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Research Article

Gene repertoire of IGHV-IGHD-IGHJ rearrangements in Macedonian patients with chronic lymphocytic leukemia-single centre experience

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ABSTRACT

Background: B-cell chronic lymphocytic leukemia (CLL) is a clinically heterogeneous disease with many patients surviving for decades with watch and wait strategy or no treatment, whereas others surrender to their disease despite therapy. In recent years, new molecular prognostic factors came to light that have significantly improved the stratification of the CLL patients. One of the most important molecular predictors, the immunoglobulin VH gene mutational status, divides CLL into two prognostic groups, depending on the presence or absence of somatic hypermutation, where unmutated U-CLL are associated with remarkably worse prognosis than mutated U-CLL. The aim of the study was evaluation of rearrangement of IG genes profile in Macedonian CLL patients in line with facts that there are some geographic linked variations in IG genes.
Methods: In this study, mutational status and configuration of IGHV-IGHD-IGHJ rearrangements in 70 treatment naïve CLL patients were analyzed using reverse transcriptase– polymerase chain reaction (RT-PCR) and sequencing methodology at the center for bimolecular pharmaceutical analyses, faculty of pharmacy, Skopje, Macedonia.
Results: Our evaluation have shown that 52.8% patients belonged to the U-CLL subset, whereas 47.1% belonged to the M-CLL subset. The most frequently expressed IGHV subgroup was IGHV3 (41.4%), followed by IGHV1 and IGHV4 (28.5%), IGHV5 (1.4%). In the IGHD and IGHJ sets most frequently expressed was IGHD3 (55.7%), IGHJ6 gene (37.1%) respectively.
Conclusions: Our evaluation of mutational status on IGVH, IGDH, and IGJH gene in Macedonian CLL patients resulted with data which are consubstantial to those from Mediterranean area and West Balkan.

Keywords: Chronic lymphocytic leukemia, Prognosis, Mutational status

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is puzzling disease. There are more than 150 years when this disease had first clinical explanation, but aetiology, biology is still not full announced. CLL lymphocytes have characteristic immunophenotype: CD5+, CD19+, CD23+, CD20 dim, surface immunoglobulin dim. Although the majority of patients are asymptomatic at the time of diagnosis, some patients very fast have implacable accumulation of CLL cells with presentation of symptomatic disease and need for CLL therapy, at the other side there are patients which have indolent course of the disease for years.

Two staging systems that we use, Rai stage 0-4 and Binet (A-C) are not appreciate to predict the CLL course at the time of diagnosis.[1,2] Over the past decade essential in the prognosis are tolls like CD38 expression, ZAP 70 and chromosomal abnormalities (del13, del17, del11, trisomy 12).[3-6] There are correlation with disease progression, but the investigation of the immunoglobulin (IG) gene has led to findings that are fundamental to the understanding

of CLL. The mutational profile of IG genes has been shown to be associated with disease prognosis. There are two types of CLL-one arise from less differentiated (naïve) B cells with unmutated heavy chain genes (U-CLL) with inferior survival and other type with origin from more differentiated B lymphocytes (memory B cells) with somatically mutated heavy chain genes (IGHV), with good prognosis (M-CLL).

There are some geographic linked variations in IGHV genes.[7,8] There are interplay between different genetic atmosphere and environmental settings resulted in shaping of IGHV-IGHD-IGHJ in CLL cells. Here our interest is focused in that theme, in our patients, who are part from Balkan area, so in this article we are reporting the rearrangement of IG genes profile in Macedonian CLL patients.

METHODS

Patients

A total of 70 consecutive treatment naive patients from the University clinic for haematology, Skopje, Macedonia, diagnosed with B-cell CLL based on clinical criteria and laboratory features were studied for IGHV mutational status and gene repertoire. The study was approved by the medical ethics committee of the Medical Faculty, University Ss. Cyril and Methodius, Skopje, Macedonia.

The study included 40 men and 30 women (male-female ratio 1:3), with a median age of 62.8 years (range 42-85 years) at the time of diagnosis.

The distribution of clinical Binet stages was as follows: 46 patients (65.8%) stage A, 14 patients (20%) stage B, and 10 patients (14.2%) stage C.

