Candidate locus analysis of the TERT-CLPTM1L cancer risk region on chromosome 5p15 identifies multiple independent variants associated with endometrial cancer risk.

Several studies have reported associations between multiple cancer types and single-nucleotide polymorphisms (SNPs) on chromosome 5p15, which harbours TERT and CLPTM1L, but no such association has been reported with endometrial cancer. To evaluate the role of genetic variants at the TERT-CLPTM1L region in endometrial cancer risk, we carried out comprehensive fine-mapping analyses of genotyped and imputed SNPs using a custom Illumina iSelect array which includes dense SNP coverage of this region. We examined 396 SNPs (113 genotyped, 283 imputed) in 4,401 endometrial cancer cases and 28,758 controls. Single-SNP and forward/backward logistic regression models suggested evidence for three variants independently associated with endometrial cancer risk ($P = 4.9 \times 10^{-6}$ to $P = 7.7 \times 10^{-5}$). Only one falls into a haplotype previously associated with other cancer types (rs7705526, in TERT intron 1), and this SNP has been shown to alter TERT promoter activity. One of the novel associations (rs13174814) maps to a second region in the TERT promoter and the other (rs62329728) is in the promoter region of CLPTM1L; neither are correlated with previously reported cancer-associated SNPs. Using TCGA RNASeq data, we found significantly increased expression of both TERT and CLPTM1L in endometrial cancer tissue compared with normal tissue (TERT $P = 1.5 \times 10^{-18}$, CLPTM1L $P = 1.5 \times 10^{-19}$). Our study thus reports a novel endometrial cancer risk locus and expands the spectrum of cancer types associated with genetic variation at 5p15, further highlighting the importance of this region for cancer susceptibility.