SPERM MUTATIONS AND AGING

As men age, the spermatogonial stem cells (SSCs) that continuously produce sperm gradually accumulate DNA mutations. Two complementary studies by Neville et al. (1) and Seplyarskiy et al. (2) [News&Views (3)] show that some of these mutations are not merely passive products of aging but actually confer a selective growth advantage to mutant SSCs. As these mutant clones expand in the testis, they become over-represented in the sperm pool, increasing the probability that such mutations are transmitted to offspring.

Using ultra-sensitive NanoSeq sequencing of bulk sperm, Neville et al. quantify a linear accumulation of approximately 1.7 new mutations per haploid genome per year, driven by canonical age-related mutational signatures. They estimate that the fraction of sperm carrying a disease-causing mutation rises from ~2% at age 30 to ~4.5% at age 70, due to the steady growth of many small clones, rather than the dominance of a few large ones. They identify about 40 genes under positive selection in the male germline, using dN/dS metrics and targeted sequencing.

Seplyarskiy et al., analyzing ~55,000 parent–child trios with a statistical model ("Roulette"), independently detect 40 genes enriched for de novo mutations beyond what would be expected by chance. These include both gain-of-function "hotspot" mutations and loss-of-function alleles that appear repeatedly in sperm, consistent with selective clonal expansion. Their results hold in additional cohorts (>6,000 trios), suggesting these driver mutations act broadly in the germline.

Together, the studies expand the list of driver genes beyond the classical RAS–MAPK pathway (long known from "selfish spermatogonial selection") to include genes involved in WNT, TGFβ–BMP, and epigenetic regulation. Although only 17 genes overlap between the two studies, the pathway-level concordance is strong.

This age-dependent clonal selection in the male germline therefore represents an evolutionary trade-off: it increases the individual risk of transmitting pathogenic mutations, yet simultaneously contributes to the emergence of new genetic variants that enrich human genetic diversity and long-term adaptability.

A key implication is that germline selection can enrich deleterious mutations in sperm faster than natural selection can remove them from the population. This means that some genes may appear "disease-associated" in de novo mutation studies not because they cause disease, but because mutant SSCs outcompete normal ones. This insight suggests the need to annotate germline variants in public databases with information about positive selection in SSCs.

Overall, the work provides the most comprehensive picture to date of how age-related mutation and clonal selection sculpt the male germline — influencing disease risk in children and contributing to human genetic diversity.

1. https://www.nature.com/articles/s41586-025-09448-3

2. https://www.nature.com/articles/s41586-025-09579-7
3. Nature Nov. 13, 2025, pag. 324