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Genetic link to Barrett's esophagus, esophageal cancer discovered

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Mutations in three genes have been identified that are more prevalent in patients with esophageal cancer and Barrett esophagus, a premalignant metaplasia (change in cells or tissue) caused by chronic gastroesophageal reflux disease (GERD), according to preliminary research reported in the July 27 issue of *JAMA*.

The incidence of esophageal adenocarcinoma (EAC) in the United States and Europe has increased 350 percent since 1970, with the cause uncertain. Esophageal adenocarcinoma is believed to be preceded by Barrett esophagus (BE), according to background information in the article. Barrett esophagus is common, estimated to occur in 1 percent to 10 percent of the general population. "Finding predisposition genes may improve premorbid risk assessment, genetic counseling, and management," the authors write.

Charis Eng, M.D., Ph.D., of the Cleveland Clinic, and colleagues conducted a study to identify a gene or genes associated with BE/EAC predisposition. The research included an analyses of 21 concordant (both)-affected sibling pairs with BE/EAC and 11 discordant sibling pairs (2005-2006). The study also included data from 176 white patients with BE/EAC and 200 ancestry-matched controls (2007-2010). Data from 19 BE/EAC tissues yielded 12 "priority" candidate genes for mutation analysis. Genes that showed mutations in cases but not in controls were further screened in 58 cases.

Analyses indicated that three major genes, MSR1, ASCC1, and

CTHRC1 were associated with BE/EAC. Mutational analyses of the 12 priority candidate genes in BE/EAC cases found mutations in these three genes in 13 of 116 patients (11.2 percent), with the most frequently mutated being MSR1 (approximately 7 percent), followed by ASCCl and CTHRC1. "Findings of germline [those cells of an individual that have genetic material that could be passed to offspring] MSRl and CTHRCl mutations were replicated in an independent validation series," the authors write.

"These 3 genes together accounted for 11 percent of our cases, reflecting what is normally considered a moderate-to high-penetrance genetic load for a disease," they write. "Nonetheless, future independent studies are needed to replicate our data in other patient populations to confirm the conclusions."

The researchers add that larger cohort studies may be necessary to determine the usefulness of these genes and their variants in risk assessment and premorbid diagnosis.

More information: *JAMA*. 2011;306[4]410-419.

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