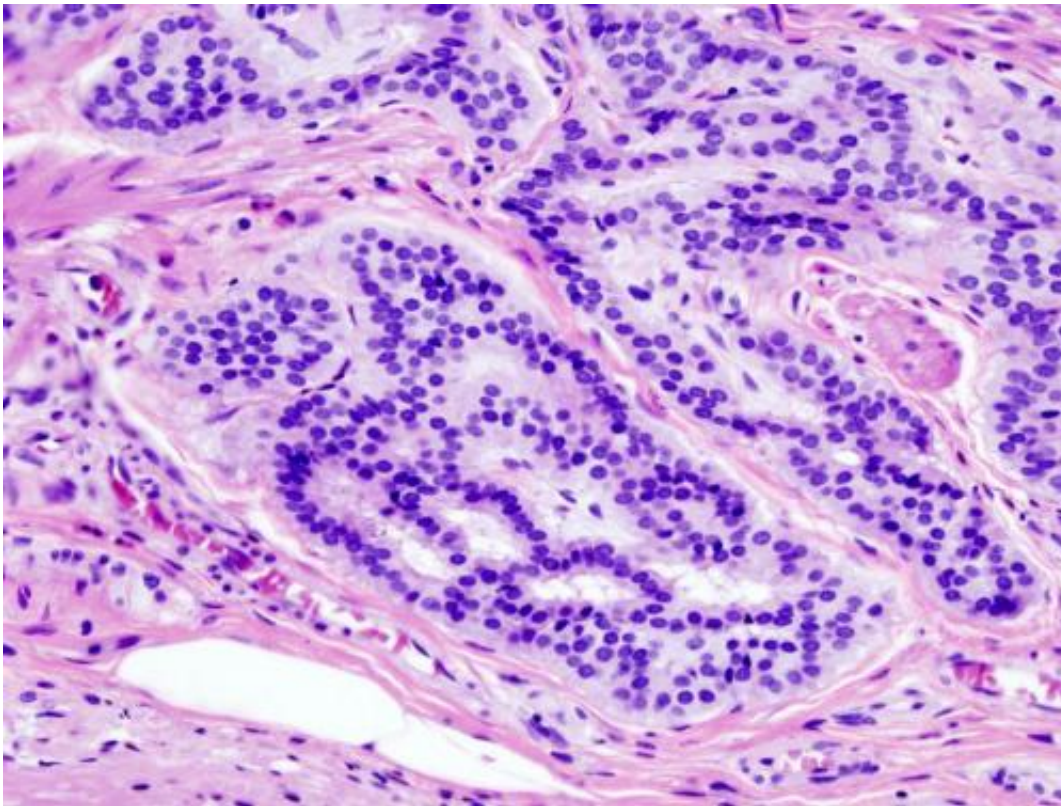


Study identifies new gene mutations linked to colorectal cancer in African-Americans

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Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

Case Comprehensive Cancer Center researchers have identified new gene mutations unique to colon cancers in African Americans - the population with the highest incidence and death rates of any group for this disease.

This discovery - namely, that colorectal cancers appear different on a molecular level in African Americans - offers new hope for these patients. With this groundbreaking knowledge, scientists now will seek to develop treatments that target the distinct nature of the disease in African Americans - and, they hope, begin to reduce the devastation disproportionately wrought on this population.

The findings, published in the Jan. 12 edition of *PNAS (Proceedings of the National Academy of Sciences)*, only became possible because of technological advances in gene sequencing and computational analysis. The study that revealed this invaluable information ultimately involved review of 1.5 billion bits of data.

"This milestone study builds on our previous genetic research on colorectal [cancer](#)," said Sanford Markowitz, MD, PhD, corresponding author on the study, and principal investigator of the \$11.3 million federal gastrointestinal cancers research program (GI SPORE) that includes this project. "It illustrates the extraordinary impact that dedicated, collaborative teams can make when they combine scientific experience and ingenuity with significant investment."

