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CLL10,000: Robust Classification of 1,338 *ATM* Variants employing a Five-Factor Score derived from matched Non-Tumor Controls

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OBJECTIVES

- Development of a scoring system to classify *ATM* variants as benign or pathogenic, thereby enabling the investigation of their prognostic relevance in large cohorts.
- Somatic/germline status as the basis for deriving the scoring system.
- Validation in an independent patient cohort.

CONCLUSIONS

- Our scoring system reliably distinguishes somatic/pathogenic from germline/benign *ATM* variants (accuracy: 90.6%).
- Consideration of ClinVar annotations, gnomAD population frequencies, VAF (adjusted for 11q deletions), mutation type (truncating vs. non-truncating), and localization to functional domains C-terminal of amino acid 1899 improves classification of VUS.
- Some germline variants with pathogenic characteristics (e.g. truncating) may reflect a heterozygous A-T carrier status.
- This framework may enable future clinical and prognostic assessment of *ATM* mutations in CLL.

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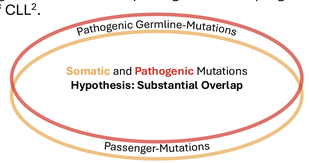
INTRODUCTION

Ataxia Telangiectasia Mutated (*ATM*) is located on chromosome 11q and encodes a protein essential for the DNA damage response[1]. *ATM* mutations are common in chronic lymphocytic leukemia (CLL) but challenging to assess. Due to a dispersion across a large gene (63 exons, coding region >9,000bp) without hotspots and mostly missense mutations it is difficult to distinguish mutations from rare, non-pathogenic congenital variants, and thus to investigate their role in the pathogenesis and prognostic significance of CLL[2].



Standardized frameworks for variant pathogenicity assessment, such as the AMP/ACMG[3]- or the ClinGen/CGC/VICC[4] guidelines, classify approximately 70% and 30% of variants, respectively, as variants of uncertain significance (VUS). We aimed to develop a system to classify as many *ATM* variants as possible as either benign or pathogenic. We hypothesized that pathogenic *ATM* driver variants in CLL are tumor-specific, i.e., somatically acquired, and therefore absent from the germline.

METHODS

We screened 3,148 untreated patients, enrolled in seven different CLL-trials, for *ATM* variants by NGS

- Confirmation of somatic/germline-status of 427 variants in 297 patients using NGS of CD19-negative mononuclear cells from peripheral blood as a germline control (Fig. 1)
- Derivation-Set (203 patients, 299 variants)
  - Calculation of Odds Ratios for association of variant characteristics with somatic origin
  - Development of a weighted five-factor score, based on the sum of the natural logarithms of the odds ratios (lnOR) (Fig. 2)
- Validation-Set (94 patients, 128 variants)
  - Evaluation of score accuracy

RESULTS

- 1,338 *ATM* variants (659 unique) across 1,002 patients
  - 19.7% truncating, 77.7% SNVs, 2.5% non-frameshift indels
- **Germline Matching:** 287 variants confirmed as somatic, 140 as germline (Fig. 4)
- **Application of our score:** 691 variants classified as somatic/pathogenic, 647 variants as germline/benign (Fig. 5)
  - 483 (15.3%) individuals harbored at least one somatic/pathogenic *ATM* mutation
    - 245 (50.7%) individuals with only SNVs, 140 (29.0%) with only truncating variants, 86 (17.8%) with both truncating variants and SNVs, 12 (2.5%) with only non-frameshift indels
  - 520 (16.5%) individuals harbored only germline/benign *ATM* variants
  - Individuals carrying at least one somatic/pathogenic *ATM* mutation, compared with those harboring only germline/benign *ATM* variants, were significantly more likely to have unmutated IGHV status (75.1% vs. 58.4%, p<0.001), more frequently presented del(11q) (46.2% vs. 16.4%, p<0.001), and less frequently presented del(17p) (2.3% vs. 6.4%, p=0.002).
- **Score accuracy:** Concordance rates (Fig. 3) indicate a notable improvement in variant classification compared with the AMP/ACMG and ClinGen/CGC/VICC guidelines, with a low proportion of discordantly classified variants.
  - Concordance rate in an independent validation cohort: 90.6%
- Possible findings suggestive of heterozygous ataxia-teleangiectasia (A-T) carrier status:
  - Four truncating, confirmed germline variants
  - Some variants that have been confirmed as germline but classified discordantly have been previously reported in A-T (e.g., G1003T, G5932T)

