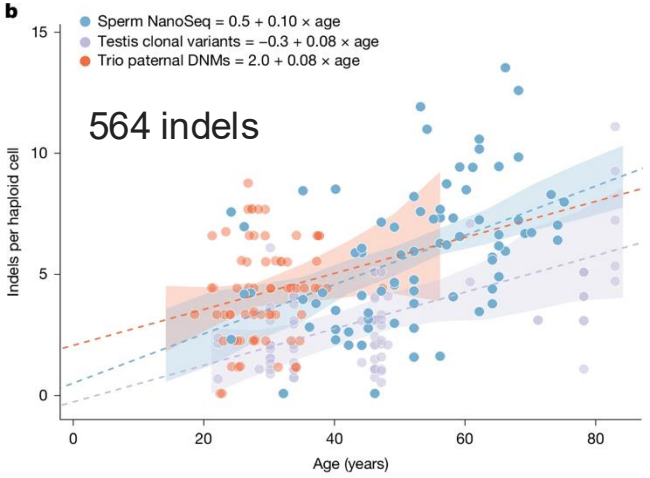
Mutational burden



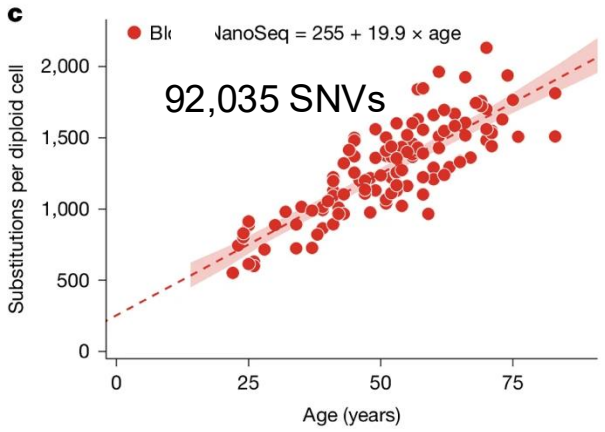
- Aged 24–75
- Whole-genome NanoSeq
- Sperm: 3.7 duplex coverage
- Blood: 4.3 duplex coverage

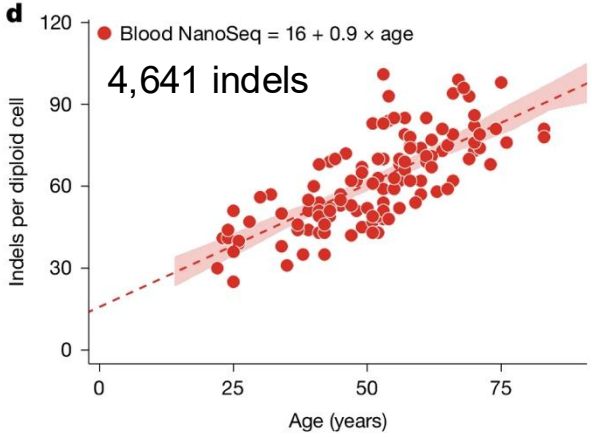
Sperm 1.67 substitutions per year per haploid genome

