Identification of Circulating lncRNAs Associated with Gallbladder Cancer Risk by Tissue-Based Preselection, Cis-eQTL Validation, and Analysis of Association with Genotype-Based Expression

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Abstract

Long noncoding RNAs (lncRNAs) play key roles in cell processes and are good candidates for cancer risk prediction. Few studies have investigated the association between individual genotypes and lncRNA expression. Here we integrate three separate datasets with information on lncRNA expression only, both lncRNA expression and genotype, and genotype information only to identify circulating lncRNAs associated with the risk of gallbladder cancer (GBC) using robust linear and logistic regression techniques. In the first dataset, we preselect lncRNAs based on expression changes along the sequence "gallstones → dysplasia → GBC". In the second dataset, we validate associations between genetic variants and serum expression levels of the preselected lncR-NAs (cis-lncRNA-eQTLs) and build lncRNA expression prediction models. In the third dataset, we predict serum lncRNA expression based on individual genotypes and assess the association between genotype-based expression and GBC risk. AC084082.3 and LINC00662 showed increasing expression levels (p-value = 0.009), while C22orf34 expression decreased in the sequence from gallstones to GBC (p-value = 0.04). We identified and validated two cis-LINC00662-eQTLs (r^2 = 0.26) and three cis-C22orf34-eQTLs (r^2 = 0.24). Only LINC00662 showed a genotyped-based serum expression associated with GBC risk (OR = 1.25 per log2 expression unit, 95% CI 1.04–1.52, p-value = 0.02). Our results suggest that preselection of lncRNAs based on tissue samples and exploitation of cis-lncRNA-eQTLs may facilitate the identification of circulating noncoding RNAs linked to cancer risk.

Author keywords
EQTLs; gallbladder cancer; Genetic association study; LncRNAs; Molecular phenotypes