XPO1 mutations identify early stage CLL characterized by shorter time to first treatment and enhanced BCR signaling

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1. INTRODUCTION

The *XPO1* gene, which codes for a nuclear exportin responsible for the partitioning of macromolecules essential for cell homeostasis, represents one of the chronic lymphocytic leukemia (CLL) driver genes. In cases of *XPO1* mutations a negatively charged glutamic acid at position E571 is substituted with a positively charged lysine, thus promoting *XPO1* interaction with proteins bearing a negatively charged nuclear export signals (NES). Most of newly diagnosed CLL patients do not require therapy initially and are managed with a watch and wait strategy. CLL is characterized by a high grade of molecular heterogeneity and the analysis of gene mutations may further improve the stratification of time to first treatment (TTFT).

2. OBJECTIVES

The aims of the study were:

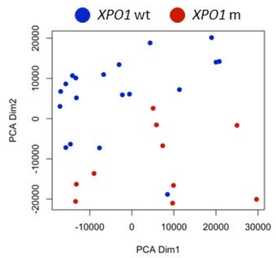
- to characterize the transcriptomic and the epigenomic profile of *XPO1* mutant *versus XPO1* wild type CLL
- to evaluate whether *XPO1* mutations may predispose to disease progression and early treatment requirement

3. METHODS

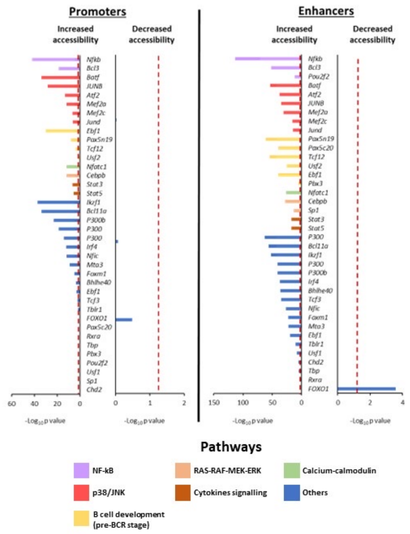
- RNA-seq and ATAC-seq were performed on CD19+/CD5+ tumoral cells from 8 *XPO1* mutated CLL patients and 15 *XPO1* wild type CLL cases, matched for IGHV status, *TP53* status and FISH karyotype for comparative purposes
- RT-qPCR was used to assess miR-155-5p expression
- *XPO1* mutations were detected by NGS and/or Sanger sequencing
- The primary endpoint of survival analysis was TTFT

4. RESULTS

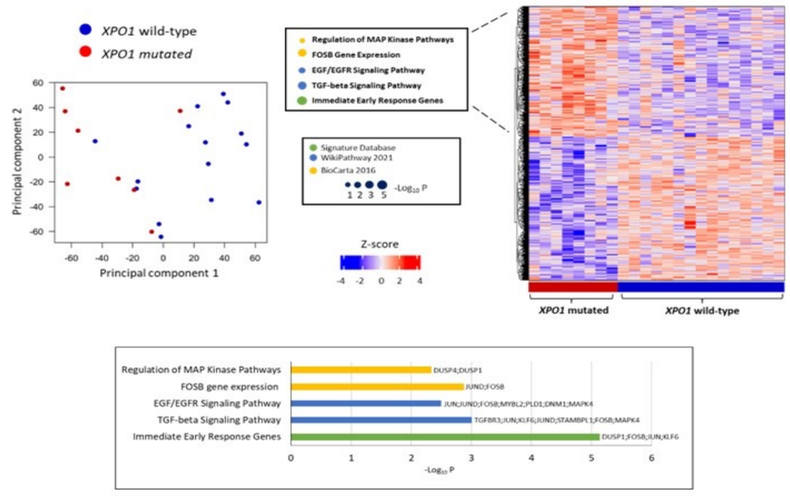
4.1 *XPO1* MUTATIONS IMPACT ON CHROMATIN ACCESSIBILITY OF CLL CELLS



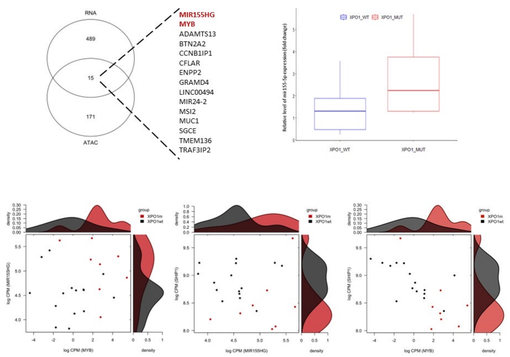
By principal component analysis (PCA), *XPO1* mutated CLL clearly separated and showed a distinct chromatin profile compared to wild type cases. Overall, *XPO1* mutated CLL had a chromatin landscape more accessible than that of *XPO1* wild type CLL, with 6391 enhancer/promoters being more accessible and only 3283 enhancers/promoters being less accessible in *XPO1* mutated compared to *XPO1* wild type (FDR < 0.1).



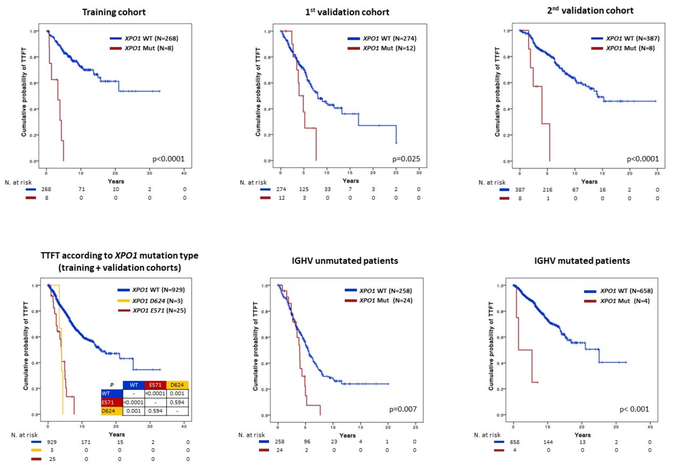
4.2 THE TRANSCRIPTOME OF *XPO1* MUTATED CLL CELLS IS ENRICHED IN MAPK AND INFLAMMATION SIGNALING GENES



4.3 *XPO1* MUTANT CLL ARE CHARACTERIZED BY UPREGULATION OF THE MIR-155/MYB PATHWAY



4.4 *XPO1* MUTATIONS ASSOCIATE WITH SHORTER TTFT IN EARLY STAGE CLL PATIENTS



5. CONCLUSIONS

- *XPO1* mutations represent an independent predictor of shorter time to first treatment in early stage CLL
- *XPO1* mutations, conceivably through increased miR-155 levels, may enhance BCR signaling leading to higher proliferation and shorter TTFT in early stage CLL.

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