Differential CG Promoter Methylation Patterns: Implications for Cancer Development

Chanhee Park, Deepali Juneja, Reyhan Koyun, Roman Gofman, Veronika Bykova

University of Washington Bothell, School of STEM, Division of Biological Sciences

Abstract

Aberrant DNA methylation patterns play a crucial role in cancer development. We investigated the impact of methylation at CG promoter sites in the neuroblastoma breakpoint family genes NBPF10 (cancerous; Fig. 1) and NBPF11 (noncancerous; Fig. 2). Our findings revealed a marked disparity in methylation patterns. NBPF10 exhibited a significant spike in mCG (methylated cytosine followed by guanine) levels, while NBPF11 displayed stable methylation. These results suggest that CG promoter methylation may be a critical factor in cancer development. Altered methylation patterns at CG sites can lead to gene silencing or altered gene expression. Further investigations are warranted to unravel the precise mechanisms underlying these differential methylation patterns.

Understanding the role of CG promoter methylation in cancer-associated genes provides insights into oncogenesis. It may aid in identifying potential therapeutic targets and diagnostic markers for cancer detection and treatment. In conclusion, our study highlights the importance of DNA methylation patterns, specifically at CG promoter sites, in cancer biology. The distinct methylation profiles observed in NBPF10 and NBPF11 genes shed light on their divergent cancerous and noncancerous phenotypes within the neuroblastoma breakpoint family. Further research will deepen our understanding of the underlying molecular mechanisms contributing to cancer development.

Introduction

Cancer initiation and progression are accompanied by significant alterations in the epigenome. Decades of research have revealed a well-established pattern: cancer cells exhibit widespread CpG methylation loss, affecting regions with low CpG density, repeat elements, retrotransposons, and lamin-associated domains (LADs) (Lakshminarasimhan & Liang,

2020). DNA methylation, an essential epigenetic modification, plays a pivotal role in gene regulation and has been implicated in various diseases, including cancer. Specifically, methylation at CG promoter sites has garnered significant attention due to its potential impact on gene expression and subsequent tumorigenesis. Understanding the involvement of DNA methylation in cancer development is crucial for unraveling the underlying molecular mechanisms and identifying potential therapeutic targets.

The neuroblastoma breakpoint family (NBPF) genes have emerged as intriguing candidates in cancer research. NBPF10 and NBPF11 exhibit distinct phenotypes, with NBPF10 associated with cancer while NBPF11 remains noncancerous. Exploring the differential methylation patterns at CG promoter sites in these genes holds promise for elucidating the epigenetic changes driving their disparate outcomes.

The critical question driving this research is: How does CG promoter site methylation differ between NBPF10 (cancerous; Fig. 1) and NBPF11 (noncancerous; Fig. 2) genes, and what are the potential implications for cancer development? By addressing this question, we hope to provide novel insights into the epigenetic alterations driving cancer and pave the way for future advancements in cancer prevention and treatment strategies. Therefore, this study aims to shed light on the distinct methylation profiles between NBPF10 and NBPF11 genes, contributing to our understanding of the role of CG promoter site methylation in cancer biology.

Methods

Our research aims to explore the impact of CG promoter site methylation on the NBPF10 and NBPF11 genes and its implications for cancer development. To compare the methylation profiles of these genes and identify potential differences in DNA methylation patterns, we employed the sequence alignment functionality of BLAST.

To perform the sequence comparison using BLAST, we utilized the Bio.Blast module from the Biopython library. We conducted a BLAST comparison (blastn) by submitting the gene sequences (Fasta Files for NBPF10 and NBPF11) to the NCBI BLAST web service (NCBIWWW.qblast) against the nucleotide database. The resulting BLAST searches were parsed (NCBIXML.read) to extract the alignment information for each gene. We stored the alignment results for both genes in a table, which included columns for sequence ID, length, and E-value. Subsequently, we used the tabulate function to create a well-formatted table presenting the alignment information.

To visually represent the similarities or matches between the gene sequences and the reference sequences in the nt database, as indicated by the alignment results, we generated a bar graph using Matplotlib. We utilized the seaborn library to ensure accurate and visually appealing data representation.

Results

Methylation of CG in the promoter region has been identified as a potential cause of cancer, particularly when compared to other forms of methylation or specific gene sequences. Specifically, we focused our analysis on two genes, NBPF10 (cancerous; Fig. 1) and NBPF11 (non-cancerous; Fig. 2), which are located on chromosome 1 and belong to the neuroblastoma breakpoint family.

We examined various databases and genes to investigate the potential negative effects of DNA methylation. Our findings, depicted in Table 4, indicate that the cancerous gene (NBPF10) exhibits higher levels of methylation compared to Table 3's results. By comparing both graphs, we noticed a higher CG content in the promoter region of the cancerous gene. Although the differences between the two graphs are minimal, it is noteworthy that NBPF10

shows a pronounced peak in mCG methylation in the promoter region. This observation suggests that our hypothesis holds some validity and could be supported by further evidence and examples.

