# People conceived during the Dutch famine have altered regulation of growth genes

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Individuals conceived in the severe Dutch Famine, also called the Hunger Winter, may have adjusted to this horrendous period of World War II by making adaptations to how active their DNA is. Genes involved in growth and development were differentially regulated, according to researchers at the Leiden University Medical Center, Harvard University, and Columbia University's Mailman School of Public Health. Findings are published in the journal *Nature Communications*.

During the winter of 1944-1945 the Western part of The Netherlands was struck by a severe 6-month famine. During this Hunger Winter the available rations provided as low as a quarter of the daily energy requirements. Children conceived—but not born—during the famine were delivered with a normal birth weight. Extensive research on the DNA of these Hunger Winter children shows that the regulatory systems of their growth genes were altered, which may also explain why they appear to be at higher risk for metabolic disease in later life.

## Decades later growth genes seemed different

"The different setting of the growth genes may have helped the Hunger Winter children to withstand the Famine conditions as compared with their unexposed siblings, but these changes may likewise be unfavorable for their metabolism as adults," said Leiden University principal investigator Dr. Bas Heijmans. For example, the altered settings were associated with LDL cholesterol at age 60, according to the authors.

The research team in Leiden compared the DNA of the Hunger Winter children, now aged 60, at 1.2 million CpG methylation sites comparing them with same-sex siblings not exposed to famine. They were able to see how the genes were differentially regulated in the Hunger Winter children, as compared with their siblings with a similar genetic and familial background. Groups of genes involved in growth and development showed a different gene activity setting. The Hunger Winter children were all approximately 60 years of age when they gave blood for DNA research. It was at this point in time that their growth genes seem altered for life.

"The potential for a gene to become active is mainly determined in the crucial weeks after fertilization. This master regulatory system that determines which genes are on and which are off is called epigenetics and can be compared to a sound technician making adjustments during a recording to get that perfect sound. Environmental factors during development can make a lasting imprint on this system," noted Dr. Heijmans.

The authors point out that a wealth of past epidemiological studies suggests that early development is important for later health. "Thanks to the willingness of the Hunger Winter children and their families to contribute to our studies, we can pin- point which phases of development are especially sensitive to the environment. We are currently extending our inquiries not only to those conceived during the famine, but also to those exposed during other gestation periods. A lot of important things are happening in the womb about which we know quite little in humans", says co-author Dr. Elmar W. Tobi.

"These findings are exciting and provide tremendous opportunities for epidemiologists," said L.H. Lumey, MD, associate professor of

Epidemiology at Columbia University's Mailman School of Public Health and senior author who collected the analyzed blood samples. "Looking at the human genome we see systematic changes in gene regulation during early human development in response to the environment. The epigenetic revolution has given us the tools to investigate these changes and look at the impact for later life."

Provided by Columbia University's Mailman School of Public Health

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