

# Genome-wide epigenetic profiling of B cell leukemia and lymphoma

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i hörsal **Sahlgrens aula**, Blå stråket 5, Sahlgrenska, Göteborg

Fredagen den **10 Januari 2020**, klockan **13:00**

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Avhandlingen baseras på följande delarbeten

- I. Pradeep Kumar Kopparapu\*, **Mohammad Hamdy Abdelrazak Morsy\***, Chandrasekhar Kanduri and Meena Kanduri. Gene-body hypermethylation controlled cryptic promoter and miR26A1-dependent EZH2 regulation of TET1 gene activity in chronic lymphocytic leukemia. *Oncotarget* ,2017, Sep 29; 8(44): 77595-77608.  
\* Equally contributing first author.
- II. Kosalai ST, **Morsy MHA**, Papakonstantinou N, Mansouri L, Stavroyianni N, Kanduri C, Stamatopoulos K, Rosenquist R, Kanduri M: EZH2 upregulates the PI3K/AKT pathway through IGF1R and MYC in clinically aggressive chronic lymphocytic leukaemia. *Epigenetics* 2019:1-16.
- III. **Mohammad Hamdy Abdelrazak Morsy**, Mohamad Moustafa Ali, Chandrasekhar Kanduri and Meena Kanduri. DNA methylation at intragenic CpG islands controls PRC2-mediated transcriptional regulation of *MNX1* in Chronic lymphocytic leukemia. (Manuscript)

# Genome-wide epigenetic profiling of B cell leukemia and lymphoma

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## Abstract

Epigenetic modifications, at the level of DNA methylation and post-translational modifications of histone tails cooperatively function in the organization of the genome, and thereby establish the gene expression profiles, phenotypes, and cellular fates. In this work, we investigated the aberrant epigenome in chronic lymphocytic leukemia (CLL) which is one of the most frequent lymphoid malignancies in the west including the Nordic countries. The overall aim of this work is to address the impact of altered epigenetic patterns in CLL on the disease progression with respect to gene expression profile and gain mechanistic insights on the interplay between the different epigenetic mechanisms, such as DNA methylation and histone modifications, in regulating the expression of CLL signature genes. The first study in this thesis aims to investigate the impact of gene body hypermethylation on transcriptional activation which was not completely understood then. Based on our previous MBD seq data (Methyl-CpG-Binding Domain based next generation Sequencing) datasets on CLL samples, of the top differentially methylated genes in CLL compared to normal B cells, we nominated Ten-eleven translocation (*TET1*) which was shown to harbor hypermethylation at CpG islands within gene body. We found that gene body of *TET1* harbors an overlapping cryptic promoter, the transcript of which attenuates the corresponding gene transcription when unmethylated and its hypermethylation in CLL was found to be associated with the overexpression of *TET1*. The second study aimed at globally mapping the genomic targets of enhancer of zeste homolog 2 (EZH2) the catalytic subunit of Polycomb repressive complex 2 (PRC2) in CLL by chromatin immunoprecipitation followed by sequencing (ChIP-seq) along with its prototypical repressive chromatin feature (H3K27me3). The findings of this study unraveled a non-canonical implication of EZH2 in transcriptional activation apart from PRC2. We show a mechanism by which EZH2 transactivates *IGF1R* gene in the more adverse CLL subgroups with IGHV mutations (mutated CLL) and how it contributes to activating PI3K/AKT pathway through IGF1R signaling. The third project is somehow pertinent to the aforementioned first study and aims at drawing a more detailed mechanistic link between CpG methylation and transcriptional regulation in terms of the residence of PRC2, as it preferentially locates GC-rich elements. Integration of our previous global methylome datasets in CLL patients and transcriptome analysis by RNA-seq after induction of global demethylation in CLL cell lines has revealed a set of genes that are supposedly prone to hypermethylation within their intragenic regions in CLL, and such hypermethylation is found to be positively correlated with their overexpression in CLL. Out of the top significant genes, *MNX1* was selected to probe the mutual exclusivity of PRC2 and intragenic CpG islands and the possible implication of gene body hypermethylation in upregulating *MNX1* in CLL through impeding the PRC2-mediated repression. Altogether, the findings of our work underscore that aberrant epigenome is more likely to be the niche within which the cancer type-relevant aggressive traits are acquired and might pave the way for further detailed investigations that look forward to improve the therapy options and accordingly the clinical outcomes in CLL.

**Keywords:** CLL, PRC2, EZH2, Epigenetics, CpG islands, DNA methylation, ChIP-seq, RNA-seq