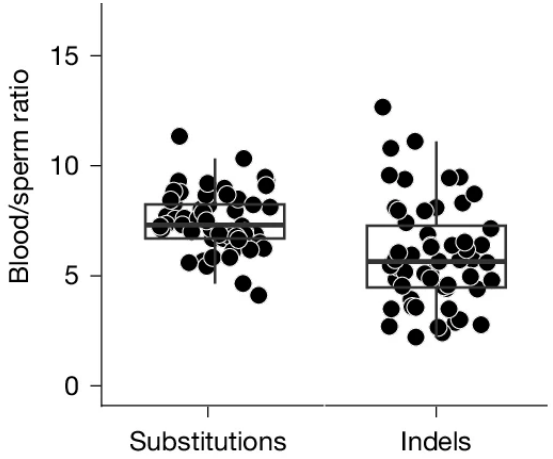




Blood

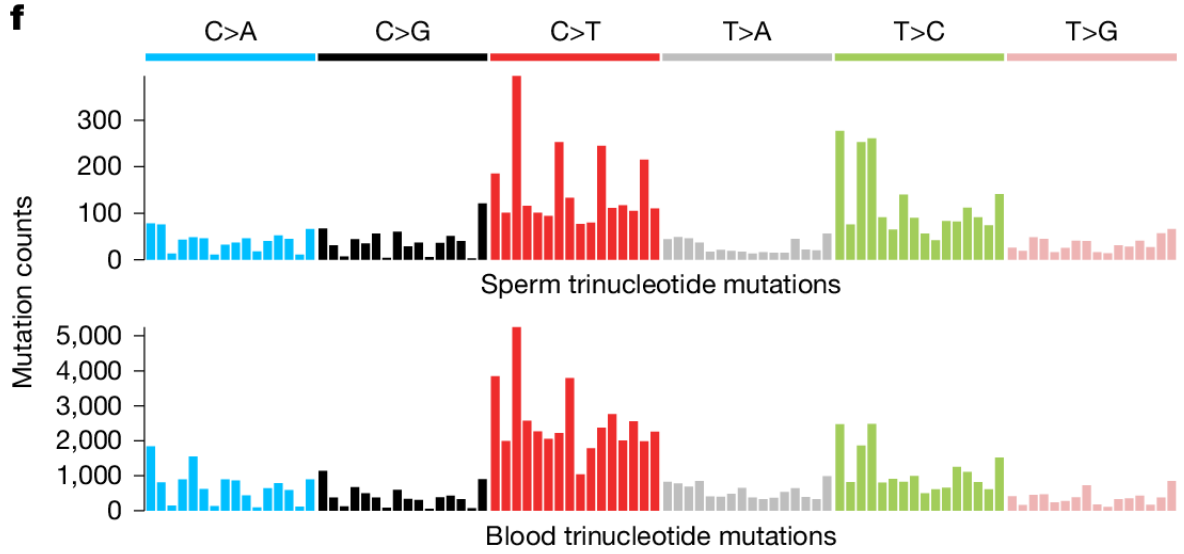






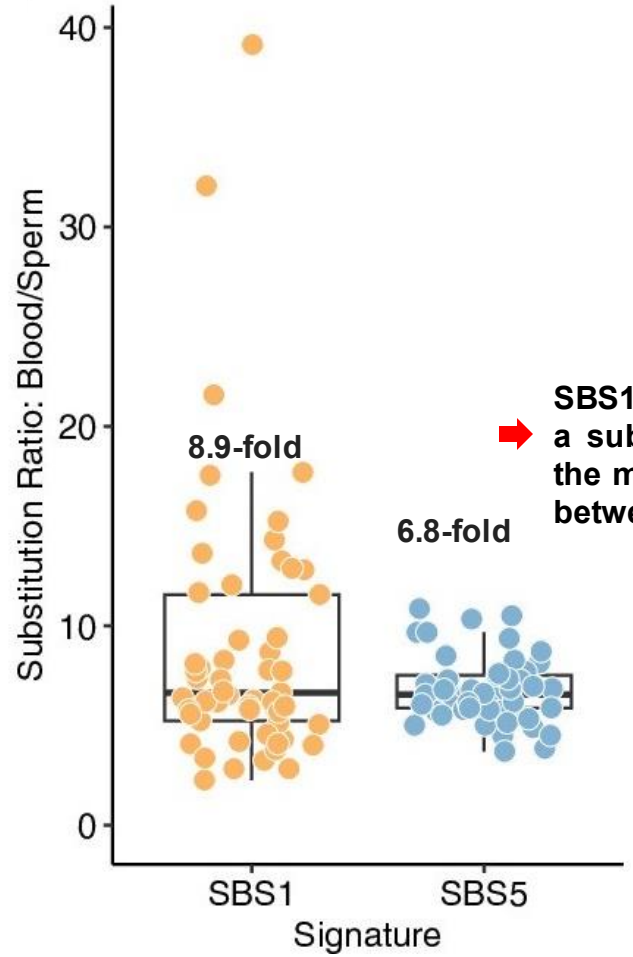
➢ **Individuals had a mean of 7.6-fold more substitutions per base pair per year (range of 4.2–11.5) and 6.3-fold more indels per base pair per year (range of 2.2–18.7) in blood than in sperm.**

Mutation signature



Does this blood-specific SBS19 explain the huge excess of mutations in blood?

