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EXPRESSION OF IMMUNOGLOBULIN LIGHT CHAIN GENES IN STEREOTYPED CASES FROM UKRAINIAN COHORT OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

Background. Analysis of immunoglobulin heavy chain gene (*IGHV*) rearrangements expressed in chronic lymphocytic leukemia (CLL) cells has provided insights into the B-cell receptor (BCR) repertoire in CLL. In more than 40% of CLL patients, (quasi)identical or stereotyped BCR is expressed. The recent data point at the non-stochastic expression of immunoglobulin light lambda (*IGLV*) or kappa (*IGKV*) chains as well. Several pairs of *IGHV* and *IGK/LV* have been described for some major stereotyped subsets, but most subsets have not been characterized. **Aim**. To study the *IGK/LV* gene expression in stereotyped CLL cases. **Materials and Methods**. Analysis was performed in a group of 105 CLL patients with stereotyped BCR. The cases with stereotyped BCRs were identified according to Agathangelidis et al. (2021). The *IGHV* and *IGK/LV* gene expressions were studied by a polymerase chain reaction followed by direct sequencing. **Results**. The expression of the *IGK/LV* genes in the most presented major stereotyped subsets (#1, #2, #3C3, #4, #6, #28a) was in agreement with the data reported by other authors. For the cases of subsets #5b, #9D1, #9D4, #16, #50, #59, and #77, differences were found. The new data on the *IGK/LV* gene expression in 55 minor clusters were presented. A number of patterns of the *IGK/LV* gene expression depending on the phylogenetic clan and mutational status of the *IGHV* genes have been described. **Conclusion**. The non-stochastic distribution of the *IGKV/LV* gene expression in the individual stereotyped subsets was confirmed. Taking into account the complementary role of the light chains in antigen recognition by the clonotypic BCRs, it was suggested that the subsets with the heterogeneous *IGK/LV* expression might be reclassified and divided into separate subgroups based on the *IGHV* and *IGK/LV* association.

Keywords: chronic lymphocytic leukemia, stereotyped subset, *IGK/LV* genes.

One of the characteristics of the B-cell receptor (BCR) in chronic lymphocytic leukemia (CLL) is the nonrandom repertoire of the immunoglobulin heavy chain variable region (*IGHV*) genes and the presence of a significant proportion of patients with similar or almost identical variable heavy chain

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complementarity-determining region 3 (HCDR3) sequences strongly suggesting the recognition of a common antigenic determinant [1—3]. More than 40% of CLL patients expressed (quasi)identical or stereotyped BCR [4]. The incidence of stereotyped cases in the Ukrainian CLL cohort reached 50.5% [5]. The mutations of the prognostically significant genes (namely, *NOTCH1* and *SF3B1*) are associated with certain stereotyped clusters, and patients belonging to them display similar clinical features [6, 7]. In addition, there is evidence that the expression of immunoglobulin light lambda (*IGLV*) or kappa (*IGKV*) chains is also non-stochastic. The association of several *IGKV* and *IGLV* genes with the stereotyped clusters in CLL has been established. In particular, the expression of *IGKV1-39/1D-39* is typical for clusters #1 and #8 while clusters #4 and #2 are characterized by *IGKV2-30* and *IGLV3-21* expressions, respectively [8—10]. Thus, the light chains together with *IGHV* form the structure of a stereotypical BCR. However, for most stereotyped clusters, *IGKV/LV* gene expression has not been studied. In light of the above, the aim of our work is to further study the *IGK/LV* gene expression in stereotyped CLL cases.

Materials and Methods

The expression of the immunoglobulin light chain genes was studied in 105 CLL patients with stereotyped BCR. The group included 73 men and 32 women aged 56.26 ± 0.81 years (median 56 years). The study was approved by the local Ethics Review Committee, and all patients gave their informed consent before participating in the study. The diagnosis of CLL was based on clinical history, lymphocyte morphology, and immunophenotypic criteria. The stage of the disease was defined according to Rai [11, 12] and Binet [13].

