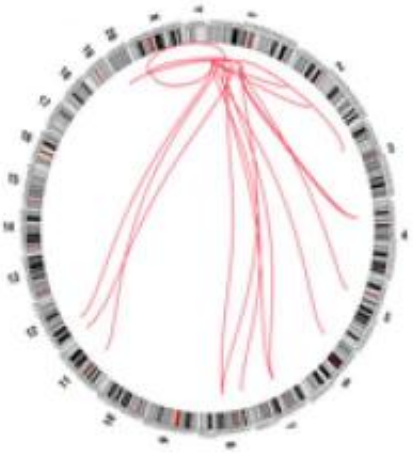
Genomic study shows colon and rectal tumors constitute a single type of cancer

July 18 2012



This image shows translocations involving chromosome 1 in a set of colon and rectal samples. The locations of the breakpoints leading to the translocation and circular representations of all rearrangements in tumors with a fusion are shown. The red line lines represent fusions, black lines indicate other rearrangements. Credit: The Cancer Genome Atlas (TCGA), National Cancer Institute

The pattern of genomic alterations in colon and rectal tissues is the same regardless of anatomic location or origin within the colon or the rectum, leading researchers to conclude that these two cancer types can be grouped as one, according to The Cancer Genome Atlas (TCGA) project's large-scale study of colon and rectal cancer tissue specimens.

In multiple types of genomic analyses, colon and rectal cancer results

were nearly indistinguishable. Initially, the TCGA Research Network studied colon tumors as distinct from rectal tumors.

"This finding of the true genetic nature of colon and rectal cancers is an important achievement in our quest to understand the foundations of this disease," said NIH Director Francis S. Collins, M.D., Ph.D. "The data and knowledge gained here have the potential to change the way we diagnose and treat certain cancers."

The study also found several of the recurrent genetic errors that contribute to colorectal cancer. The study, funded by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health, was published online in the July 19, 2012, issue of the journal *Nature*.

There is a known negative association between aggressiveness of colorectal tumors and the phenomenon of hypermutation, in which the rate of genetic mutation is abnormally high because normal DNA repair mechanisms are disrupted. In this study, 16 percent of the specimens were found to be hypermutated. Three-fourths of these cases exhibited microsatellite instability (MSI), which often is an indicator for better prognosis. Microsatellites are repetitive sections of DNA in the genome. If mutations occur in the genes responsible for maintaining those regions of the genome, the microsatellites may become longer or shorter; this is called MSI.

NCI estimates that more than 143,000 people in the United States will be diagnosed with colorectal cancer and that 51,500 are likely to die from the disease in 2012. Colorectal cancer is the fourth most common cancer in men, after non-melanoma skin, prostate and lung cancer. It is also the fourth most common cancer in women, after non-melanoma skin, breast and lung cancer.

The researchers observed that in the 224 colorectal cancer specimens examined, 24 genes were mutated in a significant numbers of cases. In addition to genes found through prior research efforts (e.g., APC, ARID1A, FAM123B/WTX, TP53, SMAD4, PIK3CA and KRAS), the scientists identified other genes (ARID1A, SOX9 and FAM123B/WTX) as potential drivers of this cancer when mutated. It is only through a study of this scale that these three genes could be implicated in this disease.

"While it may take years to translate this foundational genetic data on colorectal cancers into new therapeutic strategies and surveillance methods, this genetic information unquestionably will be the springboard for determining what will be useful clinically against colorectal cancers," said Harold E. Varmus, M.D., NCI director.

The research network also identified the genes ERBB2 and IGF2 as mutated or overexpressed in colorectal cancer and as potential drug targets. These genes are involved in regulating cell proliferation and were observed to be frequently overexpressed in colorectal tumors. This finding points to a potential drug therapy strategy in which inhibition of the products of these genes would slow progression of the cancer.

A key part of this study was the analysis of signaling pathways. Signaling pathways control gene activity during cell development and regulate the interactions between cells as they form organs or tissues. Among other findings, the TCGA Research Network identified new mutations in a particular signaling cascade called the WNT pathway. According to the researchers, this finding will improve development of WNT signaling inhibitors, which show initial promise as a class of drugs that could benefit colorectal cancer patients.

In addition to examining the WNT pathway, the investigators also identified RTK/RAS and AKT-PI3K as pathways that are altered in a

substantial set of colorectal tumors, which may show promise for targeting therapies for colorectal cancer. Because of these findings, drug developers may now be able to narrow their scope of investigation with an expectation of producing more focused therapeutic approaches, noted the researchers.

"It takes a critical group of researchers to conduct research at this scale and of this quality," said Eric. D. Green, M.D., Ph.D., NHGRI director. "This study is among the most comprehensive of its kind to date and vividly illustrates how TCGA data sets can shed new light on fundamental properties of human cancers."

More information: TCGA Research Network. Comprehensive Molecular Characterization of Human Colon and Rectal Tumors. July 19, 2012. *Nature*. DOI: 10.1038/nature11252

Provided by National Cancer Institute