- **SBS1 and SBS5 accumulate roughly 7-to-9 times faster in blood than in sperm.**



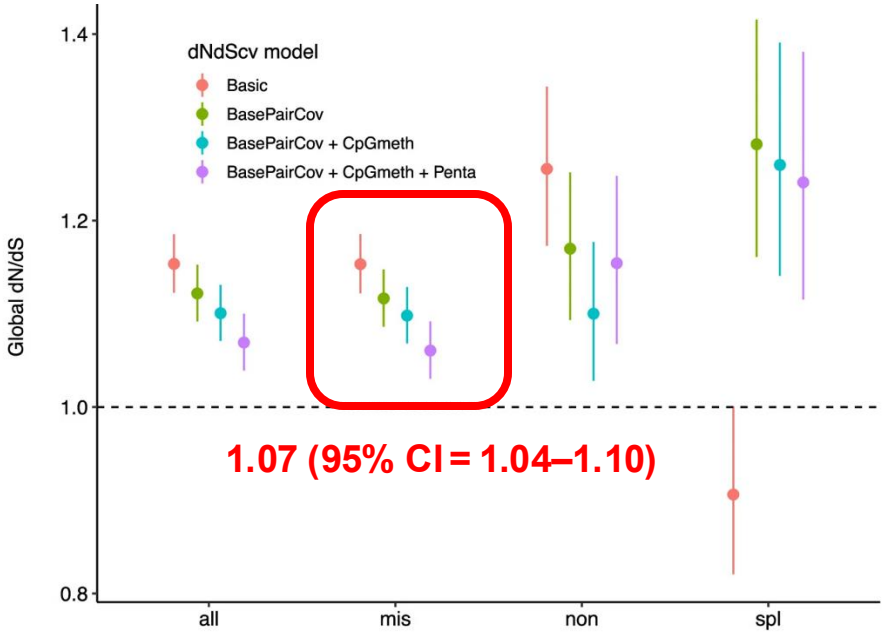
SBS19 does not explain a substantial fraction of the mutation burden gap between the two tissues

Selective pressure dynamics in sperm

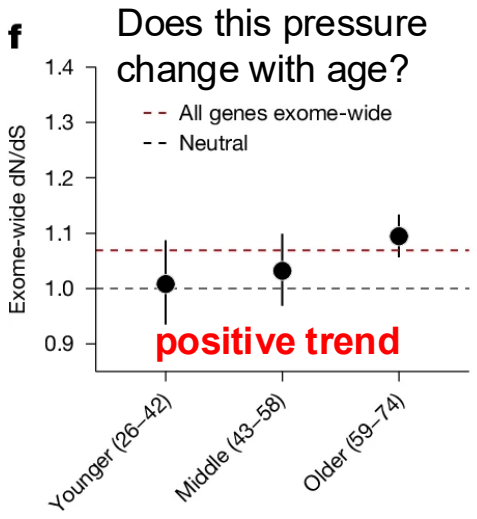
- protein-coding regions
- 38 samples
- whole-exome NanoSeq
- mean depth: 551 dx

