COMPARATIVE ANALYSIS OF MUTATIONAL GENE PROFILE AND RECURRENT SOMATIC MUTATIONS IN CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL).

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a chronic malignant B lymphoma and the most frequent hematologic cancer, accounting for 30-40% of all adult leukemias. It is a profoundly heterogeneous disease at both molecular and cellular levels. This heterogeneity is partly reflected by the differences in the mutational state of the variable heavy chain (IgHV) genes of the immunoglobulins and by the recurrent genetic mutations in the genes involved in certain signaling pathways in CLL. Patients with non-mutated IGHV (≥98% germline identity) have a more aggressive disease course and develop genetic deletions or more unfavorable mutations than patients with mutated IGHV (≤98% germline identity).

The aim of this study was to characterize CLL patients not previously treated according to their biological profile.

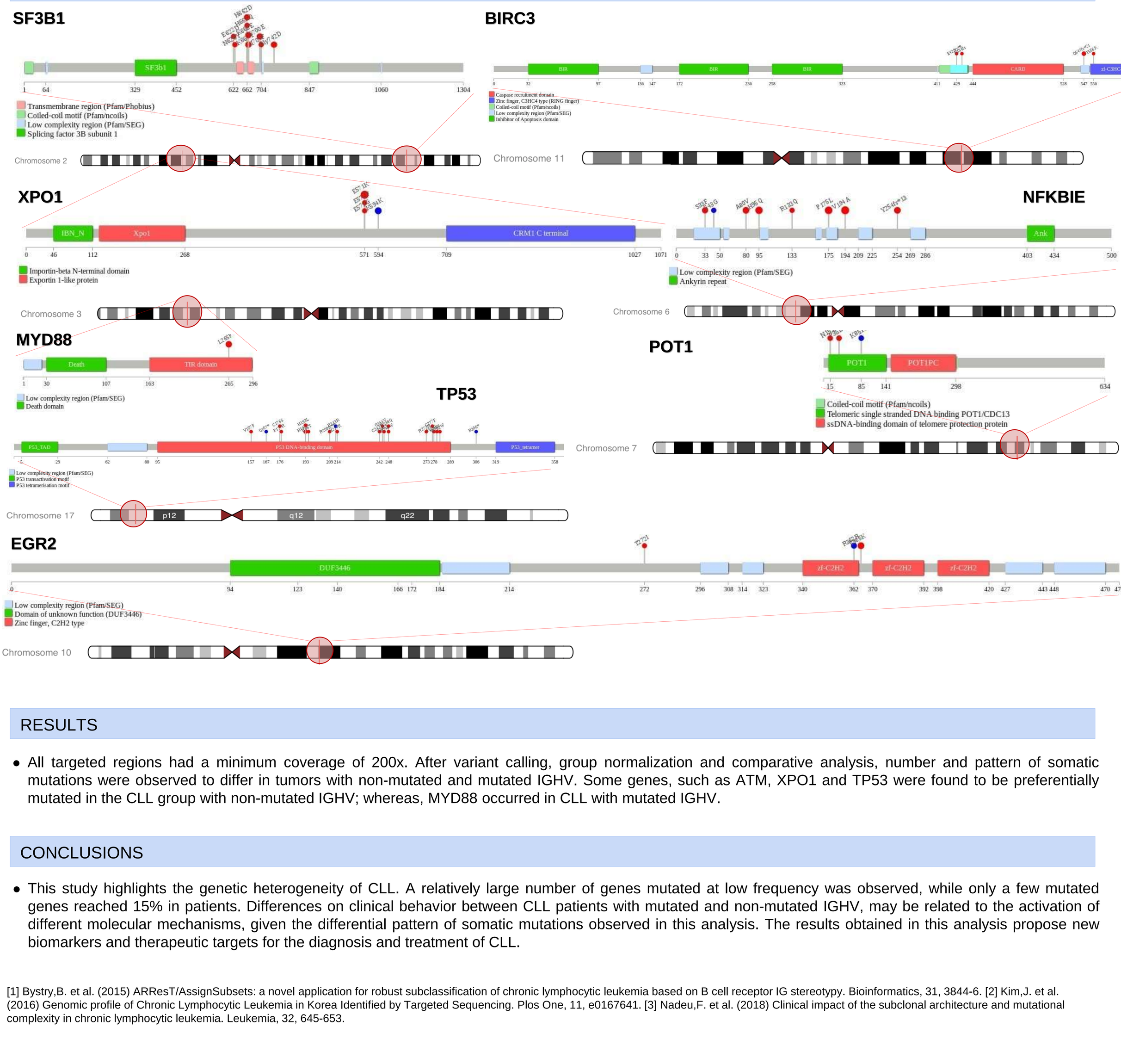
METHODS

We studied 169 patients diagnosed of CLL according to the NCIWG guidelines in our institution between 1986 and 2017, with available DNA for sequencing using a Miseq platform.

A custom panel designed by Sequencing Multiplex was used to investigate somatic mutations in regions of interest of the following genes:

- TP53
- BIRC3
- SF3B1
- MYD88
- NOTCH1
- ATM
- XPO1
- EGR2
- POT1
- NFKBIE

PATTERN OF SOMATIC MUTATIONS



RESULTS

- All targeted regions had a minimum coverage of 200x. After variant calling, group normalization and comparative analysis, number and pattern of somatic mutations were observed to differ in tumors with non-mutated and mutated IGHV. Some genes, such as ATM, XPO1 and TP53 were found to be preferentially mutated in the CLL group with non-mutated IGHV; whereas, MYD88 occurred in CLL with mutated IGHV.

CONCLUSIONS

- This study highlights the genetic heterogeneity of CLL. A relatively large number of genes mutated at low frequency was observed, while only a few mutated genes reached 15% in patients. Differences on clinical behavior between CLL patients with mutated and non-mutated IGHV, may be related to the activation of different molecular mechanisms, given the differential pattern of somatic mutations observed in this analysis. The results obtained in this analysis propose new biomarkers and therapeutic targets for the diagnosis and treatment of CLL.

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