Folate deficiency creates hitherto unknown problems in connection with cell division

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Folate deficiency creates more problems in connection with DNA replication than researchers had hitherto assumed, researchers from the University of Copenhagen show in a new study. Once a person lacks folate, the damage caused by this cannot be reversed. The researchers therefore encourage people to be more aware of the level of folate in the blood.

Folate deficiency can severely affect one of the most important processes in the body, cell division, researchers from the University of Copenhagen have demonstrated in a new study published in the scientific journal *PNAS*. In the study, the researchers show that folate deficiency can cause problems in connection with cell division and DNA replication. In fact, it creates far more damaging chromosomal abnormalities than previously known.

Folate is a type of vitamin B found in, for example, broccoli, spinach, peas, mushrooms, shellfish and fruit such as bananas and melon. The Danish Health Authority recommends that pregnant women and women trying to get pregnant take a daily supplement of folic acid. But everyone—not just pregnant and soon to be pregnant women—should focus on this vitamin, concludes the last author of the study, Associate Professor Ying Liu from the Center for Chromosome Stability at the Department of Cellular and Molecular Medicine, UCPH.

'The problem with folate deficiency is that it affects chromosome maintenance, and once a cell has lost a chromosome or part of it, it can never be fixed. That is, once cell division has gone wrong, you cannot fix it subsequently by consuming a lot of folic acid. Once the damage is done, it is irreversible.'

'Therefore, we need a guide telling us what the level of folate in the blood in the population in general should be. Once we have that knowledge, we can determine whether a person needs folic acid

supplements to make sure the level in the blood is high enough for the cells to reproduce the DNA successfully,' says Liu.

Infertility, Mental Illness and Cancer

A blood sample can determine the level of folate in the blood. Researchers have known for many years that folate deficiency is associated with mental illness, age-related dementia and deformation of the brain and spinal cord of foetuses, also known as neural tube defects. But they have not been able to establish the causality—that is, whether folate deficiency directly causes the disorders or whether the disorders are caused by the secondary effect of folate deficiency. To answer this question, the researchers studied lymphocytes, which are a type of white blood cell, from men. However, the results would also apply to women, Ying Liu argues.

The researchers analysed the area of the genome called FRAXA, which contains an extensive CGG sequence of genetic code. Here they saw that folate deficiency caused abnormalities in connection with cell division—mitosis—especially in cells with an abnormally long CGG sequence. Among other things, it caused faulty segregation of chromosomes. The researchers also saw how the entire X chromosome became unstable in cases of long exposure to folate deficiency.

'In the study, we demonstrate that folate deficiency leads to both higher levels of and more harmful chromosome abnormalities than previously thought. This causes the daughter cells to inherit the incorrect amount of DNA following cell division or, in some cases, to even lose an entire chromosome. This could explain why folate deficiency is associated with diseases like infertility, mental health disorders and cancer,' Liu explains.

Other parts of the genome also contain extensive CGG sequences. The

researchers assume that these regions will also be affected by folate deficiency. As a next step, they wish to map all the areas of the human genome that may be affected by folate deficiency.

More information: Victoria A. Bjerregaard et al. Folate deficiency drives mitotic missegregation of the human FRAXA locus, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1808377115

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