MedicalXpress

Three new genetic links to colorectal cancer

December 23 2012

Vanderbilt-Ingram Cancer Center investigators have identified three new genetic "hotspots" linked to colorectal cancer. These variants, reported Dec. 23 in an Advanced Online Publication in *Nature Genetics*, provide new insight into the biology of colorectal cancer – and could represent new therapeutic targets for the disease.

Colorectal cancer is one of the most commonly diagnosed cancers worldwide – and rates are particularly high in the United States and other developed countries. Genetics plays an important role in both sporadic and familial (inherited) forms of the disease. However, only about 6 percent of colorectal cancer cases are explained by the rare genetic variants known to confer high risk of colorectal cancer (as seen in familial forms of the disease).

Previous studies on the genetic basis of colorectal cancer have pinpointed several additional variants, but most of the studies were conducted in European/Caucasian populations.

"Looking at different ethnic groups is important because the genetic structures can be different enough that variants identified in one population do not explain risk in other populations," said Wei Zheng, M.D., Ph.D., MPH, an Ingram Professor of Cancer Research and senior author on the study. "Because of the difference in genetic structures and underlying environment exposures, it might be easier to discover some risk variants in studies conducted in non-European populations."

In 2009, Zheng and colleagues in several Asian countries established the

"Asia Colorectal Cancer Consortium" to search for novel genetic risk factors for the disease. The consortium included populations in China, Korea and Japan.

Using an approach known as a "genome-wide association study" (or GWAS), Zheng and colleagues began searching for common variants linked to disease risk.

From genomic data obtained from 2,098 colorectal cancer cases and 5,749 controls, the researchers identified 64 variants, or "single nucleotide polymorphisms" (SNPs), that were associated with colorectal cancer.

The investigators then replicated these findings in another set of samples, narrowing down the number of disease-associated variants to four. Three of those four variants were also associated with colorectal cancer risk in a larger European sample.

"The findings from this study are relevant to both Asian and European populations," said Zheng. "Interestingly, these three susceptibility loci were not discovered in previous studies conducted in European-ancestry populations."

This study highlights the importance of conducting genetic studies in non-European populations to fully uncover the genetic basis for common diseases, including colorectal cancer, Zheng noted.

While the specific functions of these newly identified susceptibility loci are not clear yet, several important genes are located in the regions near the risk variants discovered in this study. For example, one risk variant is located near CCND2, the gene encoding cyclin D2, a member of the cyclin family of proteins that regulate the cell cycle. Cyclins have been linked to cancer, but research on the CCND2 gene has been limited.

Therefore, the current findings suggest the need for further research on the role of other cyclins and cyclin-dependent kinases in carcinogenesis.

"These new discoveries are very exciting," Zheng said. "They will certainly lead to future studies regarding the biology of these regions and the translational potential of these findings in cancer prevention and treatment."

Provided by Vanderbilt University Medical Center