PCR amplification and sequencing of CLL IGH rearrangements

The analysis of IGHV-IGHD-IGHJ gene rearrangements was performed at center for biomolecular pharmaceutical analyses, faculty of pharmacy, Skopje, Macedonia. The analyses were performed on mononuclear cells obtained from peripheral blood samples by Ficoll density gradient centrifugation. Total RNA was extracted using TRIzol reagent (Ambion, Life Technologies) and reverse-transcribed using MuLV reverse transcriptase (Applied Biosystems, Foster City, CA, USA) and random hexamer primers, according to manufacturer's instructions.

IGHV-IGHD-IGHJ gene rearrangements were amplified by RTPCR using a mixture of 5' primers specific for leader sequences of IGHV1 to IGHV6 subgroups 25 in conjunction with mixed 3' primers complementary to the germ line IGHJ genes. 26 reverse transcriptase–polymerase chain reaction (RT-PCR) was carried out in a final volume of 25 μL with 10 pmol of each primer, 200 pmol of each deoxyribonucleotide, and 2.5 U Tag gold polymerase (applied biosystems, Foster City, CA, USA). Amplification consisted of an initial denaturation step of 10 minutes at 95°C, followed by 35 cycles of 95°C for 45 seconds, 60°C for 45 seconds, and 72°C for 1.5 minute, with a final extension step of 10 minutes.

Clonal PCR products were purified using low melt agarose, and was sequenced with reverse primer with BigDye terminator v 3.1 cycle sequencing kit (applied biosystems, Foster City, CA, USA), purified with BigDye X terminator purification kit (applied Biosystems, Foster City, CA, USA) and run on 3500 genetic analyzer (applied biosystems).

Mutational status was calculated as percentage of deviation from the closest germ line IGHV gene. Sequences with a germ line identity greater than or equal to 98% were considered unmutated and those with an identity less than 98% were considered mutated.

Statistical analysis

Statistical analyses were performed using the x^2test, *t* test. All statistical tests were carried out using SPSS software, version 15.0 (SPSS Inc, Chicago, IL). Statistical significance was defined as *P* - 0.05.

RESULTS

IGHV mutational status and clinical presentation

The analysis of IGHV mutational status was performed in 70 treatment naïve consecutive, patients with CLL (Table 1). It has shown that 37 patients (52.8%) belonged to the U-CLL subset, whereas 33 patients (47.1%) belonged to the M-CLL subset. The age at presentation was unrelated to both mutational status.

The distribution of clinical Binet stages was: 46 patients (65.8%) had Binet A stage, and 21 patient have U-CLL (45.6%), 14 patients (20%) had Binet B clinical stage and U-CLL profile had 64.2%, 10 patients (14.2%) had advanced clinical stage Binet C and U-CLL profile had 6 patiens (60%).

IGHV gene repertoire and mutational status

We analyzed the IGHV-IGHD-IGHJ repertoire and mutational status of a total of 70 alleles. The most frequently expressed IGHV subgroup was IGHV3 (41, 4%), followed by IGHV1and IGHV4 (28.5%), IGHV5 (1.4%), No IGHV2, IGHV6, IGHV7 subgroup members were identified (Figure 1).

IGHV3 genes were found equally expressed, in the unmutated form (51.4%) and in the mutated form (48.2%) in contrast to IGHV1 genes, which were found predominantly in the unmutated cases (80%). IGHV4 and IGHV5 subgroup members were expressed

predominantly in mutated form with frequencies of (65% and 1.4% respectively) (Figure 2).

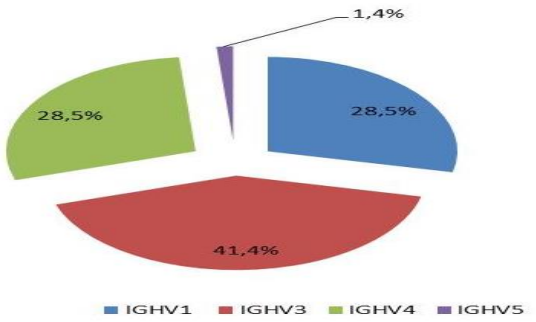

Figure 1: Frequencies of IGHV Gene.