Figure 1. Methods Overview

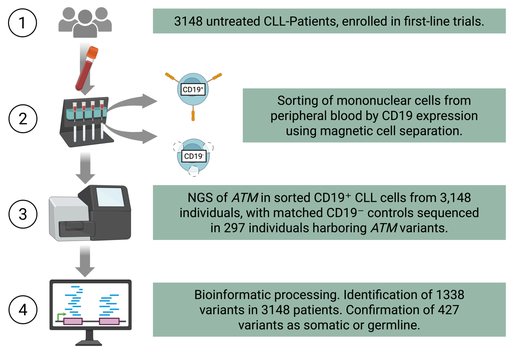
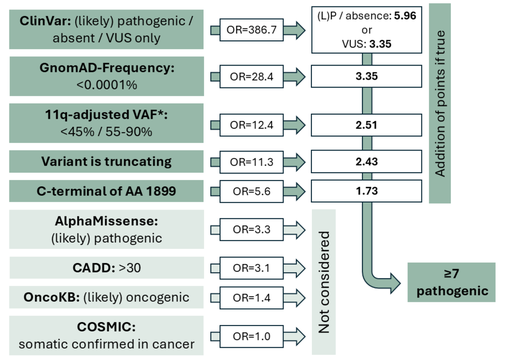


Figure 2. Score Derivation Using Odds Ratios



*$VAF_{adjusted} = VAF_{by\ NGS} \times \frac{2-f}{2}$; f=fraction of deleted alleles (1 = complete heterozygous deletion)

Figure 3. Score Validation Against AMP/ACMG, ClinGen/CGC/VICC and a Validation Cohort

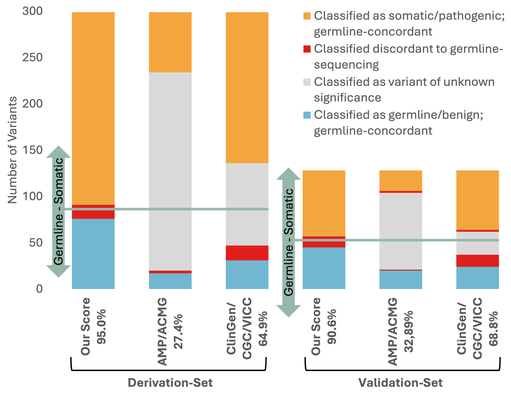


Figure 4. Variants (n=427) Confirmed as Somatic or Germline

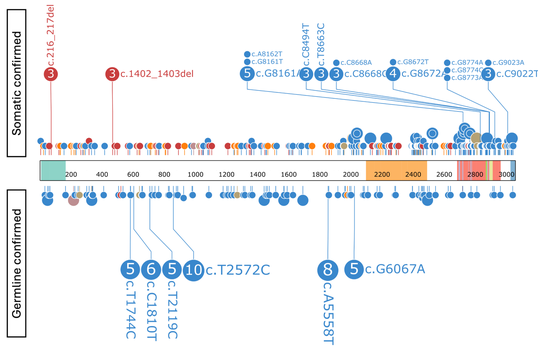
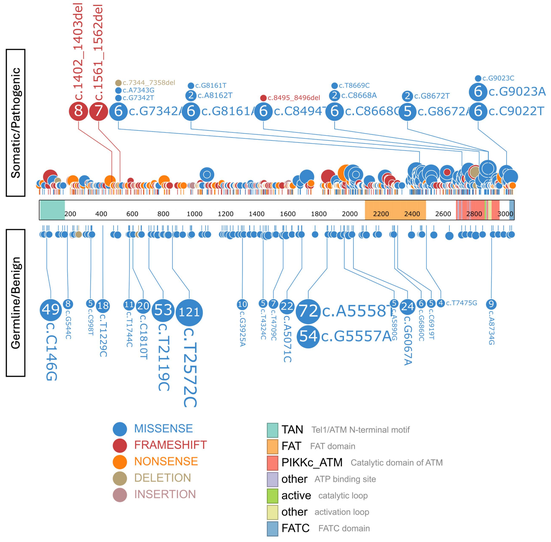


Figure 5. All Variants (n=1,338) Classified According to Our Score



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2. Stankovic et al., Leuk Lymphoma, 2014
3. Richards et al., Genet Med, 2015
4. Horak et al., Genet Med, 2022

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- Fig. 4 and 5: Created using St. Jude Programs (St. Jude Children's Research Hospital Cloud, PeCan, Proteinpaint)
- Fig. 1: Created in BioRender. Brey, C. (2025) https://BioRender.com/mpmkv7v

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