# Method of DNA repair linked to higher likelihood of genetic mutation

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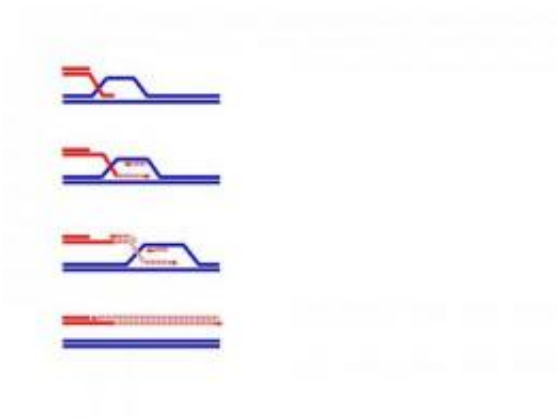

A chromosome's broken end invades an intact DNA molecule and initiates replication that can lead to a genomic instability. Credit: Anna Malkova, Ph.D., School of Science at Indiana University-Purdue University Indianapolis

Accurate transmission of genetic information requires the precise replication of DNA. Errors in DNA replication are common and nature has developed several cellular mechanisms for repairing these mistakes. Mutations, which can be deleterious (development of cancerous cells), or beneficial (evolutionary adaption), arise from uncorrected errors.

Researchers from Indiana University-Purdue University Indianapolis (U.S.A) and Umea University (Sweden) report that a method by which cells repair breaks in their DNA, known as Break-induced Replication (BIR), is up to 2,800 times more likely to cause genetic mutation than

normal DNA synthesis. When one or many cells repair themselves using the efficient BIR method, accuracy is lost. These findings will publish next week in the online, open access journal PLoS Biology.

"When BIR occurs, instead of using a "band aid" to repair a chromosomal break, the broken piece invades another chromosome and initiates replication which happens at the wrong place and at the wrong time and probably with participation of wrong proteins," said Anna Malkova, Ph.D., Associate Professor of Biology at the School of Science at IUPUI, who led the study.

The researchers used yeast to investigate the level of mutagenesis associated with BIR and found that the process's proclivity to cause mutation was not effected by where in the DNA the repair was made. But why is BIR so inaccurate as compared to normal replication?

"We didn't find a smoking gun," said Malkova, also an adjunct associate professor of medical and molecular genetics at the Indiana University School of Medicine. "We think there are at least four changes to the replication machinery that might occur to create a perfect storm or synergy that make BIR repair so mutagenic."

For example, during BIR, the researchers found a dramatic increase in the concentration of nucleotides – the building blocks used to form DNA.

"Our findings strongly suggest that mutagenesis caused by BIR doesn't happen slowly, it occurs in surges – sudden bursts which may lead to cancer," said Malkova, who is a geneticist. "We plan to continue investigating BIR in the hope of finding clues as to why this means of cell repair is so likely to cause mutations. The ultimate goal, of course, is to prevent those mutations that cause cancer."

**More information:** Deem A, Keszthelyi A, Blackgrove T, Vayl A, Coffey B, et al. (2011) Break-Induced Replication Is Highly Inaccurate. PLoS Biol 9(2): e1000594. doi:10.1371/journal.pbio.1000594