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Study discovers 40 new genetic variants associated with colorectal cancer risk

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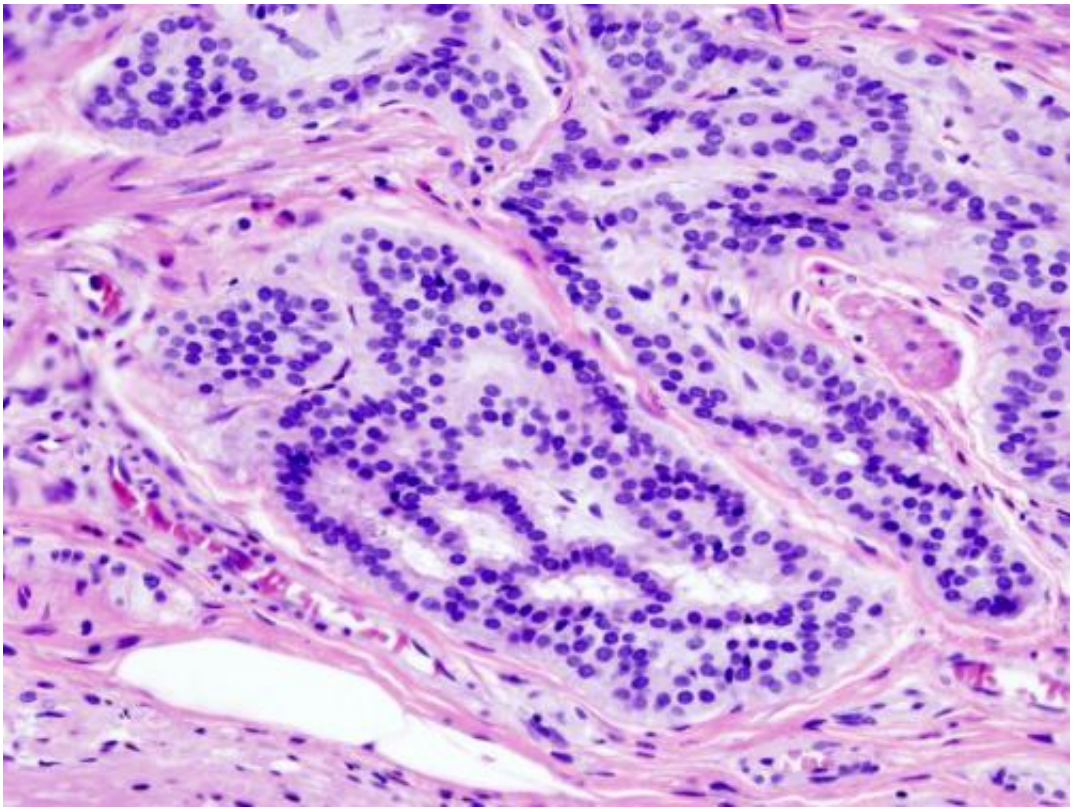

Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

The most comprehensive genome-wide association study, or GWAS, of colorectal cancer risk to date, published today in *Nature Genetics*, has discovered 40 new genetic variants and validated 55 previously identified variants that signal an increased risk of colon cancer.

The study, led by a team of investigators at Fred Hutchinson Cancer Research Center, also has identified the first rare protective variant for sporadic colorectal cancer. Sporadic colorectal cancers have no known familial syndrome and account for the vast majority of colorectal cancer cases. Together, these findings are a significant step toward creating personalized screening strategies and better informing drug development for colorectal cancer.

"A study of this magnitude was only possible through collaboration with our partners from institutions around the world," said Dr. Ulrike "Riki" Peters, associate director of the Public Health Sciences Division at Fred Hutch and recipient of Fred Hutch's 40th Anniversary Endowed Chair. "Understanding the genetic architecture of colorectal cancer will revolutionize how we assess risk and treatment for this disease, which is the second most deadly cancer in U.S." In 2009, Peters initiated and has since led the Genetics and Epidemiology of Colorectal Cancer Consortium, the world's largest molecular genetic consortium for colorectal cancer.

These findings also illuminate what the study authors call "a missed opportunity" in drug development. The study identified several loci, the physical location of the gene on a chromosome, near proposed drug targets and genes in pathways not previously known to be causally linked to colorectal cancer. Using GWAS results to inform cancer drug development, the authors believe, could improve the drug-development success rate and even lead to chemoprevention drugs for high-risk individuals.

"There's great potential in using GWAS results to inform target discovery for anti-cancer drugs. For diseases like type 2 diabetes and heart disease, the GWAS approach drives the discovery of new biology and potential drug targets," explained Dr. Jeroen Huyghe, who co-led the study's statistical genetic analysis and is a staff scientist at Fred Hutch.

"To date, the search for new targets for cancer therapy has been limited to focus primarily on the molecular characteristics of cancer cells. We think there is a huge opportunity in using the GWAS approach to inform drug development for colorectal cancer."

Researchers from more than 130 different institutions contributed to this study, many by sharing data and biospecimens that allowed the team to analyze the genomes of more than 125,000 individuals, of which there were 58,131 colorectal cancer cases and 38,296 control participants who had not developed the disease. The number of participants in this study is nearly double that of previous analyses of this type.

"Large-scale whole-genome sequencing studies have discovered millions of genetic variants that have yet to be examined systematically for association with disease," Huyghe explained. "Our research capitalized on the availability of the Haplotype Reference Consortium panel, a population reference panel of sequence data from more than 32,000 individuals. By coupling this strategy with a custom-designed genotyping chip, we were able to robustly identify a rare variant association signal and multiple additional signals involving lower-frequency variants."

Previous GWAS for colorectal cancer risk only looked at common genetic variants. In contrast, this study involved whole-genome sequencing of more than 2,000 individuals and was designed to examine the contribution of rare genetic variants to colorectal cancer risk.

"With this study, we've brought the known number of risk variants for colorectal cancer to nearly 100," said Tabitha Harrison, a shared first author of the study and a genetic epidemiologist at Fred Hutch. "Next, we're broadening the study population to include people from diverse ethnic backgrounds. This will give us a more complete understanding of risk across the entire population."

The study authors acknowledge a bias in the study sample, of which 91 percent were people of European descent.

"It is critically important that we increase diversity in our future studies because premature use of these findings to inform screening guidelines could exacerbate existing racial disparities in colorectal cancer screening and survival rates," cautioned Dr. Stephanie Bien, a shared first author of the study and staff scientist at Fred Hutch.

Genetic variants occur from differences in our DNA. Most variants are believed to be benign, some are known to be associated with various diseases and the significance of many others are unknown. While individual genetic variants have little impact on disease risk, several combined variants can become clinically relevant, and this could have an impact on future personalized screening recommendations.

"Individuals with genetic risks in the top decile could benefit from earlier screening by colonoscopy," said Dr. Li Hsu, a biostatistician at Fred Hutch and the lead biostatistician in the consortium.

To evaluate a person's full risk profile, genetic risk factors need to be combined with other epidemiological factors, such as diet, weight and exercise. In some cases, a low genetic risk score could be skewed by unhealthy lifestyle factors to yield a high overall risk profile. This type of work is currently conducted by the team, which not only collected genetic data from all studies, but also harmonized many clinical and lifestyle risk factors across more than 70 studies. Furthermore, the research team believes there may be hundreds of other genetic variants contributing to colorectal cancer risk that have yet to be identified.

More information: Jeroen R. Huyghe et al, Discovery of common and rare genetic risk variants for colorectal cancer, *Nature Genetics* (2018). DOI: 10.1038/s41588-018-0286-6

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