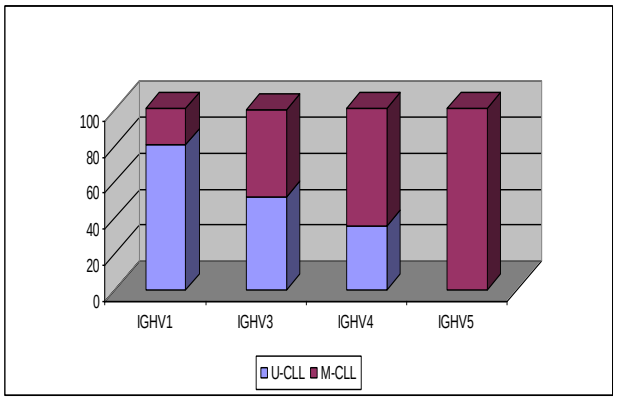

Figure 2: Frequency of IGHV in mutated/unmutated rearrangement.

The most frequently used IGHV genes were IGHV1-69 (18.5%), IGHV3-48 (8.5%), IGHV3-33 (8.5%), IGHV4-34 (7.1%) (Figure 3 and 4).

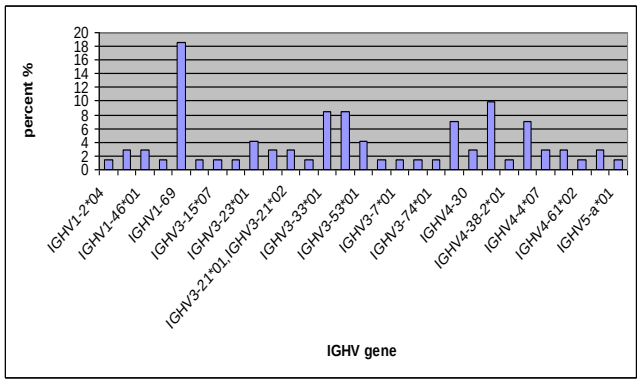

Figure 3: Frequency of IGHV gene.

IGHV1-69, the most frequently used of all genes, was expressed in 18.5% of all rearrangements, as well as in 65% of IGHV1-expressing rearrangements. Its distribution between mutated (0%) and unmutated forms (100%) was significantly significant (*P*.001) (Figure 5).

IGHV3-48 and IGHV3-33 was expressed in (8.5%) of all rearrangements, they showed similar distribution between mutated (33.3%) and unmutated forms (66.6%) (Figure 5).

IGHV4-34 was expressed in (7.1%) of all rearrangements. Its distribution between mutated (80%) and unmutated forms (20%) was significantly significant (P.001) (Figure 5).

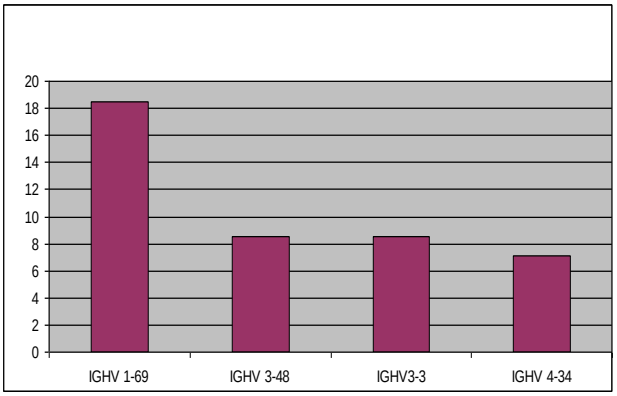

Figure 4: Frequency of IGHV subgroups.

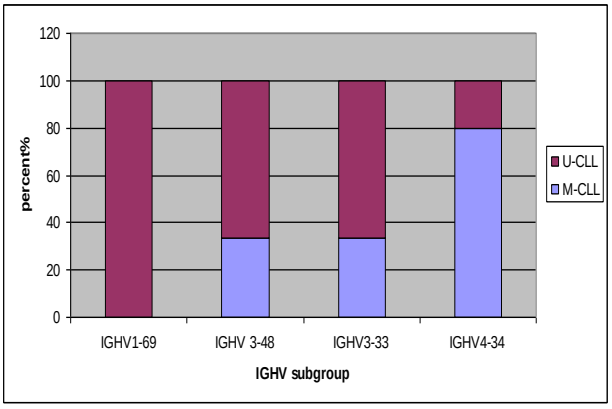

Figure 5: Frequency of IGHV subgroups in mutated/unmutated rearrangement.