Discussion

DNA methylation is a chemical modification that controls gene expression and genome stability, defining cell type and lineage. When DNA methylation control goes awry, it can lead to diseases like cancer. In cancer, there are abnormal DNA methylation patterns: the whole genome becomes less methylated (hypomethylation), while specific sites become overly methylated (hypermethylation), particularly in gene expression regulatory regions called CpG islands. This abnormal methylation can silence tumor suppressor genes (TSGs), which help prevent cancer (Vinson, 2012). However, recent studies have shown that the role of DNA methylation in cancer is more complex than just TSG silencing. This review explores the reasons behind DNA methylation abnormalities in cancer and their potential for therapy.

The association between methylation of CG sites in the promoter region and cancer is well-established, particularly in the context of specific genes such as NBPF10 (cancerous) and NBPF11 (non-cancerous) from the neuroblastoma breakpoint family, located on chromosome 1. Comprehensive genomic studies have revealed that dynamic DNA methylation regulation is pivotal in cancer initiation, progression, and maintenance. Aberrant DNA methylation changes, particularly in the CG sites of promoters, contribute significantly to the disease phenotype (Lakshminarasimhan & Liang, 2020). These findings highlight the importance of understanding and targeting CG methylation in the promoter region as a potential cause of cancer, differentiating it from other forms of methylation or separate gene sequences.

CG promoters are specific DNA sequences found in gene regions often regulated by DNA methylation. The abstract explains that in cancer, specific CpG islands in these CG promoters become hypermethylated, potentially leading to the silencing of TSGs. Understanding these differential CG promoter methylation patterns is crucial for discovering how cancer develops and finding new treatment targets (Nishiyama, 2021). CG promoters in normal cells often have low DNA methylation levels associated with active gene expression. DNA methylation at CG sites typically involves adding a methyl group to the cytosine residue, leading to 5-methylcytosine (5mC). This methylation pattern helps maintain the appropriate gene expression profiles for normal cellular functions. CG promoters in normal cells have low DNA methylation levels, allowing genes to be active. However, in cancer cells, there are abnormal methylation patterns. Two common types are:

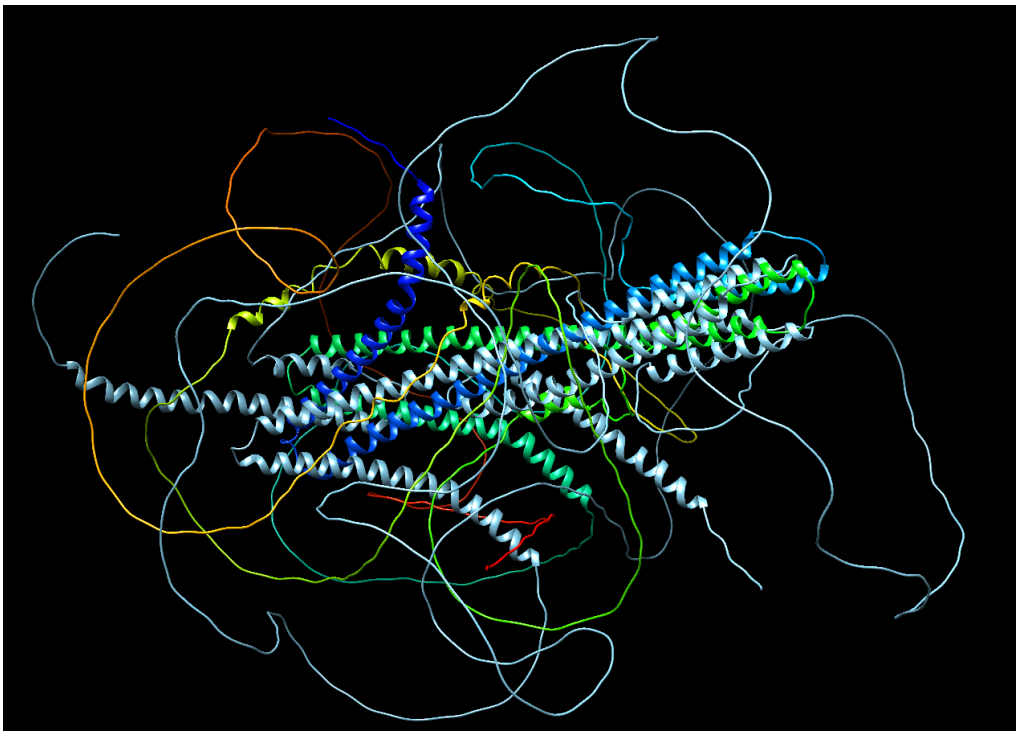
1. Genome-wide hypomethylation: There is less overall DNA methylation in the entire genome. It can lead to gene instability and abnormal gene activity, including activating cancer-promoting genes.
2. Site-specific hypermethylation: This involves excessive methylation at specific spots within CG promoters. It can turn off or reduce the activity of tumor suppressor genes. These genes usually prevent tumors from forming, so when they are silenced, it increases the risk of cancer.

