Background: Lipid mediators of inflammation, leukotrienes, are involved in tumour development and progression. Leukotriene B4 receptors 1 and 2 (LTB4R and LTB4R2) have been suggested to regulate tumor progression by promoting cell proliferation, survival, migration and metastasis. LTB4R2 was reported to increase invasiveness of breast cancer (BC) cells through IL-8 (interleukin-8) pathway. The inhibitors of leukotriene receptors have been suggested for use in anti-cancer therapy.

Methods: We conducted Xma1-RRBS (Reduced Representation Bisulfite Sequencing) protocol for genome-wide DNA methylation assessment on 170 BC samples and 10 normal breast tissue samples as a reference material. Methylation status was determined by Bismark software, and identification of epigenetic BC molecular subtypes was carried out using hierarchical cluster analysis.

Results: One of the BC epigenetic subtypes identified by genome-wide DNA methylation analysis appeared to be enriched with triple-negative breast cancer (TNBC) samples demonstrating LTB4R and LTB4R2 genes abnormal demethylation that is potent of initiating ectopic gene expression. Bisulfite Sanger sequencing has confirmed abnormal demethylation of the cytosine residues at positions +117, +121, +148, +184 and +186 relative to the LTB4R transcription start site.

Conclusions: By the present day no diagnostic panels to assess the methylation status of leukotriene B4 receptors have been published. Fine mapping of abnormal DNA methylation in the genomic region adjacent to LTB4R and LTB4R2 genes reported here allows development of a simple methylation sensitive PCR laboratory test that would identify tumours prone to leukotriene B4 receptors ectopic expression and thus potentially responsive to their inhibitors. An easy means to select such tumours promotes clinical trials aimed to improve TNBC individualized therapy by introducing the inhibitors of leukotriene receptors as anticancer agents.

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Leukotriene B4 receptors as a therapeutic target for triple-negative breast cancer

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