IGHD and IGHJ gene use and mutational status

IGHD genes were identified in 67 rearrangements (95. 7%). The distribution of IGHD subgroups was as follows: IGHD3 (55.7%), IGHD2 (18.5%), IGHD6 (10%); IGHD4 (8.5%), IGHD5 (4.2%), IGHD1 and IGHD7 (1.4%).

IGHD3 showed a significant overrepresentation in unmutated rearrangements, in contrast to the IGHD2 subgroup, which was overrepresented in mutated rearrangements.

The most common ones were IGH2-2 (10%), IGHD3-9 and IGHD3-10 (8.59%), IGHD3-22 and IGHD4-17 (7.1%).

IGHJ6 gene was the most frequent (37.1%), followed by IGHJ5 (14.2%), IGHJ4 (8.5%), IGHJ2 and IGHJ3 have equal distribution (1.4%). No IGHJ1 genes were identified. IGHJ6 was preferentially used in unmutated (65.31%) versus mutated rearrangements (36.4%), in contrast to IGHJ5, which was with similar frequency used in unmutated (60%) than in mutated rearrangements (40%).

Table 1: IGHV-IGHD-IGHJ repertoire and mutational status.

Patients	Mutational status	% of identity	IGHV gene	IGHD gene	IGHJ gene
CLL1	U	99,6	IGHV3-33*01	IGHD3-3*01	IGHJ4*01
CLL2	M	91,2	IGVH4-34*01	IGHD2-2*01	IGHJ5*02
CLL3	M	90	IGHV4-b*02	IGHD2-2*01	IGHJ6*02
CLL4	U	96,6	IGHV4-39*01	IGHD3-3*01	IGHJ5*01
CLL5	M	85,8	IGHV4-34*01	IGHD3-3*02	IGHJ6*02
CLL6	U	100	IGHV3-48*03	IGHD3-3*01	IGHJ6*02
CLL7	M	92,9	IGHV4-59*01	IGHD4-17*01	N/A
CLL8	U	100	IGHV1-69*02	IGHD3-9*01	IGHJ5*02
CLL9	U	100	IGHV3-53*01	IGHD3-3*02	IGHJ5*01
CLL10	U	100	IGHV1-69*13	IGHD2-15*01	IGHJ6*03
CLL11	U	100	IGHV3-13*01	IGHD3-3*02	IGHJ6*02
CLL12	U	98,7	IGHV3-64*05	IGHD3-3*01	IGHJ4*01
CLL13	M	95,2	IGHV4-34*01	IGHD3-22*01	N/A
CLL14	U	100	IGHV4-61*02	IGHD3-9*01	IGHJ4*03
CLL15	M	97,4	IGHV3-23*01	IGHD4-17*01	IGHJ5*02
CLL16	U	100	IGHV4-39*01	IGHD3-3*02	IGHJ4*03
CLL17	M	94,3	IGHV3-72*01	IGHD2-8*01	IGHJ6*02
CLL18	M	87	IGHV4-30-4*02	IGHD6-25*01	IGHJ5*02
CLL19	U	100	IGHV1-69*06	IGHD3-16*02	N/A
CLL20	U	99,2	IGHV3-33*01	IGHD1-26*01	N/A
CLL21	M	97,6	IGHV4-34*01	IGHD5-24*01	IGHJ6*01
CLL22	U	100	IGHV3-23*01	IGHD3-9*01	IGHJ6*03
CLL23	U	100	IGHV1-46*02	IGHD6-19*01	IGHJ5*01
CLL24	M	85,3	IGHV1-46*01	IGHD4-23*01	N/A
CLL25	U	99,2	IGHV1-69*06	IGHD3-3*01	IGHJ4*01
CLL26	U	98,8	IGHV1-46*01	IGHD2-2*02	IGHJ6*02
CLL27	U	96,5	IGHV3-23*01	IGHD6-13*01	IGHJ6*02
CLL28	U	98,4	IGHV4-4*07	IGHD4-17*01	N/A