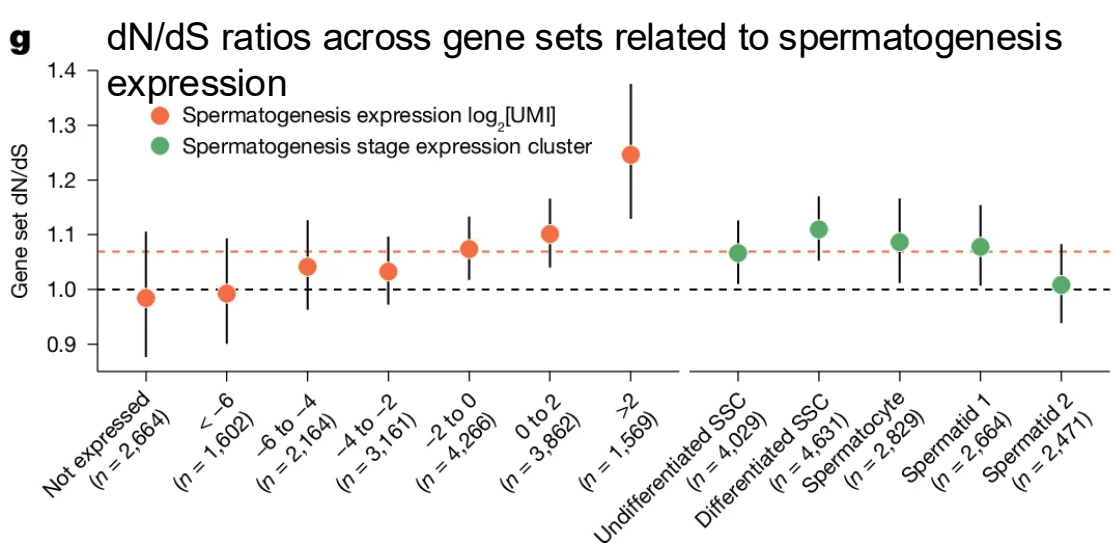
- 263 canonical cancer driver and developmental disorders genes
- 81 samples
- targeted NanoSeq
- mean depth: 985 dx

Identified more than 35,000 germline coding mutations



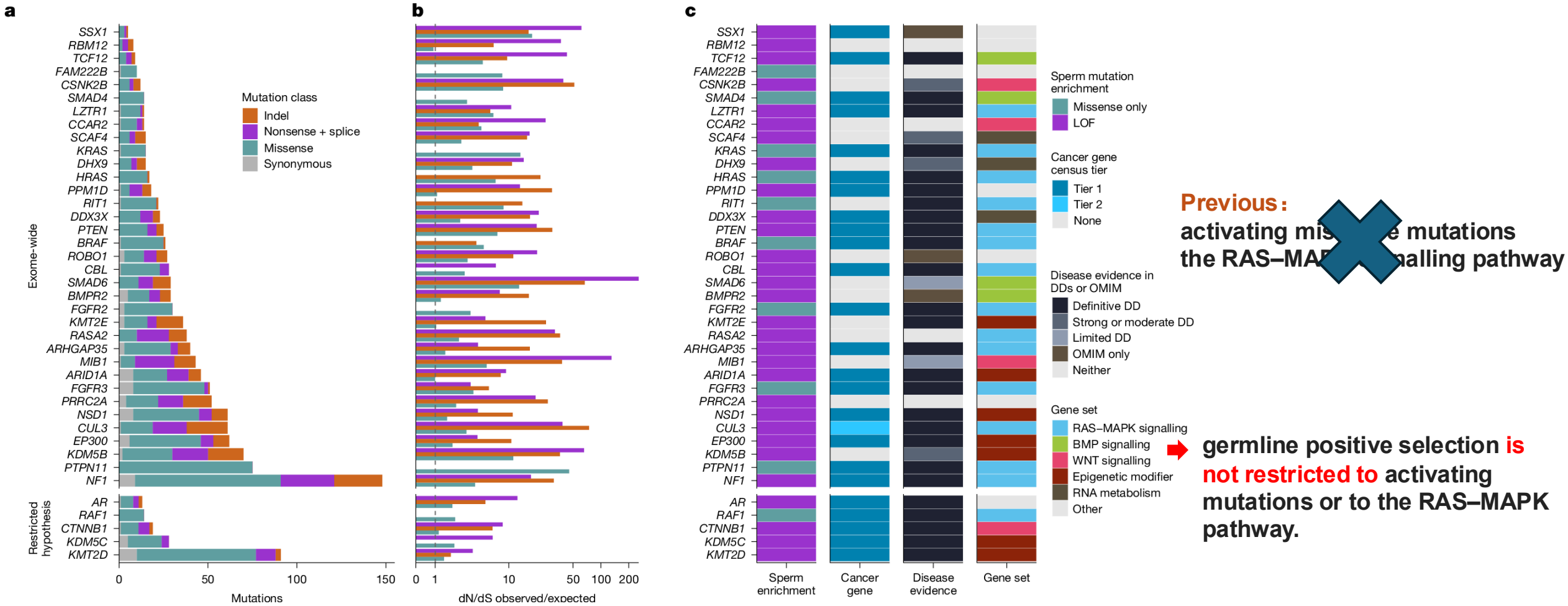
dN/dS ratio, where dN/dS = 1.0 indicates neutrality





- **6.5% of the observed nonsynonymous substitutions in sperm conferred a clonal advantage**
- **The selection may increase over the male lifespan**
- **Excess nonsynonymous mutations observed in sperm confer a competitive advantage earlier in their cell lineage**

Which genes are driving this selection?

