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GENETICS

# Selfish spermatogonia

Mutant spermatogonia, which are common in older men, sometimes replicate in a tumour-like manner, leading to an increasing proportion of mutant sperm that could be passed onto offspring, say researchers.

Whole-genome sequencing studies have shown that most mutations in children originate from the male germline and that mutations increase in frequency with paternal age, an important issue given that reproduction is now occurring later in many populations. 'Selfish spermatogonial selection' — a process likened to early tumour growth — has been proposed to contribute to the age-related increase in male mutations. "In this process, specific point mutations that confer gain-of-function to components of the growth factor receptor-RAS signaling pathway occur rarely in spermatogonial stem cells of the adult testis but show a steep increase in prevalence with age, attributed to clonal expansion of mutant spermatogonia over time," say the authors of the paper. "Fertilization of the egg by a mutant sperm leads to serious congenital disorders in the next generation, characterized by multiple malformations and, in some cases, a predisposition to malignancy."

Maher *et al.* examined seminiferous tubules of 14 testes from men aged 39–90 years who had had testicles removed for reasons unrelated to infertility or parenchymal malignancy (mostly for inguinal hernias). The testes were macroscopically normal, aside from one from one that showed evidence of severe atrophy caused by a strangulated hernia. The researchers found 11 distinct gain-of-function mutations in five genes (*FGFR2*, *FGFR3*, *PTPN11*, *HRAS* and *KRAS*) from 16 of the 22 tubules analysed. Each of the mutations have known associations with severe diseases, including congenital or perinatal lethal disorders and somatically acquired cancers.

"...this experimental approach traces the origin of *de novo* pathogenic mutations to specific germ cells of the human male, illustrating a fundamental principle in Mendelian genetics not previously described..."say the authors. "Recent studies have highlighted the widespread occurrence of somatically acquired mutant clones in a variety of tissues ... here, we have illustrated analogous phenomena, but in the unique context of the germline, with its implications for altering the genetic constitution of offspring."

*Rebecca Kelsey*

**ORIGINAL ARTICLE** Maher, G. J. *et al.* Visualizing the origins of selfish de novo mutations in individual seminiferous tubules of human testes. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1521325113 (2016)