CLL29	U	98	IGHV1-2*04	IGHD3-22*01	N/A
CLL30	M	96,6	IGHV5-a*01	N/A	N/A
CLL31	U	99,2	IGHV1-69*13	IGHD3-10*02	IGHJ5*02
CLL32	M	97,2	IGHV1-3*01	IGHD3-10*01	IGHJ6*02
CLL33	M	96,7	IGHV3-11*04	N/A	N/A
CLL34	U	100	IGHV3-48*01	IGHD3-3*01	IGHJ6*02
CLL35	M	91,8	IGHV4-34*01	IGHD3-10*02	N/A
CLL36	M	96,8	IGHV4-34*01	IGHD5-24*01	IGHJ3*02
CLL37	M	90,6	IGHV3-30*18	IGHD3-3*01	N/A
CLL38	U	99,2	IGHV4-30-4*01	IGHD3-3*01	IGHJ6*02
CLL39	M	94,2	IGHV4-39*01	IGHD2-21*01 IGHD2-21*02	N/A
CLL40	M	89	IGHV3-9*01	IGHD3-10*01	N/A
CLL41	M	92,5	IGHV3-53*01	IGHD3-9*01	N/A
CLL42	M	94,1	IGHV3-7*01	IGHD3-22*01	N/A
CLL43	U	98,4	IGHV3-21*01 IGHV3-21*02	IGHD2-2*01 IGHD2-2*03 IGHD5-5*01	N/A
CLL44	U	100	IGHV3-48*01	IGHD3-22*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL45	U	99,2	IGHV1-69*13	IGHD3-3*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL46	U	98,4	IGHV3-21*01 IGHV3-21*02	IGHD3-9*01	IGHJ6*02 IGHJ4*03 IGHJ6*03
CLL47	U	99,6	IGHV1-69*13	IGHD3-3*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL48	U		IGHV3-74*01	IGHD3-3*01	N/A
CLL49	M	93,8	IGHV3-33*01	IGHD2-21*01 IGHD2-21*02	N/A
CLL50	M	89,8	IGHV3-30*02 IGHV3-30*18	IGHD3-3*02 IGHD3-3*02 IGHD3-3*01	N/A
CLL51	U	100	IGHV1-69*13	IGHD6-13*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL52	U	100	IGHV4-38-2*01	IGHD3-3*01	N/A
CLL53	U	100	IGHV3-48*01	IGHD3-3*01	IGHJ6*02
CLL54	U	100	IGHV1-69*13	IGHD6-19*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL55	U	100	IGHV1-58*02	IGHD3-3*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL56	U	94,9	IGHV3-33*01	IGHD3-10*01	IGHJ4*01 IGHJ4*02
CLL57	M	92,1	IGHV3-48*03	IGHD5-12*01	N/A
CLL58	M	94,1	IGHV3-13*01	IGHD6-19*01	IGHJ2*01
CLL59	M	95,6	IGHV1-8*01	IGHD3-10*01	N/A
CLL60	U	99,2	IGHV3-33*01	IGHD4-17*01	N/A
CLL61	U	97,3	IGHV3-15*07	IGHD7-27*01 IGHD4-17*01 IGHD4-17*01	N/A
CLL62	M	94,1	IGHV3-33*05	IGHD2-15*01	IGHJ6*02 IGHJ6*04 IGHJ6*01
CLL63	M	87,3	IGHV4-30-4*02 IGHV4-30-4*01	N/A	N/A
CLL64	M	91,7	IGHV4-4*07	IGHD3-22*01	IGHJ6*02 IGHJ6*02 IGHJ6*02
CLL65	U	100	IGHV3-48*03	IGHD3-3*01	IGHJ6*02
CLL66	M	92,9	IGHV4-59*01	IGHD4-17*01	N/A
CLL67	U	100	IGHV1-69*02	IGHD3-9*01	IGHJ5*02
CLL68	U	100	IGHV3-53*01	IGHD3-3*02	IGHJ5*01
CLL69	U	100	IGHV1-69*13	IGHD2-15*01	IGHJ6*03
CLL70	U	99,6	IGHV1-3*01	IGHD6-13*01	IGHJ6*02 IGHJ6*02 IGHJ6*03

