DNA damage leads to genetic diseases and cancer

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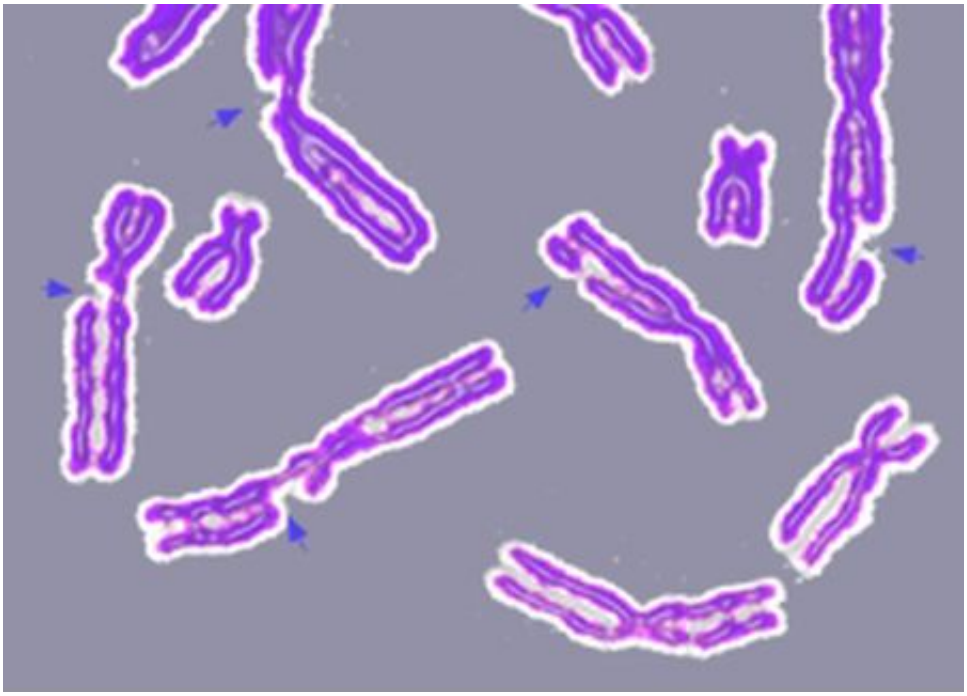

DNA damage resulting in multiple broken chromosomes. Credit: Wikipedia/CC BY-SA 3.0

Scientists have reported that many inheritance mutations are caused by DNA damage rather than errors in DNA doubling. The study was conducted by an international research group and published in *Nature Genetics*.

Unfortunately, the reasons for mutations in normal cells that have not

been exposed to ultraviolet, smoke or other external mutagens are understudied. According to the most popular beliefs, the vast majority of mutations result from inaccurate DNA copying before each cell division. These assumptions were supported by correlation between the risk of cancer and the number of cell divisions. Another argument for this was that the number of divisions of each sperm cell before its final formation is proportional to the age of the man. For example, the sperm of an 18-year-old man undergoes about 100 doublings before it becomes "mature," while for a 50-year-old man this number is around 800. With each doubling, the number of errors in the DNA increases, leading to accumulation of mutations in the sperm.

"We decided to look at this problem from a different perspective and evaluated the contribution of DNA damage to the accumulation of mutations," says Vladimir Seplyarskiy, one of the authors from the Institute for Information Transmission Problems RAS and Harvard Medical School, U.S. "We looked how the cell repair system works. Since it works only on the DNA strand from which genes are read, we looked at the rarest types of mutations that occur in these areas, and thus were able to estimate the number of mutations that are caused by DNA damage."

Next, the scientists looked at what happens to damaged DNA during cell division. They compared mutations on both leading and lagging doubling chains of DNA. It turned out that mutations associated with DNA damage occur more often on the lagging chain. This is true both for mutations caused by known mutagens during the development of a cancer tumor (for example, as a result of exposure to tobacco smoke in lung cancer, ultraviolet radiation in melanoma, and aristolochic acid in liver cancer), and for mutations inherited. Thus, many of the inheritance mutations are caused not by errors in DNA doubling, but by DNA damage.

The result was tested experimentally. The scientists asked: If so many mutations are caused by DNA damage, why is the number of accumulated mutations related to the number of cell doublings? The experiments were conducted in collaboration with scientists from the Karolinska Institute, Sweden. The cell line was irradiated with ultraviolet light, and in one case, cell division was artificially delayed for two days, while the second cell samples divided normally. It turned out that a slight delay reduced the mutagenic effect of ultraviolet radiation by 30 times. Therefore, DNA damage turns into mutations only if they occur shortly before the cell division. These results suggest that mutations leading to cancers might be caused by mutagens only in actively dividing cells. Such a hypothesis gives a completely different interpretation of the relationship between the number of cell divisions and the number of accumulated mutations.

"I have long been looking for the cause of mutations in the germ line. It has been suggested that mutations inherited from the father are a consequence of replication inaccuracies. In this work, we statistically showed that DNA damage also plays a significant role. Unfortunately, the assessment of the contribution of such damage to mutagenesis, which we have received now, is clearly underestimated, and we are looking for new approaches to clarify it," says Vladimir Seplyarskiy.

Understanding the mechanisms of mutagenesis helps to estimate the likelihood, and even partly to predict, mutations that lead to cancer and hereditary diseases. In the long run, it might become possible to prevent these diseases.

More information: Vladimir B. Seplyarskiy et al, Error-prone bypass of DNA lesions during lagging-strand replication is a common source of germline and cancer mutations, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0285-7