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'Genome editing' could correct genetic mutations for future generations

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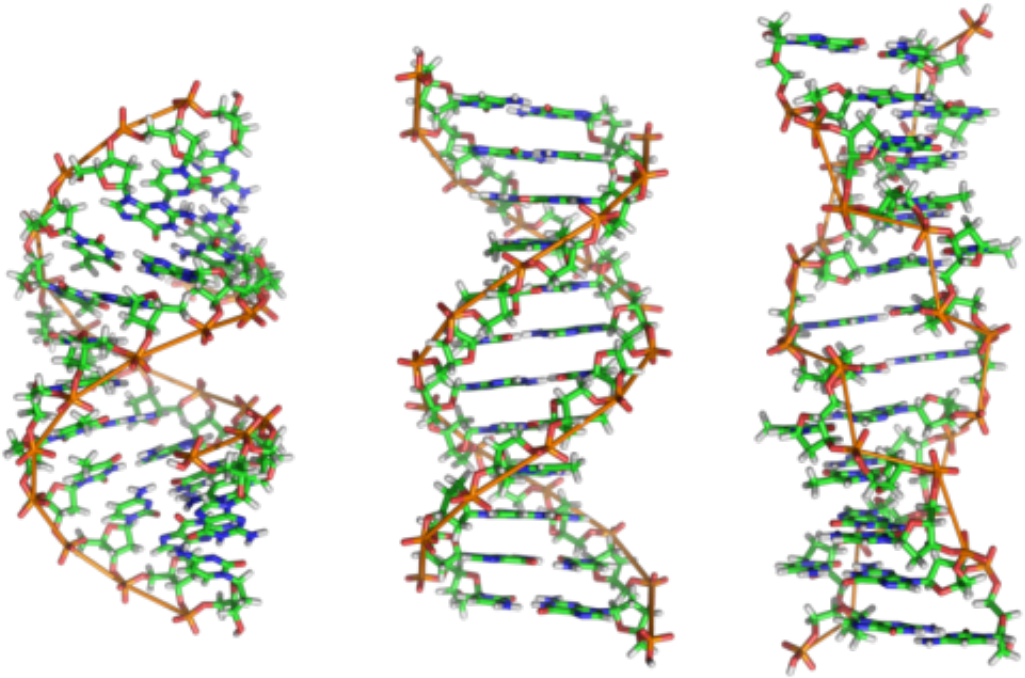

From left to right, the structures of A-, B- and Z-DNA. Credit: Wikipedia

Scientists at Indiana University and colleagues at Stanford and the University of Texas have demonstrated a technique for "editing" the genome in sperm-producing adult stem cells, a result with powerful potential for basic research and for gene therapy.

The researchers completed a "proof of concept" experiment in which they created a break in the DNA strands of a mutant gene in mouse cells,

then repaired the DNA through a process called homologous recombination, replacing flawed segments with correct ones.

The study involved spermatogonial stem cells, which are the foundation for the production of sperm and are the only adult stem cells that contribute genetic information to the next generation. Repairing flaws in the cells could thus prevent mutations from being passed to future generations.

"We showed a way to introduce genetic material into spermatogonial stem cells that was greatly improved from what had been previously demonstrated," said Christina Dann, associate scientist in the Department of Chemistry at IU Bloomington and a co-author of the study. "This technique corrects the mutation, theoretically leaving no other mark on the genome."

The paper, "Genome Editing in Mouse Spermatogonial Stem/Progenitor Cells Using Engineered Nucleases," was published in the online science journal *PLOS-ONE*.

The lead author, Danielle Fanslow, carried out the research as an IU research associate and is now a doctoral student at Northwestern University. Additional co-authors are from the Stanford School of Medicine and the University of Texas Southwestern Medical Center.

A challenge to the research was the fact that spermatogonial stem cells, like many types of adult stem cells, are notoriously difficult to isolate, culture and work with. It took years of intensive effort by multiple laboratories before conditions were created a decade ago to maintain and propagate the cells.

For the IU research, a primary hurdle was to find a way to make specific, targeted modifications to the mutant mouse gene without the

risk of disease caused by random introduction of genetic material. The researchers used specially designed enzymes, called zinc finger nucleases and transcription activator-like effector nucleases, to create a double strand break in the DNA and bring about the repair of the gene.

Stem cells that had been modified in the lab were then transplanted into the testes of sterile mice. The transplanted cells grew or colonized within the mouse testes, indicating the stem cells were viable. However, attempts to breed the mice were not successful.

"Whether the failure to produce sperm was a result of abnormalities in the transplanted cells or the recipient testes was unclear," the researchers write.

In a separate study, published this month in the journal *Cell Research*, scientists from several institutions in China used a different technology to edit a faulty gene in spermatogonial stem cells of mice. In this study, the mice were able to successfully reproduce following transplantation of the cells carrying the corrected gene.

The research developments could open doors for better understanding of stem cells and advances in gene therapy. The ability to edit the genome could facilitate analysis of gene function and the processes by which sperm cells divide and differentiate. The techniques could be used, for instance, to test the functional importance of a genetic mutation implicated in reproductive failure.

As a medical advance, the studies demonstrate techniques for correcting mutations that are more effective than previous methods. And the fact that they work on spermatogonial stem cells is especially significant. While gene therapy has been effective at treating certain diseases, patients live with the knowledge that they may transmit a genetic condition to their children. Modifying the patients' germ cells could, at

some time in the future, address that risk.

Provided by Indiana University