OLDER MEN PRODUCE MORE MUTATED SPERM THAN YOUNGER MEN DO

In older men, the frequency of germline mutations is higher than in younger men. This phenomenon has been linked to the accumulation of errors that occur during the lifelong replicative process of spermatogonia stem cells (SSCs), as well as the fact that some of these mutations confer a selective advantage to the SSCs promoting their clonal expansion. Accordingly, as men get older, the SSCs niche becomes a mosaic of mutations which in turn, increases the incidence of mutation carrying sperm, some of which may be damaging to the progeny.

A recent research paper in Genome Research[1] has optimized the duplex sequencing (DS) methodology to discover ultra-low-frequency variants of the *FGFR3* gene in spermatozoa from older and younger men. The product of this gene participates in the RTK-RAS signaling pathway and is highly expressed in SSCs. Several variants of this gene that accumulate in the SSCs have been described because the mutated protein confers a proliferative advantage.

The authors identified 34 never-before-reported variants out of a total of 75 annotated to the gene's coding regions. Some of these changes were only, or more frequently, identified in older sperm donors. Moreover, the distribution of changes was not uniform along the gene with some domains concentrating non-synonymous mutations, suggesting that these domains may be subject to stronger clonal expansions of pathogenic variants. Besides, the authors detected three amino acid substitutions associated with disorders that are thought to rise with paternal age.

This paper proves that the DS strategy is useful to uncover *de novo* germline mutations and their association with paternal age-related congenital disorders. This is particularly relevant in western societies because postponed fatherhood is more and more frequent.

1. https://genome.cshlp.org/content/32/3/499