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BASIC AND TRANSLATIONAL—ALIMENTARY TRACT

Polymorphisms Near *TBX5* and *GDF7* Are Associated With Increased Risk for Barrett's Esophagus

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BACKGROUND & AIMS: Barrett's esophagus (BE) increases the risk of esophageal adenocarcinoma (EAC). We found the risk to be BE has been associated with single nucleotide polymorphisms (SNPs) on chromosome 6p21 (within the HLA region) and on 16q23, where the closest protein-coding gene is *FOXF1*. Subsequently, the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) identified risk loci for BE and esophageal adenocarcinoma near *CRTC1* and *BARX1*, and within 100 kb of *FOXP1*. We aimed to identify further SNPs that increased BE risk and to validate previously reported associations. **METHODS:** We performed a genome-wide association study (GWAS) to identify variants associated with BE and further analyzed promising variants identified by BEACON by genotyping 10,158 patients with BE and 21,062 controls. **RESULTS:** We identified 2 SNPs not previously associated with BE: rs3072 (2p24.1; odds ratio [OR] = 1.14; 95% CI: 1.09–1.18; $P = 1.8 \times 10^{-11}$) and rs2701108 (12q24.21; OR = 0.90; 95% CI: 0.86–0.93; $P = 7.5 \times 10^{-9}$). The closest protein-coding genes were respectively *GDF7* (rs3072), which encodes a ligand in the bone morphogenetic protein pathway, and *TBX5* (rs2701108), which encodes a transcription factor that regulates esophageal and cardiac development. Our data also supported in BE cases 3 risk SNPs identified by BEACON (rs2687201, rs11789015, and rs10423674). Meta-analysis of all data identified another SNP associated with BE and esophageal adenocarcinoma: rs3784262, within *ALDH1A2* (OR = 0.90; 95% CI: 0.87–0.93; $P = 3.72 \times 10^{-9}$). **CONCLUSIONS:** We identified 2 loci associated with risk of BE and provided data to support a further locus. The genes we found to be associated with risk for BE encode transcription factors involved in thoracic, diaphragmatic, and esophageal development or proteins involved in the inflammatory response.

Keywords: EAC; Intestinal Metaplasia; Susceptibility; Cancer.

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Barrett's esophagus (BE) is a common premalignant condition that affects up to 2% of the adult population in the Western world.[1] BE comprises the second stage in the esophagitis–metaplasia–dysplasia–adenocarcinoma sequence. BE confers a 2%–4% lifetime risk of esophageal adenocarcinoma (EAC).[1] Chronic gastric acid reflux is the predominant etiologic factor for BE. In addition, BE co-occurs with conditions such as intestinal metaplasia, hiatal hernia, obesity, and hypercholesterolemia.[2–5] Several factors, including the degree of acid reflux, hiatal hernia size, and the percentage of intestinal metaplasia–positive glands, can affect the progression to cancer. A role for genetics in the pathogenesis of gastroesophageal reflux disease, including BE and EAC, has been implicated on the basis of 3 observations: concordance in monozygous and dizygous twins[6–8]; the increased risk of disease in those with a positive family history[9,10]; and, recently, the identification of single nucleotide polymorphisms (SNPs) associated with BE in Genome-Wide Association Studies (GWAS).[11,12] The proportion of variation in BE risk explained by common variants has been estimated to be 35%.[13]

***Authors share co-first authorship.**

Abbreviations used in this paper: **ASE, allele-specific expression; BE, Barrett's esophagus; BEACON, Barrett's and Esophageal Adenocarcinoma Consortium; CI, confidence interval; EAC, esophageal adenocarcinoma; eQTL, expression quantitative trait locus; GWAS, genome-wide association study; LD, linkage disequilibrium; OR, odds ratio; PC, principal component; SNP, single nucleotide polymorphism; TCGA, The Cancer Genome Atlas.**

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