

The Y-chromosome F haplogroup contributes to the development of Barrett's esophagus-associated esophageal adenocarcinoma in a white male population

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SUMMARY. Barrett's esophagus (BE) is a metaplastic condition of the distal esophagus, resulting from longstanding gastroesophageal reflux disease (GERD). BE predisposes for the highly malignant esophageal adenocarcinoma (EAC). Both BE and EAC have the highest frequencies in white males. Only a subset of patients with GERD develop BE, while <0.5% of BE will progress to EAC. Therefore, it is most likely that the development of BE and EAC is associated with underlying genetic factors. We hypothesized that in white males, Y-chromosomal haplogroups are associated with BE and EAC. To investigate this we conducted a multicenter study studying the frequencies of the Y-chromosomal haplogroups in GERD, BE, and EAC patients. We used genomic analysis by polymerase chain reaction and restriction fragment length polymorphism to determine the frequency of six Y-chromosomal haplogroups (DE, F(xJ,xK), K(xP), J, P(xR1a), and R1a) between GERD, BE, and EAC in a cohort of 1,365 white males, including 612 GERD, 753 BE patients, while 178 of the BE patients also had BE-associated EAC. Univariate logistic regression analysis was used to compare the outcomes. In this study, we found the R1a (6% vs. 9%, $P = 0.04$) and K (3% vs. 6%, $P = 0.035$) to be significantly underrepresented in BE patients as compared to GERD patients with an odds ratio (OR) of 0.63 (95% CI 0.42–0.95, $P = 0.03$) and of 0.56 (95% CI 0.33–0.96, $P = 0.03$), respectively, while the K haplogroup was protective against EAC (OR 0.30; 95% CI 0.07–0.86, $P = 0.05$). A significant overrepresentation of the F haplogroup was found in EAC compared to BE and GERD patients (34% vs. 27% and 23%, respectively). The F haplogroup was found to be a risk factor for EAC with an OR of 1.5 (95% CI 1.03–2.19, $P = 0.03$). We identified the R1a and K haplogroups as protective factors against development of BE. These haplogroups have low frequencies in white male populations. Of importance is that we could link the presence of the predominantly occurring F haplogroup in white males to EAC. It is possible that this F haplogroup is associated to genetic variants that predispose for the EAC development. In future, the haplogroups could be applied to improve stratification of BE and GERD patients with increased risk to develop BE and/or EAC.

KEY WORDS: Barrett's esophagus, esophageal adenocarcinoma, gastroesophageal reflux disease, genetic polymorphisms, Y-chromosome haplogroup.

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