ALLELE POLYMORPHISMS OF IMMUNE RESPONSE GENES IN SEVERE HAEMOPHILIA A PATIENTS WITH INHIBITORS IN UKRAINE

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Background:

The reason that inhibitors factor VIII developing in only fraction of patients with hemophlia A remains unclear. In Ukraine, where resources are limited, an increase of incidence of inhibitor development proves the importance of preventing of this severe complication. Several risk factors for development of these antibodies have been discussed, but studies of genetically related subjects with hemophilia have shown that the immunological outcomes are mainly determined by patient–related risk factors but this data are controversial.
Aims: To establish allele and genotype frequencies of *IL10* 1082G/A, *TNF-α* 308G/A, *CTLA-4* 318 C/T and 49 A/G in hemophilia A inhibitor positive and inhibitor negative patients from Ukraine.

Methods:

The *IL10* 1082G/A, *TNF-α* 308G/A, *CTLA-4* 318 C/T and 49 A/G single nucleotide polymorphisms (SNPs) were analysed by ARMS-PCR technique among 71 hemophilia A patients (26 inhibitor positive patients and 45 inhibitor negative patients) and control group (*n=50*), from Western Ukraine population.

Table1. Frequencies of allele and genotype for CTLA-4 -318 C/T and for +49 G/A gene SNP in hemophiliacs and controls

	Inhibitor negative (%)	Inhibitor positive (%)	Controls (%)
-318C/T CTLA-4			
Allele T	23(25.6)[1]	18(34.6)[1]	9(9.0)
Allele C	67(74.4)	34(65.4)	91(91.0)
CC	30(67.0)	15(58.0)	42(84.0)
CT	7(16.0)	4((15.0)	7(14.0)
TT	8(18.0)[2]	7(27.0)[2]	1(2.0)
+49 A/G CTLA-4			
Allele G	31(34.5)	19(36.5)	46(46.0)
Allele A	59(65.5)	33(63.5)	54(54.0)
AA	20(44.0)	10(38.0)	14(28.0)
AG	19(42.0)	13(50.0)	26(52.0)
GG	6(13.0)	3(12.0)	10(20.0)

[1]OR T (inhibitor negative) = 3.47, CI 95% = 1,51-7,98; OR for allele T (inhibitor positive) = 5.35, CI = 2,19-13, 06;
[2]OR for TT genotype (inhibitor negative) = 11.20, CI 95% = 1,33-94,34; OR for the TT genotype (inhibitor positive) = 19.60, CI 95% = 2.22 - 172.81;

Table 2. Frequencies of allele and genotype for 1082 G/A promoter gene SNP and for 308 G/A TNF-α promoter gene SNP in hemophiliacs and controls

	Inhibitor negative (%)	Inhibitor positive (%)	Controls (%)
-1082 G/A IL-10			
Allele G	54(60.0)	29(55.8)	51(51.0)
Allele A	36(40.0)	23(44.2)	49(49.0)
AA	10(22.0)	7(27.0)	15(30.0)
AG	16(36.0)	9(35.0)	19(38.0)
GG	19(24.0)	10(38.0)	16(32.0)
-308 G/A TNF-α			
Allele G	72(80.0)	44(84.6)	73(73.0)
Allele A	18(20.0)	8(15.4)	27(27.0)
AA	1(2.0)	0	1(2.0)
AG	16(36.0)	8(31.0)	25(50.0)
GG	28(62.0)	18(69.0)	24(48.0)

Results:

We revealed significantly higher frequency of *CTLA-4* 318T allele (OR=5,35, CI 95% = 2,19-13,6) and TT-genotype (OR=19,6, CI 95% = 2,22-172,81) in hemophilia A patients compared to control. 23,3% of inhibitor positive patients have *CTLA-4* 318TT, 49AA genotype compare to 13,3% in inhibitor negative patients and 2% in control subjects. This genotype could be discussed as predisposing genetic risk factors of inhibitor development.
The differences in distribution of *IL10* 1082G/A, *TNF-α* 308G/A allele and genotype in studied groups of patients were not significant in contrast to reports on association of certain polymorphisms with inhibitor in others populations.This is the first report from Ukraine on the association of allele polymorphisms of immune response genes with inhibitors development in hemophilia A patients. This could provide useful insights into the immune response to FVIII in inhibitor positive haemophilia A patients and possibly influence the timely prediction and prevention or treatment of FVIII antibodies.

Conclusions:

This is the first report from Ukraine on the association of allele polymorphisms of immune response genes with inhibitors development in hemophilia A patients. This could provide useful insights into the immune response to FVIII in inhibitor positive haemophilia A patients and possibly influence the timely prediction and prevention or treatment of FVIII antibodies.

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