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An esophageal adenocarcinoma susceptibility locus at 9q22 also confers risk to esophageal squamous cell carcinoma by regulating the function of *BARX1*

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Genome wide association studies (GWAS) have identified a series of genetic variants associated with the risk of esophageal adenocarcinoma (EAC)/Barrett's esophagus (BE), which was different from those loci for esophageal squamous cell carcinoma (ESCC). It is important to evaluate whether these susceptibility loci for EAC/BE are also implicated in ESCC development. In the current study, we analyzed genetic variants at 3p13, 9q22, 16q24 and 19p13 in a case-control study including 2,139 ESCC patients and 2,463 cancer-free controls in a Chinese population, and further characterized the biological relevance of genetic variants by functional assays. We found that the G allele of rs11789015 at 9q22, as compared with the A allele, was significantly associated with a decreased risk of ESCC with a per-allele odds ratio of 0.77 (95% CI, 0.65-0.90; $P=1.38\times 10^{-3}$), whereas the other three loci were not associated with ESCC risk. We further found that rs11789015-G allele correlated with decreased mRNA and protein levels of *BARX1*. Dual-luciferase reporter gene assay revealed that the A>G change at rs11789015 significantly decreased the promoter activity of *BARX1*. Both the mRNA and protein levels of *BARX1* were significantly higher in ESCC tumor tissues compared with the corresponding normal tissues. Moreover, the deletion of *BARX1* substantially reduced ESCC cells growth, migration and invasion. In conclusion, these results suggest that genetic variants at 9q22 are associated with the risk of both EAC/BE and ESCC, possibly by regulating the function of *BARX1*.

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