

Beyond associations: Colorectal cancer culprit found

April 23 2009

Genetics plays a key role in determining risk for colorectal cancer, the second leading cause of cancer-related deaths in the United States. Several common genetic markers have been found to be associated with the disease, but finding the biological events that lead to cancer can be much more difficult. In a study published online in *Genome Research*, scientists have identified a common genetic variation associated with the risk of colorectal cancer and its functional implications, shedding new light on the basis of this deadly disease.

Hunting down the genes that underlie diseases such as colorectal cancer is extremely difficult, owing to the genetic heterogeneity of <u>cancer cells</u>. Numerous mutations can be found in a cancer cell, but the key to developing new treatments and therapies is to identify the variants that cause the disease hidden amongst many mutations that are simply bystanders. Recently, researchers have been aided in this search by the genome-wide association study (GWAS), a technique that scans the genome for known common genetic variants, also known as <u>single</u> <u>nucleotide polymorphisms</u>, or "SNPs," that are more prevalent in patients with a specific disease. However, a SNP associated with a disease is not necessarily the culprit - but it raises a red flag that something important is nearby.

In this study, an international team of researchers led by Dr. Richard Houlston of The Institute of Cancer Research in the United Kingdom have delved into the biology underlying common variants on chromosome 18 that his group recently found to be associated with



colorectal cancer in a GWAS. They sequenced the region of DNA surrounding these markers in a large group of colorectal cancer cases and controls, identifying all variants residing in this chromosomal region common to colorectal cancer patients.

Houlston and colleagues then focused on the novel variant most strongly associated with colorectal cancer, and found that it resides in a DNA sequence that is conserved in many other species - so well conserved that they were able to use xenopus frogs as a model organism to test the biological consequences of this SNP. The group found that the SNP causes the expression of a nearby gene, called *SMAD7*, to decrease. SMAD7 is an inhibitory regulator of TGF-beta signaling. If cellular levels of *SMAD7* are down, critical signaling events could be set into motion, leading the cell on the path to cancer. This result is particularly important because disruption of *SMAD7* expression has been previously implicated in progression of colorectal cancer. Taken together with this knowledge, their observation supports a direct role for *SMAD7* in cancer progression, and very likely the causal basis for colorectal <u>cancer risk</u> associated with this chromosomal region.

Houlston explained, "Our efforts show that many different methodologies are required to close in and identify disease-causing variants identified through genome-wide association studies." Their work specifically exemplifies the combination of genetic and functional analyses, including regenotyping, resequencing, and use of model organisms, needed to approach the biological mechanism of cancer. By identifying the true causal variants and understanding the biological basis for cancer risk associated with those variants, researchers will be able to design better screening strategies and more effective therapies for patients.

More information: The manuscript will be published online ahead of print on April 24, 2009. Its full citation is as follows: Pittman AM,



Naranjo S, Webb E, Broderick P, Lips EH, van Wezel T, Morreau H, Sullivan K, Fielding S, Twiss P, Vijayakrishnan J, Caseres F, Qureshi M, Gomez-Skarmeta JL, Houlston RS. The colorectal <u>cancer</u> risk at 18q21 is caused by a novel variant altering SMAD7 expression. Genome Res doi:10.1101/gr.092668.109. <u>www.genome.org</u>

Source: Cold Spring Harbor Laboratory (<u>news</u> : <u>web</u>)

Citation: Beyond associations: Colorectal cancer culprit found (2009, April 23) retrieved 4 May 2024 from <u>https://medicalxpress.com/news/2009-04-associations-colorectal-cancer-culprit.html</u>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.