Genomic DNA for molecular analysis was extracted from the peripheral blood mononuclear cells using the QIAamp Blood Mini Kit (Qiagen, UK). The *IGHV* gene mutational status was assessed by polymerase chain reaction (PCR) followed by direct sequencing, as described above [14]. The sequences were analyzed using the IgBlast and IMGT databases. Sequences with ≥ 98 % homology with the corresponding germ-line *IGHV* gene were considered unmutated (UM), and cases with < 98 % homology were considered to be mutated (M) [15, 16]. The cases with the stereotyped BCRs were identified according to Agathangelidis et al. [4]. The expression of the *IGLV* and *IGKV* genes was carried out by PCR followed by sequencing according to the European BIOMED-2 protocol [17]. Statistics was performed using the SPSS 20.0 software package (SPSS, Chicago, IL). All p values are two-sided, and p value < 0.05 was considered statistically significant.

Results

The observed cases were assigned to 77 different stereotyped subsets. 45 cases belonged to 18 major subsets, 6 cases were with the M *IGHV* genes (#2, #4, #16, #73, #77, #252), and the others were with the UM *IGHV* genes. The most represented subsets were #1 (UM *IGHV*, 11 sequences), #2 (M *IGHV*, 6 sequences), #6 (UM *IGHV*, 6 sequences), and #4 (M *IGHV*, 4 sequences**).** Four major subsets consisted of 2 cases each: #28a, #3C2, #3C3, and #59 (all UM *IGHV*). The other major subsets were represented by 1 case each.

Sixty cases belonged to 59 minor subsets (9 subsets with the M *IGHV* genes, 50 subsets with the UM *IGHV* genes). Only 1 minor subset (#5b) consisted of 2 cases, the other ones were represented by 1 case each.

The expression of 28 functional *IGLV* and *IGKV* genes was revealed. 16 functional *IGKV* genes were involved in 75 *IGKV-J* rearrangements; the most frequent genes were *IGKV1-39/1D-39* (17 cases), *IGKV3-20* (15 cases), *IGKV2-30* (9 cases), and *IGKV1-33* (7 cases). 12 functional *IGLV* genes were involved in 30 *IGLV-J* rearrangements; the most frequent gene was *IGLV3-21* (13 cases).

3 *IGKV/LV* genes showed a non-stochastic distribution depending on different phylogenetic clans of *IGHV* genes and/or *IGHV* gene mutational status:

- *IGKV1-39* gene was expressed almost exclusively in combination with the clan I *IGHV* genes (25.45% *vs.* 6.0% in combination with the *IGHV* genes of other clans; $p = 0.007$);
- *IGKV2-30* gene expression was not detected in combination with the clan I *IGHV* genes (18.0% in combination with *IGHV* genes of other clans; $p = 0.004$);
- the most frequent expression of the *IGLV3-21* gene was observed in combination with clan III

IGHV genes (25.8% *vs*. 6.75% in combination with the IGHV genes of other clans; $p = 0.006$);

- expression of the *IGLV3-21* gene reached 39.1% among stereotyped clusters with the M *IGHV* genes compared to 4.9% in the UM *IGHV* cases ($p = 0.00001$).

The *IGKV/LV* gene expression significantly differed in the individual stereotyped subsets. Thus, the *IGHV* genes in 6 major stereotypic subsets (#1, #2, #3C3, #4, #6, #28a) were expressed exclusively in combination with one type of immunoglobulin light chains. These subsets display the homologous CDR3 of heavy and light Ig sequences. These results coincide with the data reported elsewhere [8—10, 18]. In addition, major #7D3 and #12 subsets, represented in our cohort by 1 case each, showed the typical light chain expression for these subsets (*IGLV3-9* and *IGKV3-15*, respectively) (Supplementary Table 1)[1].

The major subsets #3C2, #5, and #16 are known to be characterized by the heterogeneity of the *IGK/LV* gene expression. Two cases (subsets #3C2 and #5) expressed the genes already described in these subsets. Subset #16 represented by 1 case expressed *IGKV1-16*01*. It differed from the other cases belonging to subset #16 (heterogeneous *IGK/LV* expression with a predominance of *IGKV3-20* (Table 1).

