CLINICALLY RELEVANT VARIANTS FOR PROGNOSIS AND THERAPY GUIDANCE OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS MANAGED BY WATCHFUL WAITING

Maria Lucia Ferraz de Carvalho[1,3]; Fábio Ribeiro Queiroz[1]; Júlia Fernandes do Carmo Las Casas[2]; Pedro Henrique Fernandes do Carmo Las Casas[2]; Frederico Lisboa Nogueira[2]; Carolina Pereira de Souza Melo[1]; Letícia da Conceição Braga[1]

[1]Instituto Mário Penna de Ensino, Pesquisa e Inovação - Laboratório de Pesquisa Translacional em Oncologia, Belo Horizonte, Brazil; [2]Hospital Luxemburgo, Instituto Mário Penna, Belo Horizonte, Brazil; [3]Pós-Graduação em Genética, Universidade Federal de Minas Gerais, Instituto de Ciências Biológicas, Belo Horizonte/Minas Gerais

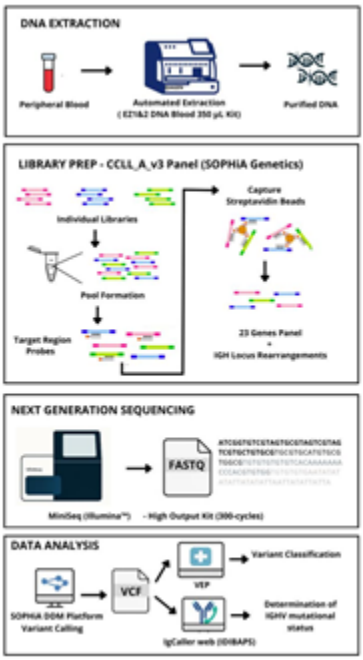
INTRODUCTION

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia in adults, characterized by the accumulation of B lymphocytes in the blood, bone marrow, and lymph nodes. Despite its clinical heterogeneity, therapeutic decisions are still often based on simple laboratory tests.[1] Genetic alterations have been shown to be significant for prognosis, making genetic profiling crucial for accurate staging and personalized treatment.[2]

OBJECTIVE

To evaluate the genetic profile of patients with CLL under Watchful Waiting (WW), identifying variants with prognostic and therapeutic relevance.

METHODS



RESULTS AND DISCUSSION

Patients' median age was 65.2 years, and 50% of them were female; 81.2% were in RAI stage 0; 50% had leukocytosis, and CD38 was negative in 5/16 patients. Using the SOPHiA DDM platform, 384 genetic variants were identified across 18/23 genes analyzed, with 84.81% classified as variants of uncertain significance (VUS) or not reported. After VEP analysis, most of them were reclassified as benign (**Figure 1**). Seven patients (43.8%) presented clinically actionable variants (**Table 1**).

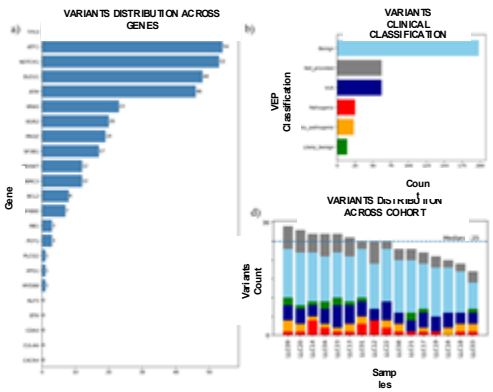


Figure 1: Distribution and clinical classification of the genetic variants identified. Only variants with coverage and allele fraction higher than 30x and 4%, respectively, were considered.

Table 1: Clinically actionable variants identified.

Gene	Potential Clinical Implication	Variant (Sample)	VAF (%)	Classification
ATM	Chlorambucil resistance and potential response to Olaparib under investigation for CLL[3,4]	p.Gly2765Val (LLC01)	36,8	Likely Pathogenic
		p.Leu565Argfs*4 (LLC01)	4,5	Pathogenic
BIRC3	Better response to the Venetoclax + Rituximab regimen, approved for CLL[5]	p.Arg555Serfs*4 (LLC14)	6,2	Pathogenic
		p.Gln547Asnfs*21 (LLC19)	4,7	Pathogenic
NOTCH1	Poor prognosis and potential response to Bronticituximab[6,7]	p.Ser2513Valfs*3 (LLC04)	4,6	Pathogenic
		p.Pro2514Argfs4 (LLC20)	4,5	Pathogenic
SF3B1	Poor prognosis and chemotherapy resistance. May be targeted by spliceosome inhibitors such as Sudemycin D1 and H3B-8800[8,9]	p.Gly742Asp (LLC09)	45,5	Likely Pathogenic
		p.Lys700Glu (LLC22)	21,5	Likely Pathogenic
XPO1	May predict a response to Selinexor, which is approved for other hematologic cancers but not yet validated for CLL[10]	p.Glu571Lys (LLC09)	48,8	Likely Pathogenic

CONCLUSION

Our findings indicate that clinically relevant variants were detected in a considerable proportion of patients. Some alterations exhibit well-established prognostic significance (e.g., *NOTCH1*, *BIRC3*), whereas others are already linked to established therapeutic strategies in other malignancies (*ATM*, *BIRC3*) or are currently under investigation in the context of CLL (*SF3B1*, *XPO1*). These results highlight the importance of integrating genomic profiling into clinical practice, as it enables personalized risk stratification and reveals opportunities for the development of innovative therapeutic approaches in CLL.

REFERENCES

ACKNOWLEDGEMENTS

FAPEMIG APQ-01819-23, APQ-3784-23, APQ-02255-22, PAPG-14237

RED00059-23

NUP:25000.079266/2015-09