UCSD researchers discover similar genetic mechanism triggers common form of dwarfism and certain cancers

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A chemical switch that remains stuck in the "on" position is responsible for the most common genetic form of dwarfism, according to a new study by biochemists at the University of California, San Diego. Surprisingly, this abnormal activation is similar to the mechanism underlying many forms of human cancers.

The study not only sheds light on this form of dwarfism, known as achondroplasia, it also could help aid in the understanding of a family of other developmental disorders responsible for a variety of skeletal malformations.

"It suggests a similar type of biochemical mechanism that underlies all these other syndromes," said Daniel Donoghue, professor of chemistry and biochemistry with UCSD's Center for Molecular Genetics. Some of these other skeletal disorders include Crouzon Syndrome, Apert Syndrome, Jackson-Weiss Syndrome and Thanatophoric Dysplasia.

Achondroplasia occurs with an estimated frequency as high as one in 15,000 births. It is brought about by a defect in the growth of cartilage in the growth plates of long bone, resulting in dwarfism.

About two years ago, geneticists traced achondroplasia to a small mutation in a gene located on human chromosome 4 that contains the instructions for fibroblast growth factor 3 (FGFR3), a protein needed for skeletal development in the embryo.

The discovery opened the possibility of prenatal diagnosis of the disorder. But it left unresolved the nature of the biochemical dysfunction that underlies achondroplasia.

The new study, published in the February issue of The EMBO (European Molecular Biology Organization) Journal, begins to answer some of those questions.

In essence, the researchers discovered that the mutated form of FGFR3 results in it being turned on all the time; by comparison, in normal individuals the protein is turned on and off as needed in response to various regulatory signals.

The defect is unlike most other congenitally linked disorders that generally result from a nonfunctioning gene. Such defects potentially can be treated through genetic therapy by simply replacing the nonfunctioning gene with a functioning gene.

While understanding the mechanism behind achrondoplasia represents a definite advance, it therefore brings with it a disappointing conclusion.

"What it implies is that you just can't simply add something in order to counteract this defect," said Melanie K. Webster, coauthor of the study and postdoctoral researcher at UCSD. "It's always on. And what you have to do is turn it off"

FGFR3 is a member of a larger family of regulatory proteins, called receptor kinases, that are central to the proper growth and development in humans. Receptor kinases generally play critical roles in regulating the growth of healthy functioning cells. Inside cells, they relay instructions that are involved in regulating cell growth and division, tissue differentiation in embryos, functioning of the central nervous system, and most of the complex instructions for cellular changes from birth to death.

Often, faulty regulation of these receptor kinases results in the proliferation of cells responsible for tumor formation, leading to breast cancer and many other types of cancer.

When the defect in question is a mutation in the fibroblast growth factor receptor, the UCSD researchers found, the result is abnormal development of cells and tissues. In the case of achondroplasia, it appears that a developmental switch responsible for differentiation of cells into cartilage and bone goes awry.

"What happens when you turn on one of these receptors abnormally, you don't get cancer, but you get a defect in the developmental program that gives rise to a human being," said Donoghue.

"This is really a remarkable thing," he continued. "When you tell most people that a receptor kinase is turned on, they ask what kind of cancer do you have. But you don't get cancer from this."

Perhaps of greater significance, Donoghue said, the study suggests that other congenital disorders of the skeleton also may arise from the abnormal activation of receptor kinases..

"This underlying mechanism demonstrated in our study is a constitutive activation, or turning on, of one of these receptors, rather than a loss of function," said Donoghue.

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