AD WINDIG/MAI/HOLLANDSE HOOGTE/EYEVINE

Children wait to be fed during the Dutch Hongerwinter of 1944–1945.

EPIGENETICS

Tales of adversity

Genetic studies of people conceived during famine reveals that prenatal malnutrition lingers long after the event.

BY FAROOQ AHMED

It is well established that a pregnant woman's habits affect the health of her unborn child, but the extent of the impact is less well known. Recent studies of tragic historical events, namely the Dutch Hongerwinter and the Great Chinese Famine, have begun to highlight the trans-generational relationship between food and genes.

The Hongerwinter (hunger winter) began late in 1944 towards the end of the Second World War. Food supplies in the northern and western regions of Nazi-occupied Holland became increasingly limited as the Germans halted overland transport of goods into Amsterdam and nearby cities.

Exacerbating this blockade, the harsh winter froze canals — cutting off a vital supply route. Rations in cities dropped to as few as 500 calories per day, less than a quarter of the recommended intake, until the country was liberated in May 1945, but not before 18,000 people starved to death.

Many children conceived during the Hongerwinter were small and underweight. What's more, certain health problems have persisted long into their adult lives. Compared to their siblings conceived before or after the famine, the Hongerwinter children are at increased risk for obesity, for example. A propensity for obesity was also found in children of the 1968–1970 Biafra famine in a recent study in Nigeria.

The Great Chinese Famine, from 1958 to 1961, was caused by a combination of leader Mao Zedong's agricultural policies during the Great Leap Forward, widespread mismanagement and severe weather. Tens of millions of people died. Studies of Chinese born during this period link prenatal famine exposure to an increased risk of schizophrenia — a link also found in the Dutch Hongerwinter cohort.

"These extreme events offer special opportunities for research in humans that you might not otherwise have," says Lambert Lumey, an epidemiologist at Columbia University, New York, who is studying the effects of the Hongerwinter. There are obvious ethical issues and long time spans involved that make recreating the circumstances of famine impossible. "These events are crucial to helping us develop and discover underlying disease mechanisms," says Lumey.

TELL-TALE DNA

Scientists have discovered that certain genes of children conceived during a prolonged period of starvation receive special epigenetic 'tags' through a process called methylation — a gene modification that typically deactivates a gene, but does not alter the genetic code. Methylation is part of normal development, but patterns vary across individuals.

Nearly six decades after the famine, Lumey and colleagues isolated DNA from Hongerwinter individuals. They found a below-average methylation of the insulin-like growth factor II gene *(IGF2)*, which codes for a growth hormone critical to gestation. Decreasing the methylation of *IGF2* should increase the expression of the hormone. In contrast, later studies in this cohort found increased methylation of five other genes, among them genes associated with cholesterol transport and ageing, as well as the gene that produces IL-10, which has been linked with schizophrenia.

The mechanisms of these epigenetic changes and whether they have a bearing on disease remain unclear. "In humans, these are the $100,000 questions," says epigeneticist Robert Waterland from Baylor College of Medicine in Texas.

Lumey hopes to study the children of the 'tagged' individuals to see if these changes persist into the next generation. Epigenetic information is almost fully reset in very early development, so the outcome, he says, is difficult to predict. "This is an important question regardless of what the data will later show."

Nevertheless, studies on these extreme events "provide the first convincing evidence that early nutritional exposure causes a persistent change in epigenetic regulation in humans," notes Waterland. "It's a proof of principle."

Lumey is now looking to high-throughput sequencing methods to measure genome-wide DNA methylation. "We expect that this will tell us whether there also are more epigenetic differences between prenatally exposed individuals and their unexposed siblings, than the ones we found studying candidate loci," says epigeneticist Bastiaan Heijmans of Leiden University in the Netherlands, who works with Lumey. If these modifications are indeed widespread throughout the genome, the cumulative effect of famine-induced epigenetic alterations might play a substantial role in disease progression.

Other research has shown that less-extreme diets also affect methylation patterns and disease susceptibility. For example, folic acid is an important supplement for pregnant women to help prevent neural tube defects in developing embryos. It has been shown to increase the methylation of *IGF2,* hinting that it works through an epigenetic mechanism.

Nevertheless, studying such catastrophes provides researchers with valuable information that is not otherwise available, revealing that the aftermath of famine and prenatal malnutrition lasts long after help arrives with life-saving food. ■

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