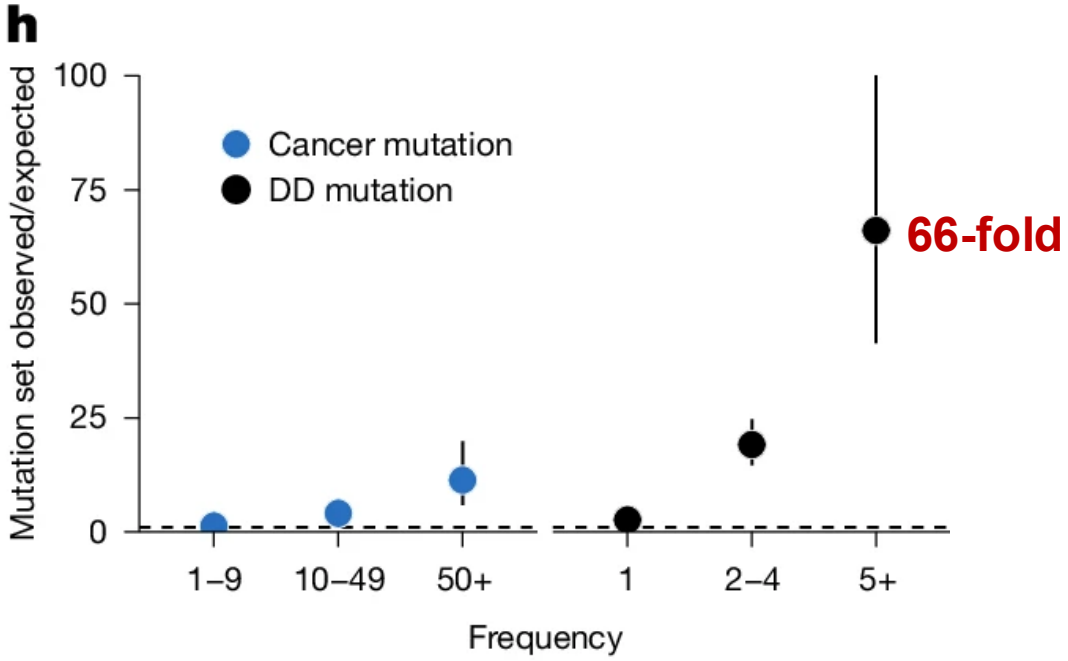


Previous:
activating mis[illegible]e mutations
the RAS–MA[illegible]nalling pathway

germline positive selection is not restricted to activating mutations or to the RAS–MAPK pathway.

