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# IGHV Repertoire in Israeli CLL Patients Reveals Markedly Low Frequency of Stereotyped Subsets

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## Introduction

- Chronic lymphocytic leukemia (CLL) is characterized by molecular and clinical heterogeneity, with immunogenetic features playing a key prognostic role.
- Stereotyped BcRs occur in ~30–40% of CLL patients globally and are associated with shared antigenic selection and distinct clinical outcomes.
- The Israeli population has distinct ethnic and genetic characteristics, yet data on IGHV gene usage and BcR.

## Objectives

- To characterize IGHV gene usage and BcR stereotypy in an Israeli CLL cohort.
- To compare the distribution of stereotyped subsets to global reference datasets.

## Methods

- IGHV Analysis: IGHV sequencing performed via next-generation sequencing (NGS) in an ERIC-certified laboratory.
- Mutation Classification: Sequences with <98% homology to germline were classified as mutated (M-IGHV); ≥98% as unmutated (UM-IGHV).
- Subset Assignment: BcR stereotypy determined using ARResT/AssignSubsets and IMGT/V-QUEST platforms.
- Statistical Comparison: Subset distribution compared with Agathangelidis et al. (Blood 2021) using the Fisher-Freeman-Halton test.

## Results

- A total of 435 CLL patients were analyzed.
- 52.4% M-IGHV, 47.6% UM-IGHV.
- Most frequently used IGHV genes: IGHV4-34 (14.0%, predominantly mutated), IGHV1-69 (10.1%, predominantly unmutated), followed by IGHV3-30, IGHV3-23, and IGHV3-7 (Figure 1).
- Stereotyped BcR subsets were identified in only 10.3% of patients, markedly lower than the ~30–40% reported in large international cohorts.
- Subsets identified were predominantly major ERIC-defined subsets (e.g., #1, #3, #4); minor or satellite subsets were rarely observed (Table 1).
- Subset #1 was the most frequent (13 patients, all UM-IGHV), followed by subset #4 (10 patients, all M-IGHV4-34).
- Interestingly, subset #2—commonly reported in international cohorts—was detected in only a single case in our cohort.
- Statistical comparison with Agathangelidis et al. (Blood 2021) showed a significant difference in subset distribution between cohorts ($p < 0.001$).

**Figure 1: Distribution of IGHV Gene Usage According to Mutation Status**

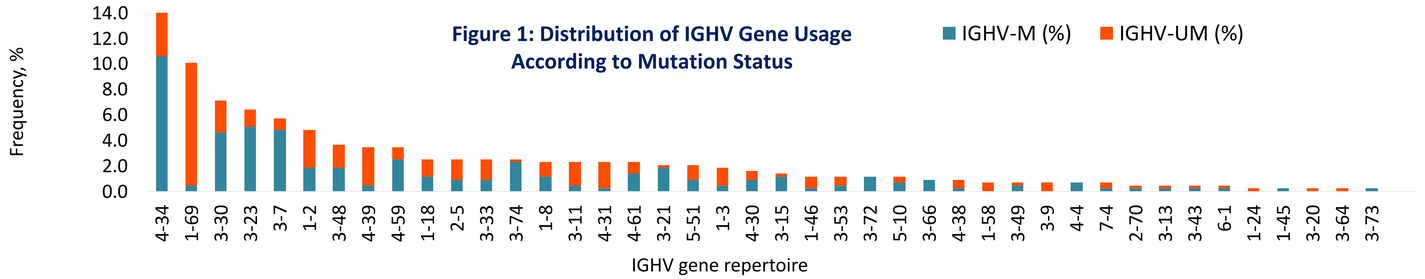


**Table 1: Distribution of Stereotyped Subsets by IGHV Gene, Mutation Status, and Frequency**

| IGHV Gene/Subset (patients [n], mutation status) | #1 | #2 | #3 | #4 | #5 | #6 | #7H | #8 | #16 | #31 | #59 | #64B | #99 | #201 | #202 | Overall, from specific IGHV gene | Overall, from all subsets (n=45) | Overall, from all cohort(n=435) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4-34 | | | | 10,M | | | | | 2,M | | | | | 3,M | | 15/61, 24.6% | 15/45, 33.3% | 15/435, 3.5% |
| 1-69 | | | 4,UM | | 1,UM | 2,UM | | | | | | | | | | 7/44, 15.9% | 7/45, 15.6% | 7/435, 1.6% |
| 3-30 | | | | | | | | | | | | | | | 1,UM | 1/31, 3.2% | 1/45, 2.2% | 1/435, 0.2% |
| 1-2 | 3,UM | | | | | | | | | | | | | | | 3/21, 14.3% | 3/45, 6.7% | 3/435, 0.7% |
| 3-48 | | | | | | | | | | 1,UM | | 1,UM | | | | 2/16, 12.5% | 2/45, 4.4% | 2/435, 0.5% |
| 3-64 | | | | | | | | | | | | 1,UM | | | | 1/1, 100% | 1/45, 2.2% | 1/435, 0.2% |
| 4-39 | | | | | | | | 1,UM | | | | | | | | 1/15, 6.7% | 1/45, 2.2% | 1/435, 0.2% |
| 3-21 | | 1,M | | | | | | | | | | | | | | 1/9, 11.1% | 1/45, 2.2% | 1/435, 0.2% |
| 1-3 | 4,UM | | | | | | | | | | | | 1,UM | | | 5/8, 62.5% | 5/45, 11.1% | 5/435, 1.1% |
| 1-8 | 2,UM | | | | | | | | | | | | | | | 2/10, 20.0% | 2/45, 4.4% | 2/435, 0.5% |
| 5-51 | 1,UM | | | | | | | | | | | | 1,UM | | | 2/9, 22.2% | 2/45, 4.4% | 2/435, 0.5% |
| 1-46 | 1,UM | | | | | | | | | | | | | | | 1/5, 20.0% | 1/45, 2.2% | 1/435, 0.2% |
| 1-58 | | | | | | | 1,UM | | | | 1,UM | | | | | 2/3, 66.7% | 2/45, 4.4% | 2/435, 0.5% |
| 1-18 | 1,UM | | | | | | | | | | | | | | | 1/11, 9.1% | 1/45, 2.2% | 1/435, 0.2% |
| 7-4 | 1, UM | | | | | | | | | | | | | | | 1/3, 33.3% | 1/45, 2.2% | 1/435, 0.2% |
| Overall, from subsets (n=45) | 13/45, 28.9% | 1/45, 2.2% | 4/45, 8.9% | 10/45, 22.2% | 1/45, 2.2% | 2/45, 4.4% | 1/45, 2.2% | 1/45, 2.2% | 2/45, 4.4% | 1/45, 2.2% | 1/45, 2.2% | 2/45, 4.4% | 2/45, 4.4% | 3/45, 6.7% | 1/45, 2.2% | | | |
| Overall, from all cohort (n=435) | 13/435, 3.0% | 1/435, 0.2% | 4/435, 0.9% | 10/435, 2.3% | 1/435, 0.2% | 2/435, 0.5% | 1/435, 0.2% | 1/435, 0.2% | 2/435, 0.5% | 1/435, 0.2% | 1/435, 0.2% | 1/435, 0.2% | 2/435, 0.5% | 3/435, 0.7% | 1/435, 0.2% | | | |

## Conclusions

Israeli CLL patients exhibit a markedly low frequency of stereotyped BcR subsets, suggesting a distinct immunogenetic landscape compared to global cohorts.