These abnormal methylation patterns disrupt regular gene activity and cellular functions, which can contribute to cancer development. By understanding and targeting these patterns, we can gain insights into cancer progression and develop new treatments in the future.

Figures

Fig.1. Cancerous: Protein structure of NBPF10

Fig. 2. Non-Cancerous: Protein structure of NBPF11



Tables

Table 1. NBPF11: Average Methylation Levels of Gene in Different Locations

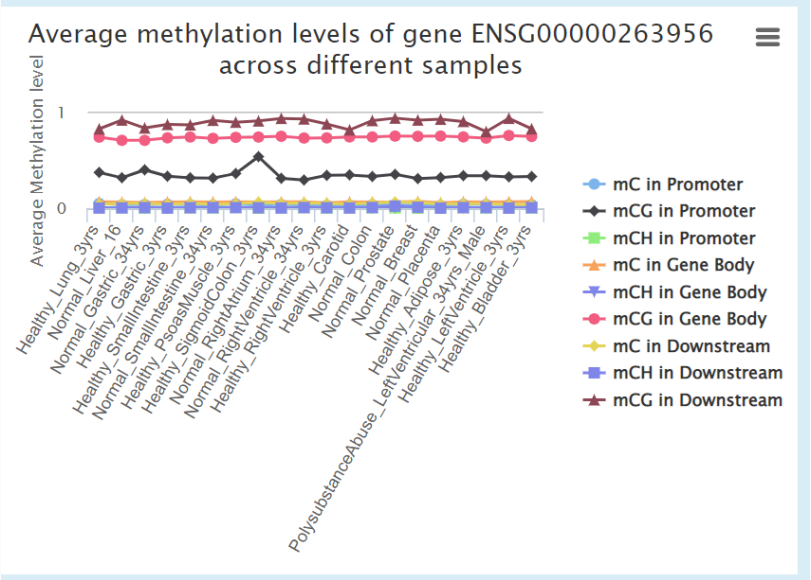


Table 2. NBPF10: Average Methylation Levels of Gene in Different Locations

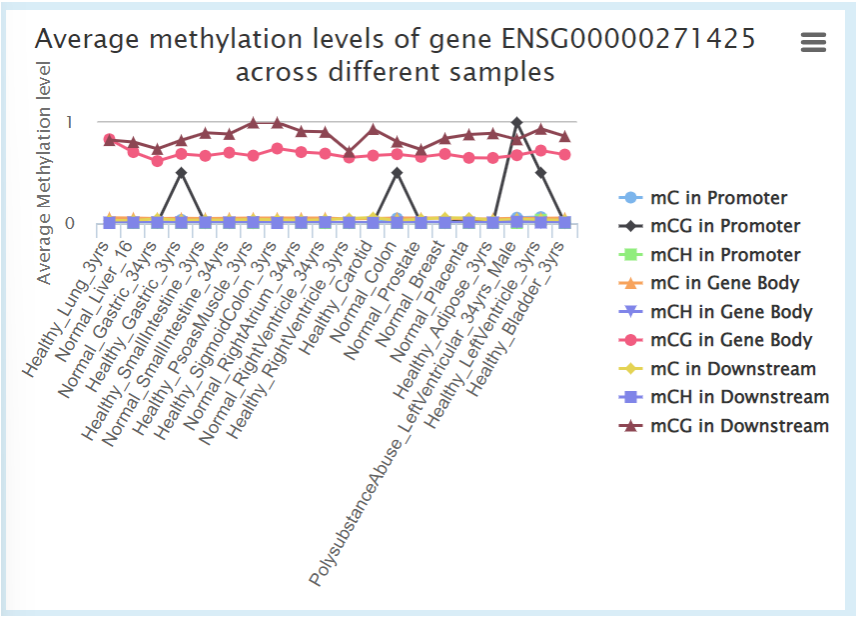