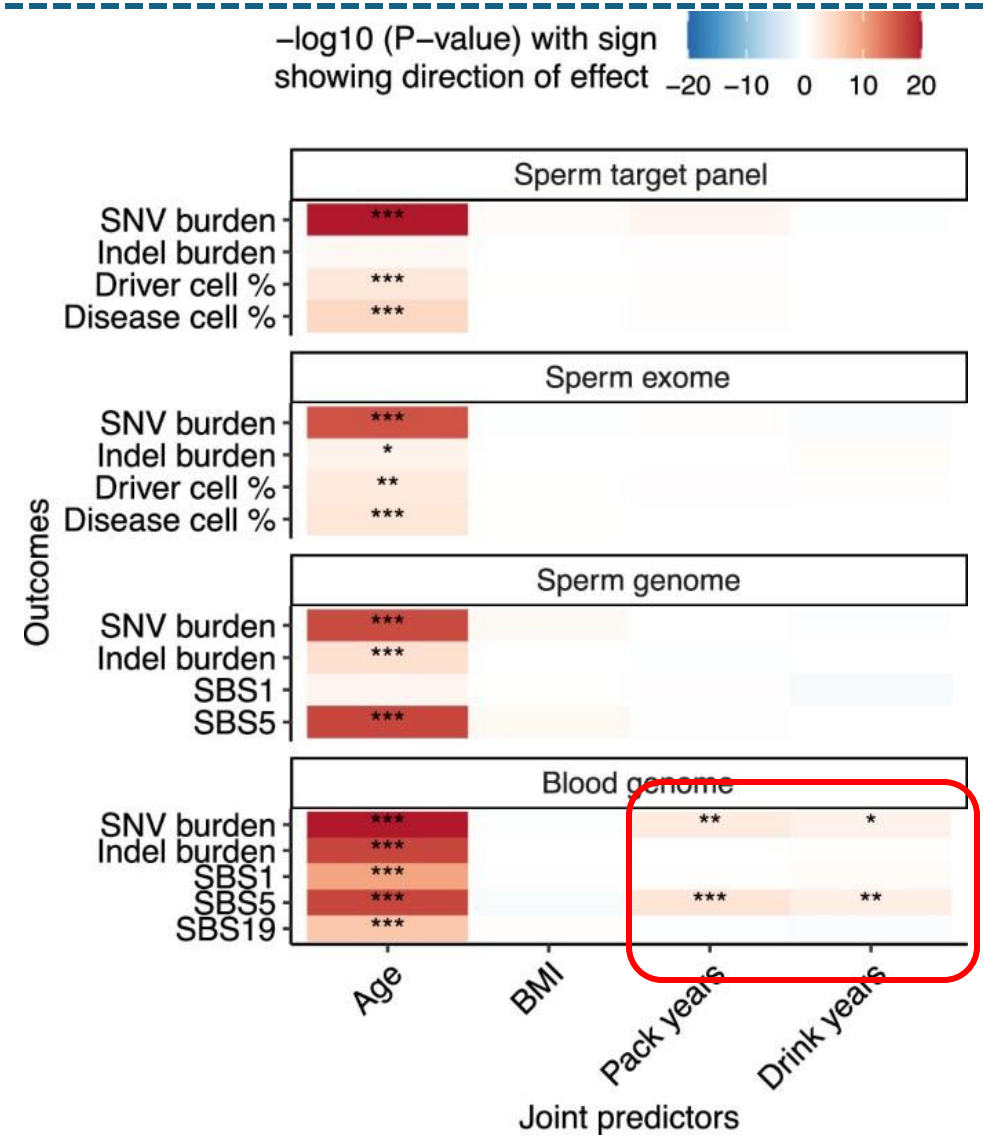
- **40 genes (31 newly identified) under significant positive selection in the male germline that have activating or loss-of-function mechanisms and are involved in diverse cellular pathways.**

