In flux? Genetics modifies the effect of reflux on Barrett's esophagus risk

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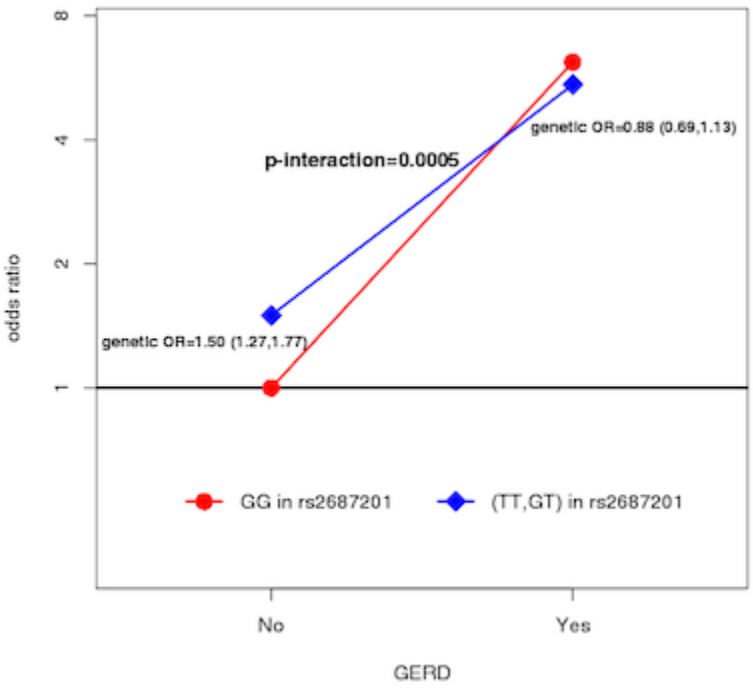

Plot of odds ratios for Barrett's esophagus for four strata defined by rs2687201 genotype (GG vs. TT, GT) and history of gastroesophageal reflux disease (GERD) (no vs. yes). The red line shows the odds ratios for individuals homozygous for the major allele (GG) and the blue line shows the odds ratios for individuals with at least one copy of the minor allele (TT, GT). The stratum GG and no GERD is the referent group.

Image provided by Dr. James Dai

Esophageal adenocarcinoma (EA) is a rare but lethal disease. The majority of EA cases arise from Barrett's esophagus (BE), a condition where the tissue in the tube connecting the mouth and stomach (esophagus) is displaced by tissue more akin to the intestinal lining. BE is most often diagnosed in those who have long-term gastroesophageal reflux disease (GERD). In GERD, contents from the stomach wash back up into the esophagus, damaging esophageal tissue. As the esophagus tries to heal itself, the damaged cells are replaced by the type of cells found in BE. However, some patients with BE have never experienced GERD, thus it is unclear what causes BE in these individuals.

BE and EA share many epidemiological risk factors including, European ancestry, male gender, obesity, tobacco smoking, and GERD. Not surprisingly, the two diseases share a large proportion of genetic heritability: The Barrett's and Esophageal Adenocarcinoma Consortium (BEACON)

conducted a genome-wide association study (GWAS) and reported that the risk of BE and EA is influenced by many germline variants of small effect.

Understanding the interplay between genetic susceptibility and epidemiologic risk factors can provide insight into disease pathogenesis and etiology. Unfortunately, the statistical power to detect genome-wide gene-environment interactions is typically low because of the high variability in interaction estimates and the p-value correction needed for genome-wide testing. To address this issue, Drs. James Dai, Thomas Vaughan, and colleagues (Public Health Sciences, Vaccine and Infectious Disease, and Human Biology Divisions) applied an alternative approach by focusing the search for gene-environment interactions to genetic loci previously found to significantly associate with BE and EA. Here the premise is if a genetic variant interacts with an exposure, the marginal association of this variant (the association regardless of exposure levels) will likely manifest. This approach provides a benefit in statistical power when compared to an agnostic genome-wide interaction search.

The authors recently presented their work in *Cancer Epidemiology, Biomarkers & Prevention*. Using data from the BEACON consortium (2,416 BE patients, 1,516 EA patients, and 2,187 controls), the authors examined gene-environment interactions of seven SNPs previously shown to associate with BE or EA. The environmental risk factors investigated include body-mass index (BMI), cigarette smoking, and GERD symptoms. Logistic regression models were used to estimate odds ratios for these risk factors stratified by SNP genotype, separately for BE and EA. The authors discovered rs2687201 (G/T, major/minor plus strand allele), which lies on chromosome 3 near the *FOXP1* gene, modified the association between GERD and BE risk. The presence of at least one minor allele of rs2687201 decreased the magnitude of BE risk associated with GERD: odds ratios (95% confidence intervals) for GERD among participants with 0, 1, or 2 copies of the minor allele were 6.17 (4.91, 7.56), 3.56 (2.85, 4.44), and 3.97 (2.47, 6.37), respectively. While the interactions of this SNP with GERD on the risk of EA were not statistically significant, the patterns of the odds ratios among the genotype groups were similar to those for BE. No other SNP-environment pairs displayed statistically significant interactions.

Next, the authors investigated the interactions between the three environmental risk factors and rs2687201 simultaneously. Here the p-value for the interaction with GERD remained nominally statistically significant, implying that the newly discovered interaction between the SNP and GERD appears to not be confounded by BMI and cigarette smoking.

Lastly, the authors examined the odds ratios for four strata defined by rs2687201 genotype and GERD status; those homozygous for the major allele and without GERD comprised the reference

group. In the absence of GERD, having at least one minor allele elevated the risk for BE. In the presence of GERD, the risk of BE substantially increased (regardless of genotype group), but those with at least one minor allele had a smaller BE risk compared to those homozygous for the major allele.

According to Dr. Dai, "the risk association of reflux symptoms and Barrett's esophagus is modified by rs2687201, a known susceptibility locus that lies approximately 75 kilo bases downstream of the transcription factor gene *FOXP1*. This novel gene– exposure interaction discovered in this study provides new insights into the etiology of esophageal adenocarcinoma." *FOXP1* encodes a member of the Forkhead box (FOX) family of transcription factors, which function as versatile regulators of a wide range of biological processes, including development and cancer. Knockout studies in mice demonstrated that *FOXP1* and *FOXP2* cooperatively regulate lung and esophageal development, while human *FOXP1* was first identified as a candidate tumor suppressor gene.

Ongoing and future work include expanding beyond known genetic loci; Dr. Dai elaborates, "genome-wide testing for gene-exposure interactions for Barrett's esophagus and esophageal adenocarcinoma will reveal more putative loci that modify the risk of known exposures."

Additional Fred Hutch investigators contributing to this project were Dr. Jean de Dieu Tapsoba, Dr. Matthew F. Baus, Lynn E. Onstad, and Dr. Brian J. Reid.

Dai JY, Tapsoba JdD, Buas MF, Onstad LE, Levine DM, Risch HA, Chow W-H, Bernstein L, Ye W, Lagergren J, Bird NC, Corley DA, Shaheen NJ, Wu AH, Reid BJ, Hardie LJ, Whiteman DC, Vaughan TL. 2015. A newly identified susceptibility locus near FOXP1 modifies the association of gastroesophageal reflux with Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev*. 24(11):1739-47. doi: 10.1158/1055-9965.EPI-15-0507.

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