Human testes may multiply mutations

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The testes in humans may act as mutation multipliers that raise the odds of passing improved DNA to offspring – but that can also backfire by increasing the frequency of certain diseases.

The new theory is part of a study, appearing in *PLOS Biology*, that tries to explain the puzzlingly high frequency of Apert syndrome, a genetic cranial deformity found in approximately one out of every 70,000 newborns.

The study's authors suggest that natural selection may favor "germline" cells – the precursors to sperm – carrying a mutation that causes Apert syndrome.

A competitive advantage for mutated sperm precursor cells could explain why Apert strikes 100 to 1,000 times more people than expected from a single mutation.

Useful mutations in sperm precursor cells also may be more likely to pass to the next generation, the authors suggest, "because the effective mutation frequency is elevated beyond the level that can be achieved by the molecular mutation process alone."

Why natural selection might favor sperm precursor cells carrying a disease mutation is not yet understood.

The authors based their conclusions on an analysis of four human testes and computer models of mutation frequency.

They say their study is the first to check the location of mutant germline cells in the testes in any species. The result was surprising.

“You would expect that when a new mutation arose, it could arise virtually anywhere in the organ,” said Norman Arnheim, holder of the Ester Dornsife Chair in Biological Sciences at USC and one of the co-leaders of the project along with computational biologist Peter Calabrese.

“But when we divided the testes up, we didn’t find that. What we found were some very big clusters of precursor cells that were mutant.”

The data did not support the theory that the site of the mutation in the Apert gene is unusually prone to DNA change.

Another explanation – that the mutations arise very early in the life of a germline cell and multiply through subsequent divisions – also did not fit the data, Arnheim and Calabrese said.

But the clusters of mutant cells could be explained if the mutant cells made copies of themselves more frequently than normal cells.

If a mutant cell divided into two copies of itself every four to five years, the extra copies would be enough to explain the clusters, the researchers said.

They added that the model explains the increase in Apert risk with paternal age, while noting that other selection-based models also may be able to explain the same data.

Citing related studies along with their findings, the authors concluded that “it now seems very likely that (natural) selection can be a driving force acting to increase the mutation frequency at a number of genes in

humans.”

Source: University of Southern California