Overlap between germline positive selection and cancer



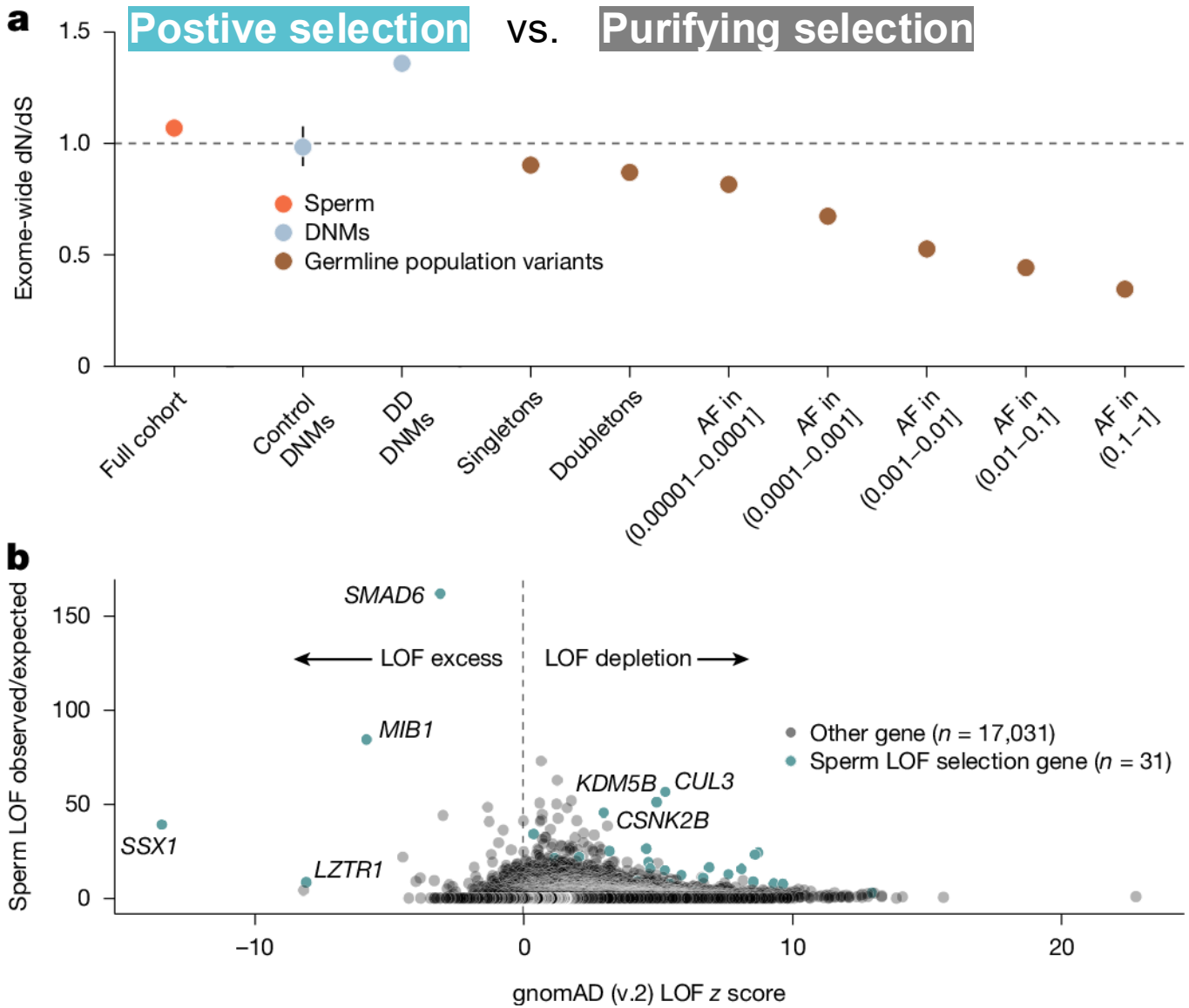
- **A clear overlap between genes, hotspots and mutation mechanisms that drive germline positive selection, cancer and developmental disorders.**

Do lifestyle factors damage our germline?



- **While somatic tissues like blood are vulnerable to these lifestyle exposures, the male germline appears to be remarkably well-protected**

How selection shapes germline variants in the population level



- Positive selection is the greater force that acts on germline mutations during spermatogenesis, whereas purifying selection predominates over generations.

Answers to main questions

■ 1. Scope:

- **Not just "Hotspots":** Positive selection is far more extensive than previously thought (40 driver genes identified, 31 new).
- **Not just "Activation":** Selection exploits diverse mechanisms, including **Loss-of-Function** and multiple pathways (WNT, TGFβ, RNA metabolism).

■ 2. Impact: the evolutionary cost

- **Direct disease link:** The same mutations driving clonal expansion in sperm are the ones causing severe developmental disorders in children.
- **Paternal age effect**: This explains why older fathers carry higher risks—it's a result of "selfish" selection over time.
- **The trade-off:** We pay for robust spermatogenesis with an increased burden of de novo mutations in the next generation.

Significance & Future Directions

➢ Advantages

This study provides the most comprehensive view so far of how acquired mutations in spermatogonial stem cells give rise to positively selected clonal expansions that accumulate over the course of a man's life and shape the mutational landscape passed to subsequent generations.

➢ Future questions

- How do other environmental factors shape clonal dynamics?
- Do germline selection patterns and mutation rates vary depending on a person's ancestral background?

Thanks for your attention!

Q & A