

OCTOBER 11, 2007

Surveying the Genetic Landscape of Breast and Colon Cancers

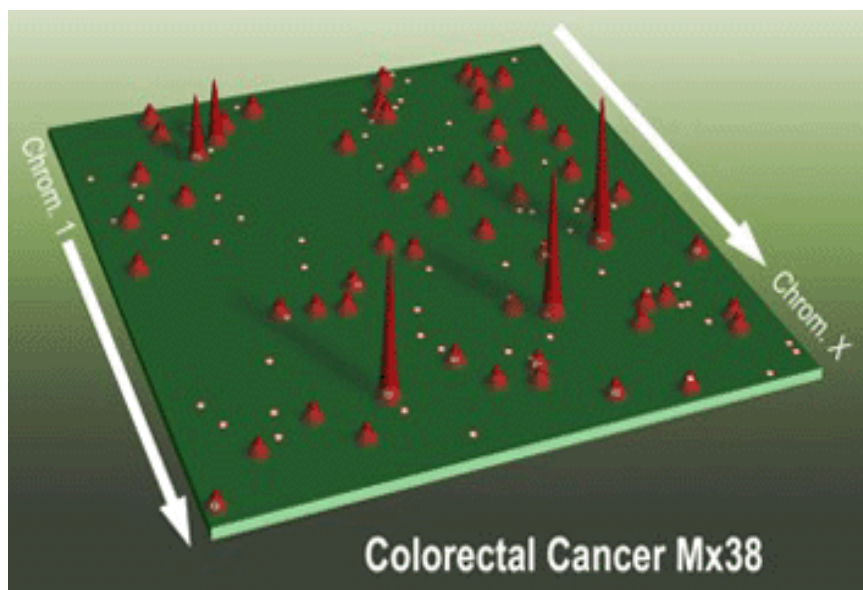


Image Title: Landscape of a typical colorectal cancer. The large peaks indicate the gene mountains, small peaks indicate the hills. The dots correspond to genes that were mutated in the particular cancer (called Mx38) illustrated. - Courtesy of Bert Vogelstein/HHMI at Johns Hopkins

An extensive study of the DNA in cancerous cells has uncovered a large number of genes likely to contribute to the development and progression of breast and colorectal cancer. The study suggests that each breast and colon tumor is unique and may arise through mutations in many different combinations of genes.

Despite the inherent complexity of the diseases, the new studies show that most of the approximately 280 candidate cancer genes identified by the researchers are involved in a much smaller number of biochemical pathways - as few as 15. Studies of these pathways are already producing new ways to diagnose and treat cancer.

“Most or all of the major pathways that contribute to at least these two kinds of cancer have been discovered,” said Bert Vogelstein, a Howard Hughes Medical Institute investigator at the Kimmel Cancer Center at Johns Hopkins, who led the study. “We need to start thinking about cancer in terms of these pathways instead of individual genes, because that’s a more accurate view of how cancers originate.”

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HHMI investigator Sanford D. Markowitz at Case Western Reserve University School of Medicine was also one of 42 authors on the article that was published October 11, 2007, in *Science Express*, which provides electronic publication of selected *Science* papers in advance of publication.

The team isolated DNA from 11 breast and 11 colorectal tumors. They then compared the DNA sequences of all of the RefSeq genes in those cells to gene sequences derived from the Reference Sequence compiled by the Human Genome Project. RefSeq is a compendium of 18,191 genes that represents the gold-standard in the field and is estimated to contain more than 90 percent of the coding information in the human genome.

More than nine percent of the genes (1,718 of 18,191) sequenced in the tumors had at least one DNA change in either a breast or colorectal cancer that altered the protein encoded by the gene. But the majority of these DNA changes were what the researchers called “passenger” mutations that were not involved in the development of the tumor. The team therefore applied statistical and bioinformatics techniques to prioritize the mutations, highlighting genes that were most likely to be causally involved in tumorigenesis (“driver” mutations). In this way, they identified 280 candidate cancer genes that were most likely to be drivers and ranked them on the basis of a variety of criteria.

When the team laid out all 18,000 or so human genes on a two-dimensional grid, the mutation frequency data for the candidate cancer genes formed a few “mountains” amidst a large number of “hills.” The mountains represented genes that are mutated in a large percentage of breast and colorectal tumors -- typically more than 20 percent -- while the hills are mutated in fewer than five percent of tumors. An average of about 15 candidate cancer genes were mutated in each colorectal and breast tumor, respectively.

“The take-home message is that there are a few mountains and many hills, so the low-frequency mutations dominate the landscape,” said Laura Wood, an M.D./Ph.D. student at Johns Hopkins who is the lead author of the paper. “That really wasn't expected when we embarked on this project a few years ago. We all expected to find more mountains hiding out there, and we didn't.”

Once the research team identified the driver mutations, it applied several different techniques to identify genes of special interest. For example, the researchers examined how the mutations they found would change the predicted structure of the protein produced by the gene, with resulting effects on the protein's function. They also discovered candidate cancer genes that produce proteins involved in the regulation of other cancer genes. “By doing that, one can establish relations that link the hills,” said Vogelstein. “This is going to start putting the pieces of the jigsaw puzzle together.”

The large number of candidate cancer genes reveals the underlying complexity of cancer. “Each tumor is genetically very different from every other tumor,” said Wood. “This is a daunting observation for those of us who are trying to figure out how to diagnose and treat cancer.”

Yet the researchers are excited about the underlying “logic” their research has uncovered. “Is it hopelessly complex?” asked Vogelstein. “I don't think it is, because there are some key simplifying concepts.”

For example, the team found that most of the candidate cancer genes are involved in a limited number of biochemical pathways - an encouraging finding, according to Wood. Drugs that manipulate those pathways may be able to block the growth of tumors no matter which genes in the pathway are mutated. A pathway involved in immune and inflammatory responses appears to be turned on in many breast cancers, and pharmaceutical companies are developing drugs that interfere with the activation of that pathway. “Our data suggest that in the subset of breast cancers in which this pathway is involved, those drugs might be worth testing,” said Vogelstein.

The identification of specific mutations in each tumor also could give physicians new ways of attacking or monitoring the disease. For example, antibodies could be directed against tumor cells distinguished by their mutations, or physicians could monitor the regression of a tumor after chemotherapy by looking for cells with those mutations.

More broadly, the discovery that each cancer is unique may give physicians an opportunity to tailor cancer treatments to individuals. “The vast majority of subtle mutations in individual patients' tumors can now be identified with existing technology, making personal cancer genomics a reality,” the researchers conclude in the *Science Express* article.