Table 3. NBPF11 Dinucleotide Counts

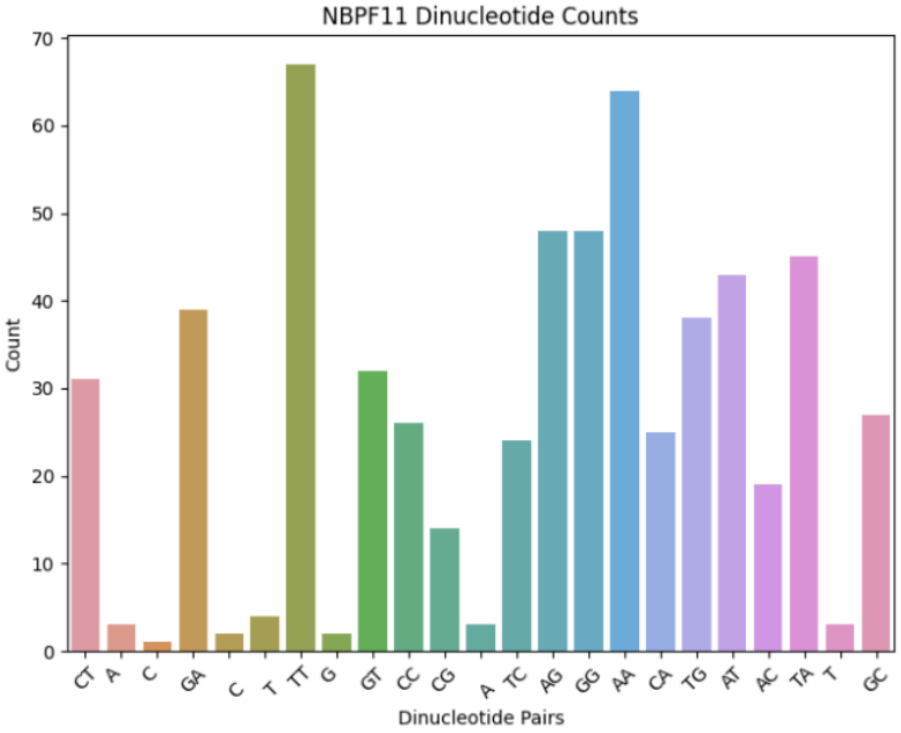
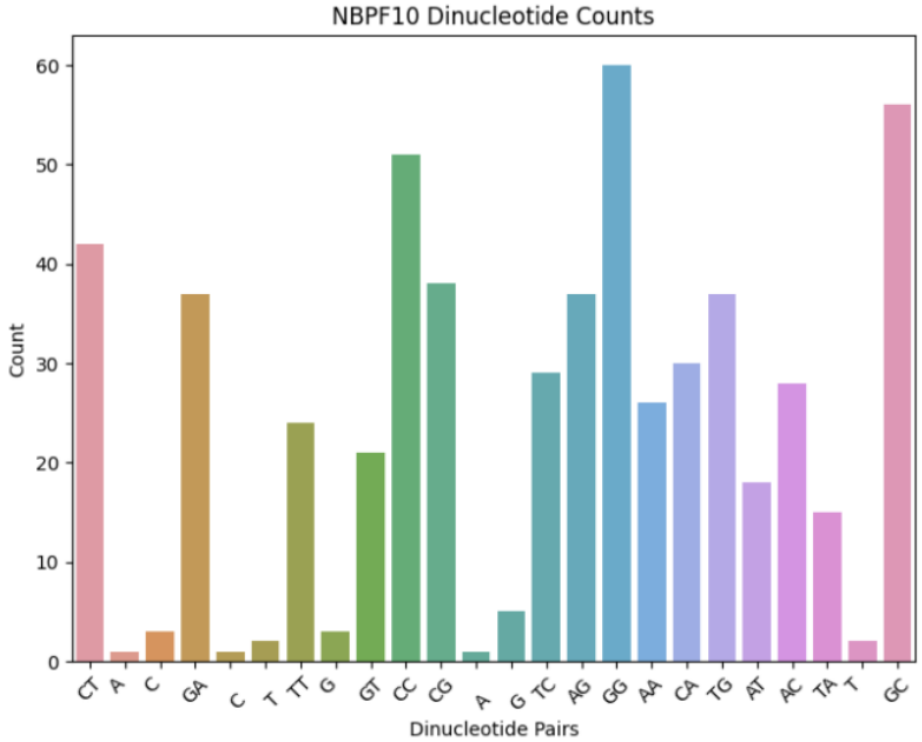


Table 4. NBPF10 Dinucleotide Counts



Supplementary Data

- NBPF10:

  https://ngdc.cncb.ac.cn/methbank/v3/srms/gene/q?species=8&accession=ENSG00000271425

- NBPF11:

  https://ngdc.cncb.ac.cn/methbank/v3/srms/gene/q?species=8&accession=ENSG00000263956

- NCBI:

  https://www.ncbi.nlm.nih.gov/

- Alpha Fold Database:

  https://alphafold.ebi.ac.uk/entry/A0A087WVG8

- Code Repo

  https://github.com/Romatomato1/BlastGeneNucleotide

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