# New type of genetic change identified in inherited cancer

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Duke University Medical Center and National Cancer Institute scientists have discovered that a novel genetic alteration - a second copy of an entire gene - is a cause of familial chordoma, an uncommon form of cancer arising in bones and frequently affecting the nervous system.

Inherited differences in gene copy number, known as copy number variation (CNV), have been implicated in some hereditary diseases but none of the previously discovered familial cancer genes has had CNV as the genetic change.

"This alteration is unlike anything we have ever seen before in families that tend to develop the same kind of cancers," says Michael Kelley, M.D., an associate professor at Duke University Medical Center and senior author of the study appearing in Nature Genetics. "We are not talking about a mutation in a single gene, but the duplication of an entire gene. This discovery is a classic example of where science answers one question but raises many, many more."

Chordoma is rare, striking only one in every million people. But it is a devastating diagnosis. People who have the disorder typically develop tumors at the base of the skull, in the pelvis, or along the spinal column. The growths are thought to arise from remnants of the notochord, an embryonic precursor to spinal column. There are few treatments and no cure for chordoma; most who have the disease usually die within 10 years.

Kelley, chief of hematology and oncology at the Durham Veterans Affairs Medical Center, has been studying chordoma for years after a collaborator at the National Cancer Institute, Dilys Parry, a co-author of the study, discovered a family with a history of the disease spanning several generations. They concluded that there had to be some sort of inherited genetic defect at work. Parry conducted clinical studies that eventually identified six additional families with multiple relatives with chordoma.

Initial work focused on possible defects on chromosome 7, but no defect was found that was shared by all of those affected. Researchers conducted linkage studies that revealed six new areas in the genome where potential mutations were likely. But it wasn't until they used a technique called array comparative genomic hybridization, a method that allowed them to see structural changes in the genome in exquisite detail, that they were able to pinpoint the source of the culprit. They identified it as the T (Brachyury) gene on chromosome 6.

"Brachyury is a transcription factor that helps regulate the development of the notochord and we know the gene is overly active in the tumor tissue in many people with chordoma," says Kelley, "so we were pretty sure we were on to something."

Investigators screened 65 individuals (21 with chordoma) in seven families with a history of the disease, specifically looking for any alterations in the T gene. They discovered that all the patients with chordoma in four of the seven families had a second copy of the T gene. The duplication did not appear among members of the three other families, nor did it appear in 100 healthy, normal controls.

Kelley says investigators do not understand what Brachyury does to cause chordoma. Brachyury expression was found in tissue from chordomas not only in patients who had inherited the duplication but

also in those who did not have the duplication.

"It is likely that other genes are at work here, or that some other mechanism we do not yet understand is in play. Based on our research, however, we do feel that it may be worthwhile to screen for complex genomic rearragements when trying to find the cause of familial cancers. It may be a more productive route than traditional gene-mapping methods."

Xiaohong Yang of the National Cancer Institute wrote the first draft of the paper, and along with David Ng, also of the NCI, analyzed the data. Ng, Sufeng Li, Kelly and David Alcorta, all of Duke, performed the laboratory studies including genotyping, sequencing and breakpoint evaluation. Parry, Ng, Eamonn Sheridan of St. James Hospital in Leeds, UK, and Norbert Liebsch, from Massachusetts General Hospital, identified and evaluated the chordoma families. Yang, Ng, Kelley, Parry and Alisa Goldstein planned the work and interpreted the results.

Source: Duke University Medical Center (news : web)

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