

Study uncovers early genetic changes in premalignant colorectal tissue

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Researchers at The University of Texas MD Anderson Cancer Center have discovered mutations that may fuel early cancer growth in precancerous colorectal tissue from high-risk patients.

Their study, published in *Cancer Prevention Research*, is the first to use advanced genetic sequencing techniques to characterize genetic changes in [precancerous polyps](#) and nearby tissue that has not yet transformed into polyps. In addition to mutations at very early stages of cancer development, the findings identify potential drug targets for colorectal cancer (CRC) prevention.

Although most of the genetic changes present in advanced CRC are known, those occurring before cancer develops have remained elusive, explained co-senior author Eduardo Vilar-Sanchez, M.D., Ph.D., assistant professor, Clinical Cancer Prevention. To identify the earliest mutations, researchers studied polyps and nearby colorectal tissue, or mucosa, from patients with familial adenomatous polyposis (FAP), a hereditary cancer syndrome caused by an inherited mutation in the APC gene.

APC mutations are responsible for 80 percent of CRC cases, making FAP an attractive model to study CRC development, explained Vilar-Sanchez. Although responsible for only 1 percent of all diagnoses, patients with FAP have a 100 percent lifetime risk of developing CRC without preventive actions.

"We have a great need to identify prevention strategies in these populations. The idea is to develop a mini pre-malignant genome atlas to better understand the genomic events in small polyps very early on. Our study sets the groundwork to identify novel biomarkers or targets for chemoprevention," said Vilar-Sanchez.

Researchers characterized genetic changes in polyps and adjacent mucosa samples, which, despite appearing normal, is considering "at-risk" tissue. Whole exome sequencing was performed on 25 [colorectal polyps](#), 10 adjacent mucosa, and 12 blood samples from 12 patients with FAP from MD Anderson and the Catalan Institute of Oncology.

A particular challenge associated with samples of this type is that the precancerous cells with mutations of interest are mixed with a majority of normal tissue.

"In addition to looking for [genetic mutations](#) in a small fraction of the DNA, there is a very limited amount of total DNA to study, since the polyps are small," said co-senior author Paul Scheet, Ph.D., associate professor, Epidemiology, and team lead for the algorithm used for the complex sequencing analysis. "As these lesions are at a very early stage of potential transition to malignancy, assessing mutations demands a highly sensitive method that makes use of all available knowledge."

Researchers identified 2,314 genetic changes in polyps, with an average of 83 mutations per polyp and an average rate of 1.75 mutations per megabase, or 1 million DNA bases. In adjacent mucosa, the researchers discovered 279 alterations, with an average of 27 mutations per sample and an average rate of 0.49 mutations per megabase.

Many of these mutations appeared to be in groups of genes that work together in cell signaling networks. Members of one network, called the Wnt signaling pathway, which includes the APC gene, appear to be

especially important for the transformation of mucosa to polyps.

"Wnt is the dominant driver for these types of polyps at a very early stage. It is completely central to the development of pre-malignancy in colorectal cancer, and targeting Wnt should be a priority for chemoprevention," said Vilar-Sanchez.

When comparing mutations identified in these samples, the research team found at least 23 percent of [mutations](#) in the polyps already were present in at-risk mucosa. A further comparison between polyps and Stage I cancers from The Cancer Genome Atlas revealed greater similarity between premalignant and cancerous tissue than expected.

"Mutation rates of adenomas were surprisingly very close to the mutation rates you will find with Stage I colorectal cancers. You obviously see the rates go up, but between polyps and cancers, there is a good degree of overlap," said Vilar-Sanchez.

Those polyps with more [genetic changes](#), similar to [early stage](#) cancers, may be more likely to develop into CRC, explained Vilar-Sanchez. Unfortunately, there is no way to be sure which polyps will transform after they have been removed from the patient.

The study was limited by a small number of samples and the small amount of available sample. In future work, the team plans to analyze similar samples from individuals with an average risk of CRC.

Additionally, they plan to analyze precancerous tissue for gene expression changes to complement genetic alterations, in order to better characterize the molecular subtypes of early polyps. Doing so may allow physicians to predict which [polyps](#) present a higher risk, and to develop treatments to prevent them from progressing to [cancer](#).

Provided by University of Texas M. D. Anderson Cancer Center

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