Exploring the impact of germline *ATM* variants in cancer susceptibility and inheritance in chronic lymphocytic leukemia

F. Morelli[1,2*],R. Santos Azevedo[1,3*], K. Mashima[1], R. Fardoun[1], S. Fernandes[1], S. Shupe[1], M. Terra[1], A. Patel, J. Yu[1], J.R. Brown[1,6]

1 Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 2 Department of Hematology, University of Florence, Florence, IT; 3 Hospital Nove de Julho, São Paulo, BR; 4 Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; 5 Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA; 6 Department of Medicine, Harvard Medical School, Boston, MA

These authors equally contributed to the work

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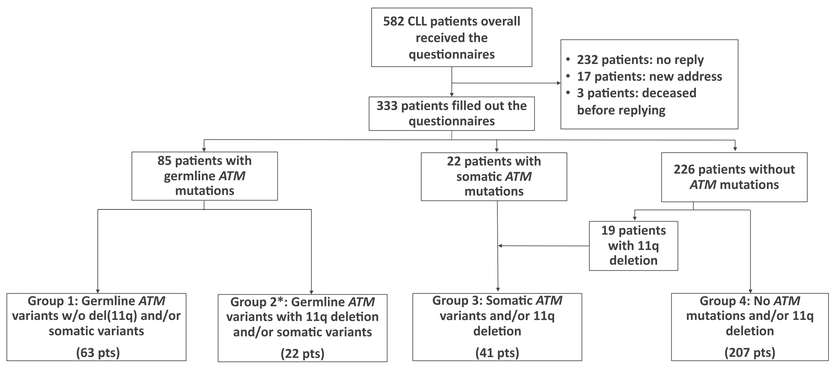
INTRODUCTION

- CLL pts face an increased susceptibility to secondary cancers.
- Rare germline *ATM* variants are detected in 24% of CLL pts; frequency higher than other hematologic neoplasms and the general population.
- The extent to which germline *ATM* variants predispose CLL pts to other malignancies remains unclear.
- To examine this potential risk, we conducted a retrospective study to assess the influence of germline *ATM* variants on the predisposition to secondary neoplasms in CLL pts and their relatives.

METHODS

- 585 pts seen at DFCI and who had NGS performed to evaluate germline *ATM* status, either through direct germline sequencing of saliva or by inference according to the hierarchical algorithm we have previously published (Lampson, 2022), were mailed a questionnaire. Of these, 333 replied (57%).
- The questionnaire investigated: demographics; personal and family history of any cancer; non-medical radiation and Agent Orange exposure; and Ataxia-Telangiectasia syndrome (AT).
- Pts were stratified into 4 groups, based on *ATM* mutational status and del(11q) (Chart 1).

Chart 1: Patients' classification according to *ATM* status



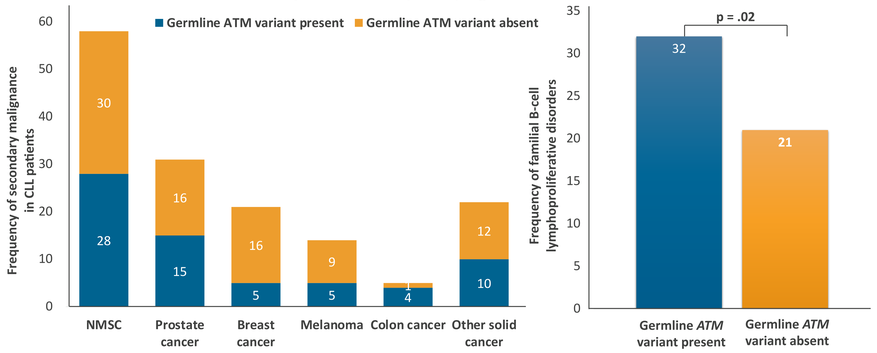
*2 patients with ATM Germline have both somatic ATM mutation and del(11q)