A clear discrepancy was observed concerning the major subsets #77 and #59 (Table 2). These subsets included rearrangements utilizing different IGHV genes [4]. Hadzidimitriou et al. [18] presen-

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Table 1. **Clusters with heterogeneous *IGK/LV* expression in comparison with known sequences**

Subset, *N_IGHV_IGHD _IGHJ_* mutational status	HCDR3	*IGK/LV*	KCDR3/LCDR3
Subset #3C2, our group			
D70_1-69_2-2_6_UM	ATGGDIVVVPAEYYYYYYGMDV	*IGLV3-11*01*	CQQRSNYPLYTF
D3_1-69_2-2_6_UM	ARDPDIVVVPASFFYYYYGMDV	*IGKV1-9*01*	CQQLNSYPSYT
Known sequences of subset #3C2 [18]			
FRA-283_1-8_2-2_6_UM	ARDWPIVVVPAAMRYYYYGMDV	*IGKV3-11*01*	CQQRSNWPWTF
FRA-292_1-69_2-2_6_UM	ASGGDIVVVPAAMTYYYYGMDV	*IGKV1-39*01*	CQQSYST F
IT01-0169_1-69_2-2_6_UM	ARGGDIVVVPAAYYYYYYGMDV	*IGKV3-11*01*	CQQRSFT F
Subset #5, our group			
E36_1-69_3-10_6_UM	ARDTVQGVINVLYYYYGMDV	*IGLV3-21*02*	CQVWDSSSDHVVF
Known sequences of subset #5 [18]			
P675_1-69_3-10_6_UM	ARDAVRGVIGVYYYYYGMDV	*IGLV3-21*02*	CQVWDSSSDHVVF
IT01-0188_1-69_3-10_6_UM	ALTMVRGVIIFTYYYYGMDV	*IGKV1-33*01*	CQQYDNLR TF
IT01-0187_1-69_3-10_6_UM	ARVMVQGVIALSYYYYYMDV	*IGLV3-25*03*	CQSADSSGTVVF
IT01-0186_1-69_3-10_6_UM	AREQVRGVISILVYYYGMDV	*IGKV1-47*01*	CAAWDDSLSG
IT01-0185_1-69_3-10_6_UM	ARSKVRGVIPIYYYYYGMDV	*IGKV1-33*01*	CQQYDNLPLFTF
Subset #16, our group			
E72_4-34_2-15_6_M	AGRFYCSGVTCQSPSFHHYSGLDV	*IGKV1-16*01*	CQQYNSYPPAF
Known sequences of subset #16 [18]			
FRA-202_4-34_2-15_6_M	ARRFYCSGGSCSHPRYYFYHGMDV	*IGKV2-28*01*	CMQSLQTPR TF
P1082_4-34_2-15_6_M	AGRFYCSGAGCDSEGFYYYYGLDV	*IGKV3-20*01*	CQQYGSSPY TF
P781_4-34_2-15_6_M	AGRFYCYGGNCNNANYYYYYGMDV	*IGKV3-20*01*	CQQYGASLPVTF
Swe-124_4-34_2-15_6_M	AGRFYCSGRSCLSPSYYYYYGMDV	*IGKV3-20*01*	CQQYGGLI TF
Swe-152_4-34_2-15_6_M	AGSFYCSGATCDSPRYYYHYGVDV	*IGKV3-20*01*	CQQYGSSPR TF

ted two sequences of subset #77 with the homogeneous IGHV4-59/IGLV10-54 gene expression. Our case differed in both IGHV4-4 and IGKV3-20 expressions. On the other hand, in the study of Hadzidimitriou et al., two #59 cases expressed different IGKV genes. Two #59 cases from our group expressed the homogeneous IGKV2-28 expression.

Five major subsets (#10, #64B, #73, #202, and #252) were represented by only one case each in our CLL group (Supplementary Table 1). We found

Table 2. **The comparison of sequences from subsets #77 and #59**

Subset, *N_IGHV_IGHD _IGHJ_* mutational status	HCDR3	*IGK/LV*	KCDR3/LCDR3
Subset #59, our group			
D92_1-58_3-3_5	AAGYDFWSGMDV	*IGKV2-28*01*	CMQALQTPPTF
F12_1-58_3-3_6	AAGTDFWSGYPD	*IGKV2-28*01*	CMQALQTPLTF
Known sequences of subset #59 [18]			
N2231_1-58_3-3_4	AAGYDFWSGYIY	*IGKV1-4*01*	CQQYYRTPLTF
P532B_1-69_3-3_4	ARAYDFWSGYY	*IGKV1-39*02*	CQQSYSNPRTF
Subset #77, our group			
E75_4-4_6-19_5	ARGPNESGWNGFDS	*IGKV3-20*01*	QQYGSSPLT
Known sequences of subset #77 [18]			
F73_4-59_6-19_4	ARGPDTSGWNSLDY	*IGLV10-54*01*	CSAWDSSLSAQVF
N2518_4-59_2-15_4	ARGPDESGWLALAY	*IGLV10-54*01*	CSAWDRSLSAQLF

