Scoping Out Genetic Contributions to Esophageal Adenocarcinoma

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Esophageal adenocarcinoma is a rare--but increasingly common--cancer with a high mortality rate. While risk factors such as gastroesophageal reflux, cigarette smoking, obesity, and Heliobacter pylori CagA seronegativity play a role in the majority of cases, the genetic contributions to esophageal adenocarcinoma risk have not yet been fully identified. Finding these genetic factors is an important step towards identifying those at highest risk in order to more precisely target prevention, surveillance, and treatment efforts. Collaborating with an international team of colleagues, Dr. Thomas Vaughan in the Public Health Sciences Division recently published two high profile papers that help to elucidate the genetic underpinnings of this commonly fatal disease. Together, these findings demonstrate that many shared genes underlie the development of both esophageal adenocarcinoma and its main precursor, Barrett's esophagus.

The first paper, in the *Journal of the National Cancer Institute*, evaluated the genetic architecture underlying gastroesophageal reflux, Barrett's esophagus, and esophageal adenocarcinoma. These three conditions were expected to share some common genetic background, as Barrett's esophagus typically arises in patients with chronic gastroesophageal reflux, and each year up to 0.5% of Barrett's esophagus cases progress to esophageal adenocarcinoma. Utilizing genome-wide association data, the authors found that 25% of esophageal adenocarcinoma cases, and 35% of Barrett's esophagus cases, were influenced by common genetic variants. They also found a high genetic correlation and a statistically significant polygenic overlap between these two conditions, but not with gastroesophageal reflux. These results suggested that shared genetic variation underlies the development of Barrett's esophagus and esophageal adenocarcinoma.

This finding proved a useful insight for the second paper, in *Nature Genetics*, in which the authors combined cases of both conditions together to perform a joint genome-wide association study on Barrett's esophagus and esophageal adenocarcinoma. Using this combined case group the authors were able to identify three new genetic loci associated with risk of these diseases, as well as extend one previously reported association with Barrett's esophagus to esophageal adenocarcinoma. Together with the findings from their *JNCI* study, says Vaughan, these results suggest that "the role of inherited susceptibility to this cancer appears to be much stronger in the early stages of the disease". In other words, much of the genetic basis for this cancer seems to lie in

"the development of Barrett's esophagus, rather than in the progression of Barrett's to esophageal adenocarcinoma".

This hypothesis is buoyed by the fact that all four loci identified (*CRTC1, BARX1, FOXP1, and FOXF1*) are in or near genes associated with early development of the esophagus or oncogenic activity. The identification of such loci, says Vaughan, "implies that we may be close to finding some important pathways in the development of this highly fatal disease".

Both projects leveraged the collective resources of BEACON, the Barrett's and Esophageal Adenocarcinoma Consortium, combining scientific resources and expertise from institutions in North America, Europe, and Australia. This collaborative effort was key to both projects, says Dr. Vaughan, which "wouldn't have taken place without the generosity and trust of the participating scientists". Combining forces provided the authors the number of cases and controls necessary to study these conditions together, and the ability to explore multiple hypotheses simultaneously. To this end, the authors already have over a dozen additional analyses underway, including projects to examine gene-environment interactions, investigate disease pathways involving multiple gene sets, and characterize overlap with somatic genomic changes. Given their recent success in elucidating the genetic underpinnings of these conditions, such follow-up certainly seems warranted.

Other PHS investigators contributing to this project were Drs. Lynn Onstad and Brian Reid.

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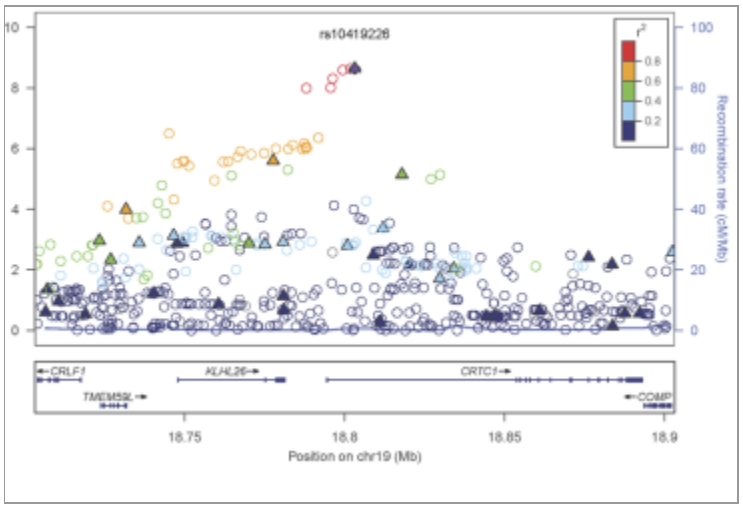

Image provided by Dr. Thomas Vaughan.

Regional association plot for the newly identified association of the CRTC1 gene with Barrett's esophagus and esophageal adenocarcinoma. The x-axis refers to genomic position, while the y-axis denotes the –log(10) p-value of the association between each single nucleotide polymorphism (SNP) in the region and the combined Barrett's esophagus and esophageal adenocarcinoma. The SNPs are color-coded according to linkage disequilibrium with the top finding, rs10419226.