Abstract: Despite advances in bladder cancer treatment, the rate of decline in bladder cancer mortality rates is decreased compared to other cancers. One of the critical clinical signs of mortality and recurrence is the muscle invasiveness. Non-muscle invasive bladder cancer has the highest rate of recurrence of all types of cancer. This study aimed to examine the association between bladder cancer recurrence and promoter DNA methylation. Using a robust regression model, we identified 135 significantly methylated genes. Subsequently, we found 16 differentially methylated genes. We found that these genes significantly affected GPCRs & 𝞫-catenin pathways. Our results find potential clinical biomarkers for bladder cancer recurrence. Future studies should attempt to identify whether these biomarkers can be reproducible in different populations.

Intro:

Bladder cancer is a complex phenotype dependent on a variety of factors including genetics1-3, exposure to environmental chemicals4-6, and psychosocial stressors. Despite advances in bladder cancer treatment over the past two decades, bladder cancer mortality has not decreased at comparable rates for other cancers, such as prostate, breast, lung, and colon cancer.7-9 Disparities are stark in bladder cancer incidence rates with the bladder cancer risk of men 4 times that of women.10 Notably, bladder cancer recurrence has been differential according to muscle invasiveness.11 Muscle invasive bladder cancer maintains increased mortality and recurrence rates compared to non-invasive bladder cancer.4,8,11-17

Epigenetic alterations have been suggested to be critical to the underlying etiology of bladder cancer and bladder cancer subtype.18,19 Epigenetic alterations, specifically DNA methylation, may conspire with genetic alterations to induce the bladder cancer phenotype and its subsequent recurrence.14,16,20-25 Epidemiological studies have found increased methylation in gene promoter regions has been found in individuals with bladder cancer.26-28 Differential DNA methylation patterns have been identified between bladder cancer subtypes: muscle invasive bladder cancer and non-muscle invasive bladder cancer.12,15,19,26-28 Previous research has not identified a verifiable DNA methylation biomarker for bladder cancer, specifically for bladder recurrence.18,29-32

This study examined the association between bladder cancer recurrence and DNA methylation. Furthermore, we identified biological pathways that differentially methylated loci significantly alter to identify potential biomarkers for bladder cancer recurrence.

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