MedicalXpress

Folic acid deficiency can affect the health of great, great grandchildren

September 26 2013

Folic acid deficiency can cause severe health problems in offspring, including spina bifida, heart defects and placental abnormalities. A study out today reveals that a mutation in a gene necessary for the metabolism of folic acid not only impacts the immediate offspring but can also have detrimental health effects on the next several generations. The new research, which also sheds light on the molecular mechanism of folic acid (also known as folate) during development, was published today in the journal *Cell*.

"Although our research focused on genetic mutations which disrupts the break down and metabolism of folic acid, we believe that folic acid deficiency in the diet would have a similar multi-generational impact on health," said Dr Erica Watson from the Centre for Trophoblast Research at the University of Cambridge, who led the study.

The detrimental effects of folic acid deficiency on development are quite well known. As a result, many countries, to include Canada and the US, have implemented folate fortification programmes which require folic acid to be added to cereal products. However, until now, very little was known about how folic acid deficiency caused the diverse range of health problems in offspring.

"Fortification programmes have reduced the risk of health effects but not eliminated them completely," said Dr Watson. "Based on our research, we now believe that it may take more than one generation to eliminate the health problems caused by folate deficiency."

The researchers, from the Universities of Cambridge and Calgary, used mice for the study as they metabolize folic acid very similarly to humans and because folic acid deficiency or mutations in the same genes required to break down folic acid in humans result in similar developmental abnormalities and diseases in mice. This enabled the researchers to explore how the molecular mechanism of folic acid deficiency impacted development, thereby causing health problems.

For the study, the scientists used mice in which a gene called Mtrr was specifically mutated. The gene is key to the normal progression of the folic acid cycle and, when mutated, it results in abnormal folic acid metabolism causing similar effects to dietary folic acid deficiency. The researchers found that when either the maternal grandmother or the maternal grandfather had this Mtrr mutation, their genetically normal grandchildren were at risk of a wide spectrum of developmental abnormalities. These developmental abnormalities were also seen in the fourth and fifth generations of mice.

Through another experiment which involved transferring the embryo from the third generation into a normal healthy female mouse, they discovered that these developmental abnormalities were not passed down genetically. Instead, the serious defects were the result of epigenetic changes which had been inherited.

Epigenetics is a system which turns genes on and off. It occurs when chemicals, such as methyl groups, bind to the DNA at specific locations to control which genes are expressed and when they are expressed. (Interestingly, the folic acid cycle is required to make sure that the cell has enough methyl groups for normal gene expression.) Epigenetic inheritance refers to the passing of these epigenetic marks from one generation to the next – despite the epigenome, for the most part, being 'wiped clean' after each generation.

The researchers hypothesize that, for a yet unknown reason, some of these abnormal epigenetic marks caused by the Mtrr mutation may escape this normal erasure and are inherited by the next generation. If these abnormal epigenetic marks that regulate genes important for development are inherited, then these generations may develop abnormalities as a result of the wrong genes being turned on or off.

"It surprised us to find that the great, great grandchildren of a parent who has had a folic acid deficiency could have health problems as a result - suggesting that the 'sins of your maternal grandparents' can have an effect on your development and your risk for disease," said Dr Watson.

"More importantly, our research shows that disease in general can be inherited through epigenetic means rather than genetic means, which has huge implications for human health. Environmental factors that influence epigenetic patterns - e.g., diet, epigenetic disruptors in the environment such as chemicals, etc. - may also have long term, multigenerational effects."

More information: The paper 'Mutation in Folate Metabolism Causes Epigenetic Instability and Transgenerational Effects On Development' will be published in the 26 September edition of *Cell*.

Provided by University of Cambridge