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Studies spot numerous undiscovered gene alterations in pancreatic and brain cancers

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HHMI investigators have detected a multitude of broken, missing, and overactive genes in pancreatic and brain tumors, in the most detailed genetic survey yet of any human tumor. Some of these genetic changes were previously unknown and could provide new leads for improved diagnosis and therapy for these devastating cancers.

The discoveries, described in two reports published September 4, 2008, in *Science Express*, which provides early electronic publication of selected Science papers, emerged from the sequencing of nearly all the known protein-making genes in pancreatic cancers and in the most common form of brain tumors, glioblastomas. The study adds numerous items to the known "parts list" of these cancers, though further research is needed to determine which gene changes actually trigger development or spread of the disease.

HHMI investigator Bert Vogelstein and colleagues at the Johns Hopkins Kimmel Cancer Center, in collaboration with investigators at Duke University and elsewhere, sequenced 20,661 genes in cells from 24 patients with pancreatic cancer and 22 patients with glioblastoma. The team identified hundreds of gene mutations associated with the cancers. The researchers also found numerous cases where tumor cells had extra or too few copies of a gene. The typical pancreatic cancer contained 63 genetic alterations, while the average brain tumor contained 60. Using "next generation" sequencing, the researchers also comprehensively assessed changes in levels of gene activity.

Taken together, the two studies suggest that a small number of commonly mutated genes - or "mountains" - and a much larger number of rarer, low-frequency gene changes - "hills" - cause these cancers, said the researchers.

The authors said their results demonstrate that "genome-wide genetic analyses…can identify the precise genetic alterations that are likely to be responsible for pathway disregulation in each patient's tumor." They found that each individual tumor had its own particular assortment of gene changes. "If you have 100 patients, you have 100 different diseases," said Vogelstein, who is a co-corresponding author of the Science paper with Johns Hopkins researchers Victor E. Velculescu and Kenneth W. Kinzler. "But this will not surprise clinical oncologists, because they see how different every patient is" in the way their tumor behaves and responds to treatment.

Cancer biologist Tyler Jacks, a Howard Hughes Medical Institute investigator at the Massachusetts Institute of Technology who was not involved in the studies, said he was not surprised by the large number of infrequent gene mutations — primarily because Vogelstein and his colleagues reported in 2007 that they had found breast and colon cancers to be similarly complex genetically. "But if you had asked me three years ago, I would have given a different answer," Jacks said.

Vogelstein said the sheer number and variability of genetic changes in the tumors pose a challenge to one of the main goals of "personalized medicine" — identifying as many cancer-causing mutations as possible and developing an array of targeted drugs, each designed to strike a specific mutation.

Jacks agreed that cancer researchers would have preferred that tumors' mutational landscapes be dominated by the high-frequency "mountains," as these make attractive targets for the design of new drugs. With

conventional DNA sequencing technologies, these prominent mountains were the mutations most readily linked to cancer, he said. But as new methods make it feasible to sequence nearly all the genes in a tumor sample, researchers are beginning to recognize that "the landscape is crowded with changes, mostly occurring at low frequency."

"It's suggesting that maybe we shouldn't even be focusing so much on the individual genes that are mutated," Vogelstein said. "Instead, we should be thinking about the functional pathways in which these genes operate. This is a different way of looking at how cancer develops."

Indeed, many of the gene abnormalities could be grouped into functional units. For example, when they analyzed the DNA in 24 pancreatic cancers, the scientists identified 12 core signaling pathways that were each abnormal in the great majority of tumors. Some of those pathways regulate apoptosis - the programmed death of abnormal cells - or repair of damaged DNA. Other altered pathways control the rate of cell division, influence how tightly cells stick together, or determine their ability to invade nearby tissues.

In the brain tumor samples, the survey found that the mutated genes could be grouped into similar pathways, such as those controlling growth and apoptosis. However, some of the newly found mutations occurred in pathways involved in nervous system signaling processes not previously known to be altered in any form of cancer. The scientists speculate that this pathway may be specific for glial cell tumorigenesis.

Similarly, one particular genetic change netted by the survey was found exclusively in brain tumors. That mutation was particularly intriguing because of its potential near-term clinical importance. Specific mutations in the isocitrate dehydrogenase gene IDH1 were found in 12 percent of the brain tumors. They were found in almost all cases of secondary glioblastomas - developing from lower-grade tumors - but

rarely in primary high-grade glioblastomas. They also tended to affect younger patients (average age 33 compared to age 53 for patients without the mutations). Patients whose brain tumors had the IDH1mutation lived significantly longer with their cancer than those who did not.

Although it is not known how the IDH1 mutation contributes to cancer, Vogelstein said that it could help single out individuals who are likely to have better outcomes. With further research, it is conceivable that the mutation could have relevance for therapy, he said.

Like the Vogelstein group's 2007 findings on breast and colon cancer, the new study suggests that many these diseases are caused not by a few major genetic kingpins, but instead by a large cast of minor culprits. How this multiplicity of cancer triggers can best be confronted is uncertain, but the authors of the two papers say it may force a shift in drug development emphasis. The best hope for new therapies, they wrote, "may lie in the discovery of agents that target the physiologic effects of the altered pathways and processes, rather than their individual genetic components."

Source: Howard Hughes Medical Institute