Editorial

Genetically linking chronic gastroesophageal reflux disease: Barrett's esophagus and esophageal adenocarcinoma

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Esophageal adenocarcinoma remains a devastating disease with incidence and mortality rates that are nearly equivalent. The most well known risk factor is gastroesophageal reflux (GERD) (1). Recent guidelines from multiple gastroenterology societies (American College of Gastroenterology, American Gastroenterology Association and British Society of Gastroenterology) now recommend selected screening primarily based on symptomatic GERD in patients with other known risk factors such as obesity, age, and Caucasian race. About 10–15% of those with GERD develop Barrett's esophagus (BE) or intestinal metaplasia of the esophageal mucosa (2). Those with BE then undergo regular surveillance endoscopy. The hope is this will result in early detection and treatment of EA to improve outcomes.

This strong association between GERD, BE, and esophageal adenocarcinoma has clearly been established but the genetic components that link the three have not been well delineated. It has always been hoped that genetic markers can be discovered to help identify the highest risk individuals for intervention. In this study, Gharankhani *et al.* have made two substantial observations regarding these concepts (3). First, they provide evidence that there is a polygenetic predisposition for GERD. This is certainly important to understanding the underlying pathology of a quite common disorder. Secondly, they report a genetic overlap between GERD, BE and EA. This latter result may represent the beginning of significant changes to how we screen and treat EA.

The group used the linkage disequilibrium (LD) score regression to establish these associations. LD score regression is a well-established technique that accounts for confounders found in GWAS studies of large populations. One such confounder is cryptic relatedness which can occur when there is unknown kinship between two populations, such as patients with BE and patients with GERD. This happens because case-control studies often obtain controls from relatives that do not have the phenotype of interest to the investigators. This has been seen in several prior publications establishing the relationship between GERD and BE.

A second major confounder in GWAS population based studies of BE is population stratification due to genetic drift in subpopulations within the study population. BE is primarily a Caucasian population disorder. Controls without the condition often contain subpopulations that will have dissimilar genetic loci simply due to non-random mating. These issues have been a problem in prior GWAS linkage analyses. Using the LD regression score, however, allows the analysis to estimate the size of the bias overcoming the cofounding. The investigator's polygenic model did this by taking the chi squared statistic of the distribution of the variant proportions of the minor allele frequencies. If the chi squared statistic is regressed against the LD score, the intercept minus one is an estimator of the mean contribution of the confounder to the inflation in association. The strength of the investigators two observed associations is they were found after this thorough controlling for these potential population confounders.

Based on our current conception of GERD, BE and EA, the finding of a genetic overlap between these conditions should not be surprising. If we suspect GERD has a genetic component, then those same genes should be present in patients with BE and EA. However, the paradigm of GERD leading to esophageal injury leading to intestinal metaplasia of the esophageal mucosa leading to dysplasia leading to EA

is built on the strong correlation between the conditions. Though the authors report that their sample size is not large enough to definitively demonstrate causation, their results are yet further evidence that the proposed pathway from GERD to BE to EA is reasonable (3).

More importantly this genetic overlap may represent the first step in improving the screening process for EA. Presumably a difference may exist between the underlying genetics of individuals with GERD that will progress to EA and individuals with GERD that will not progress to EA. That genetic difference could be exploited to determine which patients with GERD are at risk for developing EA. As such more aggressive screening and treatment could be focused on a clear high risk group. The wasted surveillance on many who have BE, but will never progress to EA, could be avoided. Likewise, many of the significant number of cases missed under our current surveillance programs could be detected.

Gharankhani *et al.*'s data suggest that the transition from GERD to BE to EA is likely a polygenetic effect with each loci implementing tiny effects (3). As they encountered, this polygenic background makes it difficult to find loci with pleiotropic effects (3). Nevertheless, the authors suggest that GWAS meta-analysis with larger sample sizes may identify specific loci that confer a risk of GERD developing into BE and EA. It is when these results are obtained that Gharankhani *et al.*'s work will start to become most clinically relevant.

The authors also mention that going forward these loci could provide targets for treatment (3). For instance the authors hypothesize the TGF-beta pathway as a potential molecular overlap between the disorders. The implication is that this pathway could be targeted for treatment that prevents progression from GERD to EA. While this goal is much further away from actualization, it represents the true direction for this research.

Overall, Gharankhani *et al.*'s work can be characterized as a very promising first step in the genetic analysis of GERD, BE and EA. It provides further evidence that a single or even small number of genes is unlikely to be sufficient to define risk of progression. It is much more likely that whole genome analysis will eventually be needed to define cancer risk. As such it is likely, that years of significant work lie ahead before clinically relevant outcomes can occur.

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Footnote

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References

1. Lagergren J, Bergström R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-31.
2. Spechler SJ, Souza RF. Barrett's esophagus. N Engl J Med 2014;371:836-45.
3. Gharahkhani P, Tung J, Hinds D, et al. Chronic gastroesophageal reflux disease shares genetic background with esophageal adenocarcinoma and Barrett's esophagus. Hum Mol Genet 2016;25:828-35.