Announced in 2011, this GI SPORE program is one of just five in the country. Markowitz, Ingalls Professor of Cancer Genetics at Case Western Reserve School of Medicine and a medical oncologist at University Hospitals Case Medical Center, included studies of the disease's behavior in minority patients as part of his team's original grant application. The disparity between colorectal cancer rates in African Americans and other groups has long existed; the most recent federal statistics, for example, put age-adjusted incidence at 46.8 cases for every 100,000 African Americans, and 38.1 cases for every 100,000 Caucasian Americans. Yet scientists have struggled to determine what factors - biological, economic, environmental, or others - account for this disparity.

"These advancements underscore the importance of university-based research," said Congresswoman Marcia L. Fudge, former chair of the Congressional Black Caucus and representative of the 11th district, which includes Case Western Reserve and UH Case Medical Center. "I am proud that researchers from Northeast Ohio are taking meaningful steps toward identifying pathways to block a devastating disease that disproportionately affects members of the African American community."

From the very start, Markowitz and his colleagues believed the answer to this question would be found through genetic analysis.

"Identifying gene mutations has been the basis of all the new drugs that have been developed to treat cancer in the last decade," Markowitz said. "Many of the new cancer drugs on the market today were developed to target specific genes in which mutations were discovered to cause specific cancers."

One of the lead researchers on the project was senior author Joseph E. Willis, MD, associate professor of pathology, Case Western Reserve School of Medicine, director of tissue management, Case Comprehensive Cancer Center, and Vice Chair of Pathology for Clinical Affairs at UH Case Medical Center.

"We wondered if colon cancer is the same disease molecularly in African Americans individuals as it is in Caucasian individuals. Or could colon cancer be the same disease behaving differently in one population compared to another," he said. "This study gave us our answer. Colon cancer in African American patients is a different disease molecularly."

The scientists made their discovery by using DNA sequencing to compare 103 colorectal cancer samples from African American patients with 129 colorectal cancer samples from Caucasian patients, all of whom

had received care at UH Case Medical Center in Cleveland. The scientists examined 50 million bits of data from 20,000 genes in every cancer.

From these extensive data, investigators first uncovered 20 new gene mutations in the colorectal cancers of African Americans that never before had been seen in patients with this disease. Investigators then confirmed that 15 of these gene mutations preferentially affected the African American patients. Just over 40 percent of cancers in African Americans carried mutations in one or more these genes. In addition, the scientists found these mutations were 3.3-fold more common in African American cancers than in colorectal cancer tissues from Caucasians.

The investigators particularly zeroed in on mutations in 2 of these 15 genes, EPHA6 and FLCN, detected exclusively in African American patients. EPHA6 belongs to a family of proteins linked to causing cancer; this study marks the first time this gene has been implicated in colorectal cancer. In addition, individuals born with FLCN mutations are known to be susceptible to certain cancers. EPHA6 gene mutations were detected in 5.8 percent of [colorectal cancers](#) of African American patients, and FLCN gene were in 2.91 percent.

"This is the first study to perform a comprehensive [gene mutation](#) characterization and comparison of these colorectal cancer tumors in two ethnicities - African American and Caucasian," said lead author Kishore Guda, DVM, PhD, assistant professor, General Medical Sciences (Oncology), Case Comprehensive Cancer Center. "Our next step will be to collaborate with other centers in investigating African American populations in different regions of the United States to determine whether they also share the unique gene signature found in the Cleveland African American community."

In addition, these investigators want to delve into exactly how these

mutations act and what they do, including whether these gene mutations make [colon cancer](#) act more aggressively. Most importantly, they hope the findings ultimately lead to more precise molecular diagnostic tests and treatments for African American patients.

"We are eager to explore and pinpoint colorectal cancer-causing gene mutations," Markowitz said, "as the first step to improving outcomes, and hopefully some day to saving lives, among African American patients affected by this illness."

More information: Novel recurrently mutated genes in African American colon cancers, *PNAS*,
www.pnas.org/cgi/doi/10.1073/pnas.1417064112

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