Muscle gene mutations implicated in human nasal/sinus cancer

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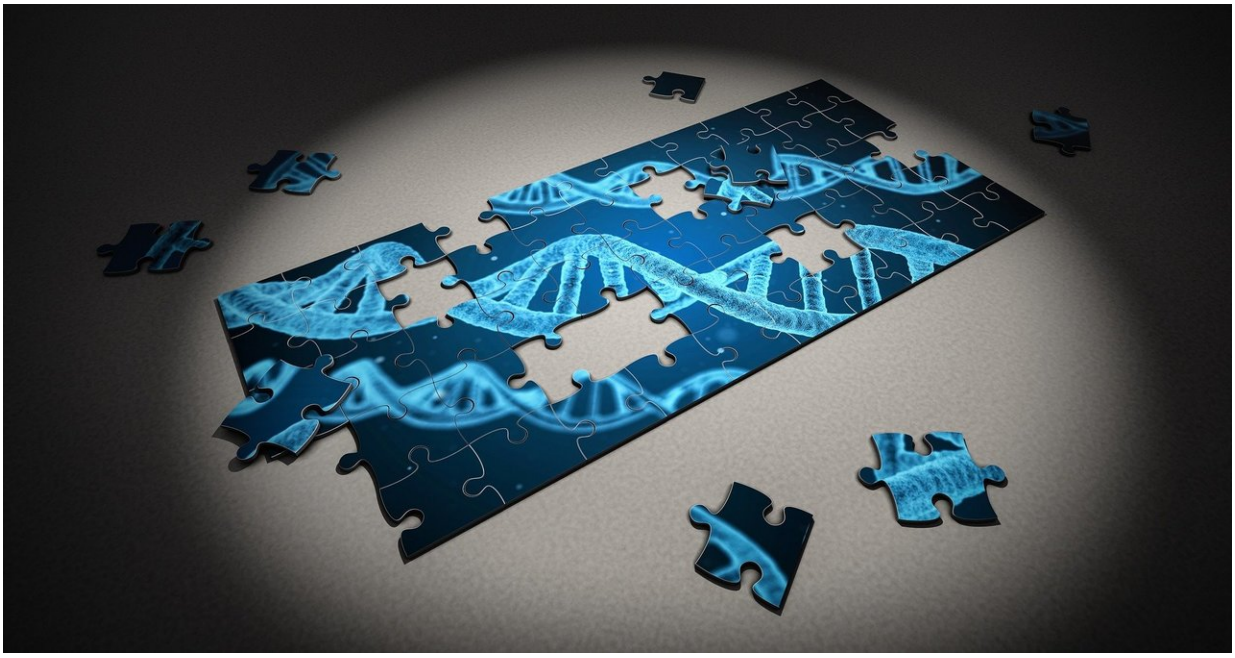

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By sequencing the entire genomes of tumor cells from six people with a rare cancer of the nose and sinus cavity, Johns Hopkins researchers report they unexpectedly found the same genetic change¾one in a gene involved in muscle formation¾in five of the tumors.

"In terms of research linking genetic alterations to cancers, this is a true

mountain and not a molehill," says Gary Gallia, M.D., Ph.D., associate professor of neurosurgery at the Johns Hopkins University School of Medicine. "It's fairly rare that a single gene is tied so tightly to the same cancers in unrelated people."

In a report on their findings, published Dec. 21, 2018, in *Nature Communications*, the researchers say the deletions they identified in a gene that codes for dystrophin, a rod-shaped protein that helps anchor muscle fibers in place, were found in olfactory neuroblastoma cells. Olfactory neuroblastomas make up just 6 percent of all sinus and nasal cancers, with a prevalence rate of one person out of every 2.5 million. Nationwide, that translates to about 100 to 200 diagnosed cases each year. Johns Hopkins Medicine's neurosurgery skull base center is among the most experienced in treating patients with olfactory neuroblastoma. The center also has a robust supply of tissue samples from these tumors.

The researchers say their findings contribute not only to a better understanding of the cause of these cancers, but also to the potential for creating animal and cell models for further study and development of treatments that target the tumor's genetic roots.

"Now that we believe we know the genetic cause of olfactory neuroblastoma, we can devise ways to disrupt the cancer, learn how it forms and explore new ways to treat it," says Chetan Bettegowda, M.D., Ph.D., associate professor of neurosurgery at the Johns Hopkins University School of Medicine and director of the Johns Hopkins meningioma center. "This was really an unexpected but fruitful finding."

Bettegowda says their finding was unexpected because perceptions of nasal and sinus tissue don't immediately bring to mind a dominant role for muscle tissues. But, among geneticists, he says, it's well known that many developmental genes that help form the tissues of the human body are multipurpose.

For their study, the researchers first sequenced the tumor and matched normal DNA of nine men and two women with olfactory neuroblastoma taken from patients treated at Johns Hopkins over seven years. The patients ranged in age from 33 to 69.

The researchers sequenced the parts of the genomes that make up the genes and not the spaces between the genes. Although they found two tumor samples had mutations in a large gene that makes the protein Titan, the researchers were unsure if these mutations may have contributed to formation of the cancer, as they didn't see much else in common among the samples.

Next, they chose six of these samples at random and did whole genome sequencing that looks at the DNA that makes up the genes and the DNA between the genes.

This time they found that five of the six samples had deletions on the X chromosome, and in every case, the deleted portion of DNA spanned the gene DMD, which codes for the protein dystrophin, one of the genes implicated in muscular dystrophy. They then reexamined the original tumor samples, as well as a few others, with other techniques to look for deletions in dystrophin. In total, they found 12 out of 14 tumors had deletions in the DMD gene. In one tumor that didn't have a DMD deletion, they found a deletion in another muscular dystrophy gene: LAMA2.

Dystrophin is one of the longest genes in the human genome, and has 79 pieces of DNA interspersed with bits that don't code for the gene. Because of the gene's large size, if part of a chromosome in which it resides is deleted or rearranged, it's statistically more likely to interrupt a large gene like dystrophin.

The researchers aren't sure if the dystrophin protein is made in the

olfactory neuroblastoma or if a shortened mutated form messes up the inner workings of the cells that form the tumor. These are experiments for future studies, they say.

The researchers still also don't know what kind of cells the cancer originates from, although they are thought to arise from the neuroepithelium—the lining—of the sinuses at the point where the smell nerves poke through.

As for whether their findings point to potential new therapies for this cancer, Bettegowda says, "Some low-hanging fruit could be to test certain therapies in the lab that have been tried in people with muscular dystrophy. Although those therapies have failed in treating muscles dystrophies, these conditions affect every cell in the body. But this cancer is found in one specific location, so the treatments might have a better chance of finding a target."

Typical signs of olfactory neuroblastoma are congestion, sinusitis, loss of sense of smell and nosebleeds.

More information: Gary L. Gallia et al. Genomic analysis identifies frequent deletions of Dystrophin in olfactory neuroblastoma, *Nature Communications* (2018). DOI: 10.1038/s41467-018-07578-z

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