DISCUSSION

B-CLL offers advantage to investigators, where the immunoglobulin (IG) component has exclusive features which imprint the tumor cell and announce the complexion of the B-cell of origin. Particularly BCR on malignant CLL clones has been investigated for many years. Recent study published at 2006 from Macedonian investigators remark that reasons for diverse prognosis between CLL groups with different mutational status might be that the two subsets differ in their capacity to transmit BCR-derived signal and by apparently different antigen reactivity of the BCRs encoded by mutated and unmutated VH genes.[9] Further investigations have endorsed some facts that geographic diagram and population characteristic have influence on BCR structure. That was the argumentation to design this study, to examine the impact of mutational status on VH, DH, and JH gene segment location and immunogenicity, in Macedonian B - CLL patients at this time point.

Our study included 70 treatment naïve patients with a median age of 62.8 years at diagnosis, fact which was not different from recent published study from the same region.[9] Although male patients predominated in this cohort, as reported in other studies, no association between sex and either IGHV mutational status could be shown. The same depletion of association was also found for the age at diagnosis.

The frequencies of patients belonging to M-CLL and U-CLL subsets (47.1% and 52.87%, respectively) were not similar to those in previous series, because in our study we have predominant U-CLL.[10] Those findings were not quite similar to recent published study where the frequencies of patients belonging to M-CLL and U-CLL subsets were (21.6% and 67.6%, respectively) with 10, 8% of the cases which could not be determined, but the same predominant U-CLL.[9]

We showed that IGHV3 was the most commonly expressed (41.4%), followed by IGHV1 and IGHV4 (28, 5%). The frequencies of IGHV subgroups were not significantly different from those reported for Mediterranean countries.[11]

The nonrandom occurrence of somatic hypermutations and their hierarchy between IGHV subgroups was also detected in our study.[10] IGHV3 and IGHV1 genes were found predominantly in unmutated form, in contrast toIGHV4 and IGHV5 genes, which were predominantly mutated.

IGHV1-69 was the most frequently expressed of all genes (18.5%) which is correlative to 23.6% determined from patients from same region.[12] Its high frequency and lacked somatic hypermutation, overrepresentation in the U-CLL subgroup, and it is consistent with the results of previous studies.[12,13] In line with previous publication the striking molecular similarities between the IGHV1-69 cases indicate that they represent homogeneous group with certain biological features different from other U-CLL cases.[12] It was predominantly recombined with IGHD3 genes and IGHD2, with IGHJ6. The high frequency of IGHV1-69 in CLL cases from the same small geographic region which were analyzed in different period, confirm the observation that antigen stimulation play an important role in pathogenesis of U-CLL.[13]

Confirming notification came out from our analyze, IGHV3-21 gene was detected with low frequency (2.8%), that is found in other countries from Mediterranean area that is in contrast to its much higher representation in Scandinavian and other northern European countries.[8,11,14.15] Only 2 patients expressing IGHV3-21 were identified, expressing an unmutated form. The frequency of IGHV3-21 in CLL patients of Mediterranean origin is 3.45% of cases and fifth among unmutated cases.[7] This frequency is at least 3 times lower than the frequency reported in cases from Northern Europe.[15] These differences in the frequency of IGHV3-21 in CLL patients of different geographic origins may reflect differences in genetic acquiring, depending on variations in germline configuration of the IGHV locus. Maybe this picture is development of a potential environmental variable less frequently encountered in different regions. A detailed analysis of the Scandinavian series revealed that, besides a higher frequency of usage, several condition characterize Scandinavian IGHV3-21-expressing CLL.[15] The authors show that an individual IGHV gene can have by itself a prognostic impact in CLL. In their cohort the patients using IGHV3-21 gene, although usually mutated, showed a poor overall prognosis and were therefore an exception to the rule of mutated CLL having good prognosis.

Our evaluation of mutational status on IGVH, IGDH, and IGJH gene in Macedonian CLL patients, resulted with data which are consubstantial to those from Mediterranean area and west Balkan.[16] Feature our investigation would have to determine the influence of IGVH, IGDH, and IGJH gene settings on survival of M-CLL and U-CLL patients with individualized treatment option.

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