Not only the gene itself, its abnormal regulation can also trigger short stature

August 25 2009

A specific gene is particularly frequently involved in the development of short stature. Researchers in Heidelberg have now discovered that sequences of genetic material on the X and Y chromosome that regulate this gene are also crucial for growth in children. These gene regulators determine how frequently a gene is copied, thus how effective it is. In many cases, the mutation of one regulatory sequence of the SHOX gene is sufficient to give rise to the full-blown syndrome.

Professor Gudrun Rappold, Director of the Department of Human Molecular Genetics at Heidelberg University Hospital and her team of researchers have published their results in the *Journal of Medical Genetics*. These results could open up new possibilities for diagnosing the cause of short stature and initiating treatment before it is too late.

The so-called SHOX gene (short stature homeobox gene) is responsible for the normal growth of bones and is often mutated in short-stature patients. Short stature is considered when final height of an individual is no more than 160 cm (men) or 150 cm (women). There are many causes, e.g. hormone disorders, malnutrition, chronic disease, or a genetic disorder. If, in addition to short stature, other symptoms such as short forearms and lower legs or other bone malformations also occur, it is considered a syndrome. However, often no exact cause can be determined and other typical features are lacking - this is then known as idiopathic short stature.

SHOX gene mutation is frequently the cause of short stature

Professor Rappold's team discovered back in 2007 that in over 4 percent of children with idiopathic short stature, the trigger for the disorder was a mutation in the SHOX gene. This gene lies on the X chromosome and is responsible for growth in the epiphyseal plate, where the long bones of the arms and legs grow in length. After puberty, epiphyseal fusion takes place. When there is a mutation of the SHOX gene, patients reach a height up to 20 cm less than expected. Up to about 15 cm can be regained if the disease is diagnosed early enough and treated with growth hormones. The SHOX gene is involved in various other syndromes with growth disorders (Léri-Weill, Langer, Ullrich-Turner syndrome).

Genetic material from 893 persons with short stature examined

The researchers' latest studies show that not only the gene itself, but its regulators as well can be crucial for developing the disease. Regulatory sequences ensure that the respective gene is copied more or less frequently and thus is more or less effective.

The researchers in Heidelberg examined the genetic material from a total of 893 subjects. About 5 percent of the patients with idiopathic short stature and 80 percent of the patients with Léri-Weill syndrome had mutations in the segment either including or around the SHOX gene. Some patients had an intact SHOX gene but an unexpectedly high number of mutations in its enhancer sequences: for 26 percent of patients with SHOX deficiency and idiopathic short stature and for 45 percent of patients with SHOX deficiency and Léri-Weill syndrome, the disease could be attributed solely to a genetic mutation of the enhancer sequence. "The astounding thing is that this enhancer mutation is quite

far away from the affected gene and yet it still leads to the exact same clinical symptoms as a mutation in the gene itself," says Professor Rappold.

Treatment with growth hormones

Genes that are responsible for growth and development are needed more or less frequently in different phases of growth. In these genes in particular, mutations in the regulatory sequences can be the decisive factor for illness. The researchers hope that their results will give them a better understanding of the causes of the disease and allow them to optimize the diagnostic possibilities for patients with SHOX gene mutations.

"Patients who suffer from their short stature often have a great need to be able to name the cause. Even if it is not possible to treat the cause, patients with mutations of the SHOX gene can benefit from a treatment of the symptoms with growth hormones," explains Professor Rappold.

More information: Jianjun Chen, Gabriele Wildhardt, Zilin Zhong, Ralph Roeth, Birgit Weiss, Daniela Steinberger, Jochen Decker, Werner F Blum, Gudrun A Rappold. Enhancer mutations of the SHOX gene as a frequent cause of short stature - the essential role of a 250 kb downstream regulatory domain, Journal of Medical Genetics, published online 2 Jul 2009. Doi: 10.1136/jmg.2009.067785

Source: University Hospital Heidelberg (news : web)