RESULTS

Table 1: Demographic and Clinical data

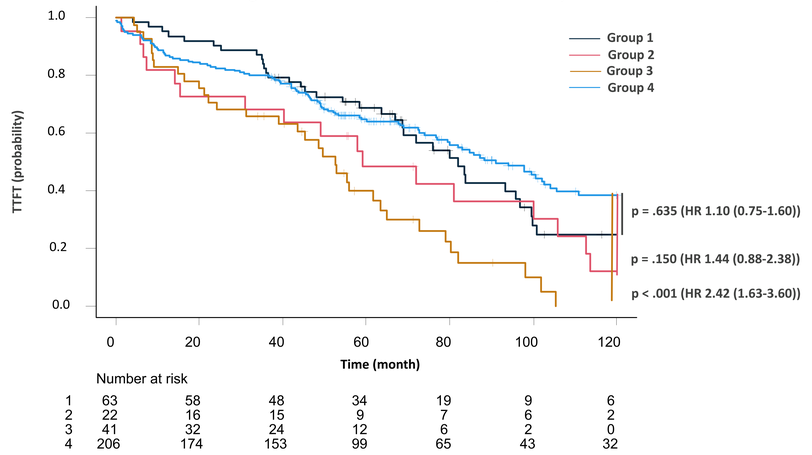
Characteristic*	Patients (N 333)	Characteristic*	Patients (N 333)
Age at diagnosis		Agent orange exposure – n (%)	
Median (range) – years	60 (28-89)	Yes	7 (2%)
Distribution – no (%)		No	324 (97%)
≤ 55 years	114 (34%)	Unknown	2 (1%)
> 55 years	219 (66%)	Richter's transformation -n (%)	
Sex – n (%)		Yes	9 (3%)
Male	189 (57%)	No	324 (97%)
Female	144 (43%)	European ancestry – n (%)	
Race – n (%)		Yes	206 (62%)
White	329 (98%)	No	127 (38%)
Black or African American	2 (1%)	IGHV status – n (%)	
Asian	1 (0.5%)	Mutated	147 (44%)
Native Hawaiian/Pacific Island	1 (0.5%)	Unmutated	152 (46%)
Ethnicity – n (%)		Unknown	34 (10%)
Not Hispanic or Latino	327 (98%)	Del(17p) and/or TP53 aberration – n (%)	
Hispanic or Latino	4 (1%)	Yes	48 (14%)
Unknown	2 (1%)	No	283 (85%)
Ashkenazi Jewish ethnicity- n (%)		Unknown	2 (1%)
Yes	23 (7%)	Year of CLL diagnosis	
No	305 (91%)	Median (range) - year	2015 (1980-2019)
Unknown	5 (2%)	1980-1990 – n (%)	4 (1%)
Non-medical radiation exposure – n (%)		1991-2000 – n (%)	13 (4%)
Yes	21 (6%)	2001-2010 – n (%)	60 (18%)
No	310 (93%)	2011-2019 – n (%)	256 (77%)
Unknown	2 (1%)		

Figure 1: (a) Frequency of secondary cancer and (b) Frequency of familial B-cell lymphoproliferative disorders in pts with CLL w/ or w/o germline *ATM* variants



- 164 pts (49%) with history of an additional non-CLL neoplasm and 221 cancers reported.
- 80 pts (60%) were diagnosed with the secondary cancer after CLL (for the 134 pts with available age for the secondary malignancy).
- 283 pts (85%) reported at least one relative with a cancer history (median 2 relatives affected (1-17)).
- Familial CLL was associated with Ashkenazi Jewish ethnicity (39% in Ashkenazi pts vs 16% in non-Ashkenazi, p=0.004).

Figure 2: Time to first treatment (months)



CONCLUSION

- Our results suggest a higher incidence of B-cell lymphoproliferative disorders in the relatives of CLL pts carrying germline *ATM* variants.
- The presence of these germline variants did not impact TTFT, compared to pts harboring somatic *ATM* mutations.

Corresponding author: Jennifer R. Brown;
e-mail: jennifer_brown@dfci.harvard.edu