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BIALLELIC LOSS OF CERTAIN GENES IN ADULT PH-NEGATIVE T- ACUTE LYMPHOBLASTIC LEUKEMIA

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INTRODUCTION

Tumor cells of the patients with Ph-negative acute lymphoblastic leukemia (ALL) may have a variety of genetic lesions [1-3]. Some of them lead to a complete loss of factors that control tumor growth. Chromosomal microarray (CMA) allow searching for biallelic loss of genes related to pathogenesis and associated with the disease prognosis [4].

AIM

To assess the landscape of tumor molecular karyotypes in Ph – negative T-ALL and to reveal biallelic loss of certain genes.

METHOD

The study included 18 patients, who received treatment according RALL-2016 clinical protocol. CMA was performed for the patients with de novo Ph – negative T-ALL, admitted to the National Medical Research Center for Hematology (Moscow, Russia) from 2021 to 2023.CMA was carried out with Thermo Fisher Scientific (Santa Clara, CA 95151, USA) equipment using the CytoScan™ HT-CMA 96F array SNP-oligonucleotide microarray (Thermo Fisher Scientific, USA) in accordance with the manufacturer's protocol. The analysis was performed at the "Genomed" laboratory of Molecular Pathology (Moscow, Russia).

RESULTS

Out of 18 patients, only one had normal molecular karyotype. Other 17 patients had multiple gains, losses, and copy neutral losses of heterozygosity. Biallelic losses were found in 8 patients (44%) (Table 1). In six patients (33%), a biallelic deletion of 9p21.3 was noted, involving a different number of genes, but in all six cases it included the loss of CDKN2A, and CDKN2B-AS1 genes. For four patients (22%), a biallelic deletion of 7q34 was found, always including only three genes - TCAF2, PRSS1, PRSS2. Moreover, in two of them this aberration was combined with 9p21.3 biallelic loss (patients #3 and #8) and in patient #7 we found a combination of three biallelic deletions: 7q34, 9p21.3 and 13q14.2 (including RB1, LPAR6, and RCBTB2 loss). In patient #6 one very small biallelic deletion of 12p13.2 containing only the ETV6 gene was found.



A. *Detail View Export chr7: 106,230,651 - 159,345,973*

B. *Detail View Export chr9: 2,268,023 - 48,399,594*

Figure 1. Molecular karyotype diagram of patient #3 with two biallelic deletions 7q34 and 9p21.3 (marked by red arrows) and detail view of 7q (A) and 9p (B)

		genes			
Patient#	Cytoband (loss area)	7q34	9p21.3	12p13.2	13q14.2
1	7q34(142309952_142795256)x0	TCAF2, PRSS1, PRSS2			
2	9p21.3(21909980_22233512)x0		CDKN2A, CDKN2B-AS1, CDKN2B		
3	7q34(142709652_142795256)x0, 9p21.3(20703929_22332570)x0	TCAF2, PRSS1, PRSS2	FOCAD, HACD4, IFNB1, IFNW1, IFNA21, IFNA4, IFNA7, IFNA10 , IFNA16 , IFNA17 , IFNA14 , IFNA5, KLHL9, IFNA6, IFNA13 , IFNA2, IFNA8 , IFNA1, MIR31HG, IFNE, MIR31 , MTAP , CDKN2A, CDKN2B-AS1, CDKN2B		
4	9p21.3(20272224_22647015)x0 [0.5]		MLLT3, FOCAD, HACD4, IFNB1, IFNW1, IFNA21, IFNA4, IFNA7, IFNA10 , IFNA16 , IFNA17 , IFNA14 , IFNA5, KLHL9, IFNA6, IFNA13 , IFNA2, IFNA8 , IFNA1, MIR31HG, IFNE, MIR31 , MTAP , CDKN2A, CDKN2B-AS1, CDKN2B, DMRTA1		
5	9p21.3(21866502_21996864)x0		MTAP, CDKN2A, CDKN2B-AS1		
6	12p13.2(11592806_11983676)x0			ETV6	
7	7q34(142637680_142796623)x0, 9p21.3(21471728_22313094)x0, 13q14.2(48411504_48496038)x0	TCAF2, PRSS1, PRSS2	MIR31HG, IFNE, MIR31, MTAP, CDKN2A, CDKN2B-AS1, CDKN2B		RB1, LPAR6, RCBTB2
8	7q34(142659319_142785320)x0, 9p21.3(21682143_22103814)x0	TCAF2, PRSS1, PRSS2	MTAP, CDKN2A, CDKN2B-AS1, CDKN2B		

Table 1. Biallelic losses of genes in tumor genomes of adult Ph-negative T- acute lymphoblastic leukemia patients

CONCLUSIONS

Thus, in a small cohort of adult patients, a high incidence of biallelic deletions was revealed. Most of them are found in 9p21.3 and 7q34 loci. Two more include genes RB1 and ETV6 known to be affected in a variety of tumors. One can conclude, that narrow regions of biallelic deletions found in this study might be directly related to the pathogenesis of T-ALL. The significance of the identified gene losses requires further study on an expanded cohorts of patients with long-term follow-up.

REFERENCES

1. **Gianni F et al.** The Genetics and Mechanisms of T-Cell Acute Lymphoblastic Leukemia. *Cold Spring Harb Perspect Med. 2020 Mar 2;10(3):a035246.*

2. **De Bie J et al.** Cytogenetics in the management of T-cell acute lymphoblastic leukemia (T-ALL): Guidelines from the Groupe Francophone de Cytogénétique Hématologique (GFCH). *Curr Res Transl Med. 2023 Oct-Dec;71(4):103431.*

3. **Girardi T et al.** The genetics and molecular biology of T-ALL. *Blood. 2017 Mar 2;129(9):1113-1123.*

4. **Van Vlierberghe P et al.** Prognostic relevance of integrated genetic profiling in adult T-cell acute lymphoblastic leukemia. *Blood. 2013 Jul 4;122(1):74-82.*

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