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Timing of mutation determines the outcome

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A single genetic mutation can lead to completely different diseases, depending on the time and location at which the mutation occurs. This finding emerged from the PhD study conducted by Rocio Acuña-Hidalgo of Radboudumc. For example, a mutation in the SETBP1 gene that occurs early in development leads to Schinzel-Giedion syndrome, but later in life it results in myeloid leukemia. "Determining the timing of mutation is crucial for its interpretation and for providing careful genetic counseling," explained Acuña-Hidalgo.

Our inherited characteristics are recorded in our DNA. Children receive half of their DNA from the sperm cell of the father, and the other half from the egg cell of the mother. But during life, mutations also occur in the DNA, resulting in new genetic characteristics. These characteristics can be beneficial, neutral or pathogenic. Known as de novo mutations, these changes can take place during the formation of sperm and egg cells, resulting in a mutation in all cells throughout the body. But mutations can also occur later in development, resulting in their presence in only part of the body.

Intellectual disability and cancer

Acuña-Hidalgo studied the timing of de novo mutations and their effect on health and disease. She performed the study in a group of patients with the rare Schinzel-Giedion syndrome. This developmental disorder, which is associated with intellectual disability, is the result of a mutation in the SETBP1 gene during the development of sperm or egg cells. The mutation leads to a surplus of SETBP-1 protein, which disturbs

neurological development. But this protein accumulation is also seen in patients with leukemia who do not have this syndrome. In this group, the mutation occurred later in life.

Timing of mutations

Acuña Hidalgo: "We see that malignant tumors result from very severe mutations in SETBP1, while children with Schinzel-Giedion syndrome have milder mutations in the same gene and occasionally develop cancer. Other xamples of syndromes that are associated with an increased risk of cancer are also known. A mutation that occurs at birth can have multiple consequences later in life. A malfunctioning gene can appear in various organs and at different times during development."

Mixed blood

Acuña Hidalgo also looked at mutations in blood-forming stem cells. Because these stem cells transmit the mutation to the blood cells they form, the amount of mutated blood increases gradually with age: "Previously, we could detect mutations if these occurred in at least 4% of the blood cells. But with Next Generation Sequencing we can now identify mutations that occur in only 0.5% of the blood cells." In a study led by Alexander Hoischen, which is published in the *American Journal of Human Genetics* on June 29, Acuña-Hidalgo estimates that approximately two out of ten people between the age of 60 and 70 have blood with a genetically mixed composition. For people older than 70, this percentage is even higher. This is twice as much as previously assumed: "This is a universal phenomenon. The idea that every cell in our body is genetically identical is simply not true."

Small risk of cancer

"We see that our somatic cells accumulate mutations during our lifespan.

This is an important step in the development of diseases of aging and cancer. However, it is important to realize that the development of a disease such as leukemia from this mutation takes a long time. If you examine the blood carefully, you can find potentially precancerous cells. But there are so many steps between these precancerous stages and actual cancer that only a few people go through the entire process. Only 0.5% to 1% of people with these mutations actually develop cancer."

Population studies

Acuña-Hidalgo's findings are important for genetic population studies: "With large-scale population studies, we often look for genetic deviations in the blood. But we now understand that many mutations occur in blood. This makes it difficult to interpret such genetic deviations. Does the mutation occur throughout the body, or only in mutated blood stem cells? It is important to use multiple sources for genetic research, especially with the elderly." Alexander Hoischen adds: "Our study highlights the accuracy with which we can detect somatic mutations; this is of particular interest as a very recent study by scientists from the U.S. have shown that these types of mutations may give an increased risk for coronary artery disease and myocardial infarction."

More information: Rocio Acuna-Hidalgo et al. Ultra-sensitive Sequencing Identifies High Prevalence of Clonal Hematopoiesis-Associated Mutations throughout Adult Life, *The American Journal of Human Genetics* (2017). DOI: 10.1016/j.ajhg.2017.05.013

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