A Large-Scale Analysis of Genetic Variants within Putative miRNA Binding Sites in Prostate Cancer.

Prostate cancer is the second most common malignancy among men worldwide. Genome-wide association studies have identified 100 risk variants for prostate cancer, which can explain approximately 33% of the familial risk of the disease. We hypothesized that a comprehensive analysis of genetic variations found within the 3' untranslated region of genes predicted to affect miRNA binding (miRSNP) can identify additional prostate cancer risk variants. We investigated the association between 2,169 miRSNPs and prostate cancer risk in a large-scale analysis of 22,301 cases and 22,320 controls of European ancestry from 23 participating studies. Twenty-two miRSNPs were associated (P<2.3×10(-5)) with risk of prostate cancer, 10 of which were within 7 genes previously not mapped by GWAS studies. Further, using miRNA mimics and reporter gene assays, we showed that miR-3162-5p has specific affinity for the KLK3 rs1058205 miRSNP T-allele, whereas miR-370 has greater affinity for the VAMP8 rs1010 miRSNP A-allele, validating their functional role. Findings from this large association study suggest that a focus on miRSNPs, including functional evaluation, can identify candidate risk loci below currently accepted statistical levels of genome-wide significance. Studies of miRNAs and their interactions with SNPs could provide further insights into the mechanisms of prostate cancer risk.