Table 3. **The comparison of sequences from minor subsets**

Subset, *N_IGHV_IGHD _IGHJ_* mutational status	HCDR3	*IGK/LV*	KCDR3/LCDR3
Subset #5b, our group			
E91_1-69_3-3_6_UM	ARATIFGVVDIFYYYYYGMDV	*IGKV2-14*01*	CMQATQFPLF
F39_1-69_3-3_6_UM	ARETIFGVVNINYYYYYGMDV	*IGKV3-15*01*	CQQYNNWPPLTF
Known sequences of subset #5b [18]			
FRA-1271-69_3-3_6_UM	ARVEVRGVIGIYYYYYYGMDV	*IGLV3-21*02*	CQVWDSGSDHPWVF
Subset #9D1, our group			
E28_1-69_3-3_6_UM	ASGGKITIFGVVIPPEGYYYMDV	*IGLV3-10*01*	YSTDSSGNHYV
Known sequences of subset #9D1 [18]			
FRA-003_1-69_3-22_6_UM	ARVGGITIFGVVIQRNYYYYMDV	*IGKV1-33*01*	CQQYDNLPLTF
Subset #9D4, our group			
F44_1-69_3-3_6_UM	ASKSLPITIFGVVISDYYYYGMDV	*IGKV4-1*01*	CQQYYSTPGGF
Known sequences of subset #9D4 [18]			
P324_1-69_3-22_6_UM	AKDKQRITIFGVVIMAGYYYGMDV	*IGKV2-28*01*	CMQALQTPPWTF
Subset #50, our group			
D62_4-59_3-22_6_UM	ARGVGDYYDSSGYLHYYYGMDV	*IGKV1-33*01*	QQYDNLPPL
Known sequences of subset #50 [18]			
N1647A_1-69_3-22_6_UM	ARDQDYYGSGSHVRYYYYGMDV	*IGLV1-40*01*	CQSYDSSLSGWVF
Swe-3_1-69_3-22_6_UM	ARDSDYYDSSGYRYYYYGMDV	*IGLV1-40*01*	CQSYDSSLSGWVF

no data available to compare *IGK/LV* expression in these cases.

When the *IGK/LV* chain expressions in 4 minor subsets in our group were compared to the available literature data, the sequences were different in all cases (Table 3). It should be noted that according to the latest classification, subset #50 includes the cases with *IGHV4-59* expression only [4]. At the same time, *IGLV1-40* gene expression was revealed in *IGHV1-69* expressing cases with similar HCDR3 [18].

We found no data available to compare *IGK/LV* expression in the other 55 minor stereotyped subsets, represented in Table S1. It is interesting to note that in the minor subset #202b, which is a satellite of the major subset #202, the expression of the same *IGKV3*-15*01 gene with identical KCDR3 was observed. On the contrary, in similar cases of major #64b and minor #64a subsets (HCDR3 sequences differ only in the shift of a characteristic amino acid motif), the expression of different *IGKV2-28* and *IGLV1-47* genes was observed.

Discussion

The expression of the *IGK/LV* genes in the most presented major stereotyped subsets (#1, #2, #3C3, #4, #6, and #28a) was in agreement with the data of other authors [8—10, 18]. The homogeneous *IGHV* and *IGK/LV* gene expression indicates the true identity of the BCR and, therefore, an antigenic determinant that can be recognized.

Widhopf et al. [19] suggested that the Ig HCDR3 structure predicts a nonstochastic pairing of heavy and particular light Ig chains. Depending on the HCDR3 structure, in the *IGHV1-69*-positive cases, the genes were co-expressed with different light chains, namely *IGHV1-69*/*IGHD2-2*/*IGHJ6* with HCDR3 amino acid motif PDIVVVPAAIXYYYGMDV (subset #3C3) characterized by *IGKV1-39* expression*; IGHV1-69/IGHD3-16/IGHJ3* with HCDR3 amino acid motif GGXYDYIWGSYRPNDAFDI (subset #6) expressed *IGKV3-20*; and *IGHV1-69*/IGHD3-3/*IGHJ6* with HCDR3 amino acid motif YDFWSGYYPNYYYYGMDV (subset #7D3) expressed *IGLV3-9*. However, in many cases with identical/quasi-identical HCDR3, different light chains are expressed, as evidenced by our data as well. This corresponds to the formation of the antigenic response in various infectious diseases. For example, *IGHV3-53* and *IGHV3-66*-positive anti-SARS-CoV-2 antibodies with a similar HCDR3 pair with at least 14 light-chain genes [20]. It is important to note that depending on the expression of the light chain, the activity of the antibodies with the same HCDR3 sequence (in particular, the ability to neutralize the virus) changes [20, 21].

