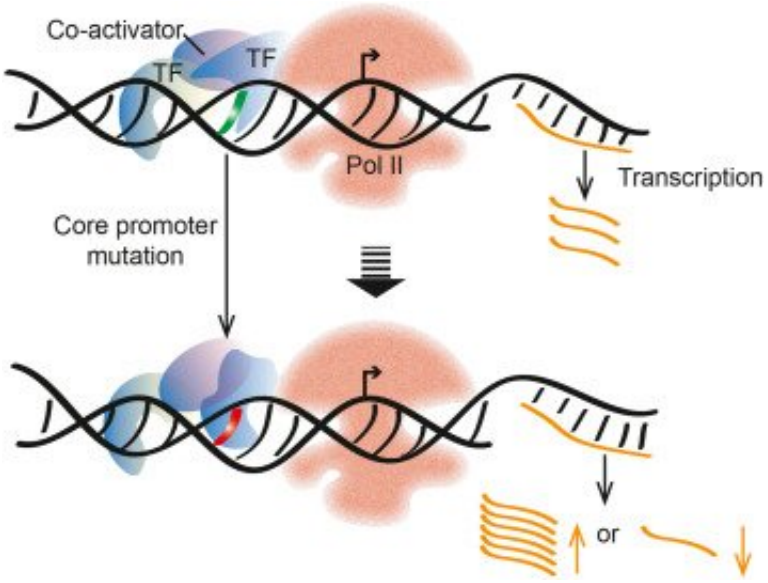
# Unraveling the role of core promoter variation in triple-negative breast cancer: Study

July 25 2023




Variants in core promoter interfere with the cis–trans interaction and the organization of transcriptional initiation complex, leading to increased or decreased transcription initiation. Green line represents wild-type and red line represents mutant. Credit: *Genes & Diseases*

TNBC is a particularly aggressive subtype of breast cancer, characterized by the absence of three key receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Approximately 10–20% of all breast cancers are TNBC. TNBC patients face a poorer prognosis due to the lack of

specific drug targets. Therefore, the discovery of new factors influencing the development and progression of TNBC is crucial for improving patient outcomes.

A study published in *Genes & Diseases* centered on the core promoter, a DNA region surrounding the transcription start site (TSS), for the potential roles of genetic variation in core promoter in abnormal gene expression in TNBC. Core promoters contain multiple highly conserved cis-motifs interacting with different transcriptional factors like RNA polymerase II, TFIIB, and TFIID.

This interaction forms the transcription initiation complex to regulate transcriptional initiation. Genetic variation in the core promoter sequences could interfere with this interaction therefore the proper organization of the transcriptional initiation complex, causing altered transcription initiation and pathological consequences.

Researchers hypothesized that core promoter in TNBC could be highly mutable in contributing to its abnormal gene expression. To test their theory, they analyzed the genomes of 279 TNBC patients using a method called Exome-based Variant Detection in Core-promoters (EVDC).

After filtering out normal genomic polymorphisms, researchers discovered a staggering 19,427 recurrent somatic variants and 1,694 recurrent germline variants in the core promoters of various genes, many of which are known to be oncogenes and tumor suppressors.

The analysis of RNA-seq data from breast cancer revealed altered gene expression in hundreds of these affected genes, providing substantial evidence that core promoter variation could significantly influence gene expression. The researchers further compared these findings with core promoter variation data from 610 unclassified breast cancers. Interestingly, the core promoter variants in TNBC were highly TNBC-

specific, suggesting that these variations could contribute significantly to the unique characteristics of TNBC.

This study makes a clear case that the core promoter is mutable and can significantly contribute to the development of cancer, in particular TNBC. While it sheds light on an entirely new aspect of cancer research, there is still much to uncover.

The complex, dynamic nature of gene expression and the variety of mechanisms that can influence it, including epigenetic modification and variation in distal regulatory regions, means that this is just the beginning. The researchers concluded that core promoter variation could provide a new paradigm for studying the mechanisms behind abnormal gene expression in cancer.

While this study focused on TNBC, future research could potentially uncover similar roles of core promoter variation in other types of cancer, leading to even broader applications for cancer detection and treatment.

**More information:** Teng Huang et al, Etiological roles of core promoter variation in triple-negative breast cancer, *Genes & Diseases* (2022). DOI: 10.1016/j.gendis.2022.01.003

Provided by Chongqing Medical University