These data raise two important questions, the first of which is the criteria for identifying the individual clusters of stereotypical receptors. Today such criteria are the use of *IGHV* genes of the same phylogenetic clan; at least 50% amino acid identity and 70% similarity within HCDR3; identical HCDR3 length, and identical offset of the shared amino acid pattern [4]. Taking into account the complementary role of light chains in antigen recognition by the clonotypic BCRs, the subsets with the heterogeneous *IGK/LV* expression may be reclassified and divided into separate subgroups (as an example, the division of subsets #3, #5, #7, and #9), and the *IGK/LV* expression of chains can complement the criteria of stereotypy. The accumulation of the data concerning *IGHV* and *IGK/LV* association in stereotyped subsets will be useful.

The second question is related to the possible differences in the functional activity of BCR in CLL (belonging to the same subset) depending on the expression of light chains, which may be related to the characteristics of the clinical course, and the spectrum of the typical gene mutations (*NOTCH1*, *SF3B1*, etc.).

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ЕКСПРЕСІЯ ГЕНІВ ЛЕГКИХ ЛАНЦЮГІВ ІМУНОГЛОБУЛІНІВ В СТЕРЕОТИПНИХ ВИПАДКАХ В УКРАЇНСЬКІЙ КОГОРТІ ХВОРИХ НА ХРОНІЧНУ ЛІМФОЦИТАРНУ ЛЕЙКЕМІЮ

Стан питання. Аналіз перебудови генів важких ланцюгів імуноглобулінів (*IGHV*) у хворих на хронічну лімфоцитарну лейкемію (ХЛЛ) визначив особливості побудови В-клітинного рецептора (ВКР) при цьому захворюванні. Лейкемічні клітини понад 40% хворих на ХЛЛ експресували (квазі)ідентичний або стереотипний ВКР. Останні дані свідчать про нестохастичне використання і генів легких лямбда (*IGLV*) або каппа (*IGKV*) ланцюгів імуноглобулінів. Описано декілька стабільних пар *IGHV* та *IGK/LV* для деяких основних стереотипних кластерів, але більшість кластерів не охарактеризовано. **Мета**: подальше вивчення експресії генів *IGK/LV* у стереотипних випадках ХЛЛ. **Матеріали та методи.** Аналіз проводили в групі 105 хворих на ХЛЛ зі стереотипним ВКР. Кластери стереотипних ВКР були виявлені відповідно до Agathangelidis та ін. (2021). Експресію генів *IGHV* та *IGK/LV* визначали за допомогою полімеразної ланцюгової реакції з подальшим прямим секвенуванням. **Результати**. Експресія генів *IGK/LV* у найбільш представлених основних стереотипних кластерах (#1, #2, #3C3, #4, #6, #28a) співпадала з даними інших авторів. Для кластерів #5b, #9D1, #9D4, #16, #50, #59, #77 виявлено відмінності. Наведено нові дані щодо експресії генів *IGK/LV* у 55 мінорних кластерах. Описано особливості експресії генів *IGK/LV* залежно від філогенетичного клану та мутаційного статусу генів *IGHV*. **Висновок**. Підтверджено нестохастичний розподіл генів *IGK/LV* в окремих кластерах стереотипних ВКР при ХЛЛ. Враховуючи значення легких ланцюгів імуноглобулінів у розпізнаванні антигену клонотиповими ВКР, висловлено припущення, що кластери з гетерогенною експресією генів *IGK/LV* можна поділити на окремі підгрупи. Накопичення даних щодо асоціації генів *IGHV* та *IGK/LV* у стереотипних кластерах при ХЛЛ, чому й присвячена робота, буде сприяти цьому.

Ключові слова: хронічна лімфоцитарна лейкемія, стереотипні кластери, гени *IGK/LV*.