IMPACT OF HLA AND CYTOKINE POLYMORPHISMS ON INHIBITORS DEVELOPMENT IN CHILDREN WITH SEVERE HAEMOPHILIA A.

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INTRODUCTION

The development of inhibitors (Inh) against factor VIII in Haemophilia A (HA) patients is the most serious complication, affecting patients' care because they render substitution therapy ineffective. HLA alleles, cytokine polymorphisms and FVIII gene intron-22 inversion are included among genetic predisposing factors for Inh formation in children with severe HA.

The **aim** of the study was: 1) to investigate a possible impact on the risk for Inh development of i) HLA-A, B, C, DRB1 and DQB1 alleles and ii) cytokines polymorphisms in TNF-α, TGF-β1, IL-10, IL-6, IFN-γ genes, and 2) to correlate Inh formation with intron 22 inversion in the Greek pediatric haemophilia A population.

PATIENTS - METHODS

Possible correlations of HLA alleles, cytokine polymorphisms and FVIII gene intron-22 inversion with the risk for Inh development were investigated in 52 Greek children with severe HA, exclusively treated with recombinant FVIII products. The detection of intron-22 inversion was performed by Long Range PCR.

PCR-SSP and PCR-SSO were applied for HLA class I and II genotyping and also for cytokine polymorphisms of TNF-α, TGF-β1, IL-10, IL-6, IFN-γ.

Statistical analysis was performed by x^2 test and Fischer's exact test.

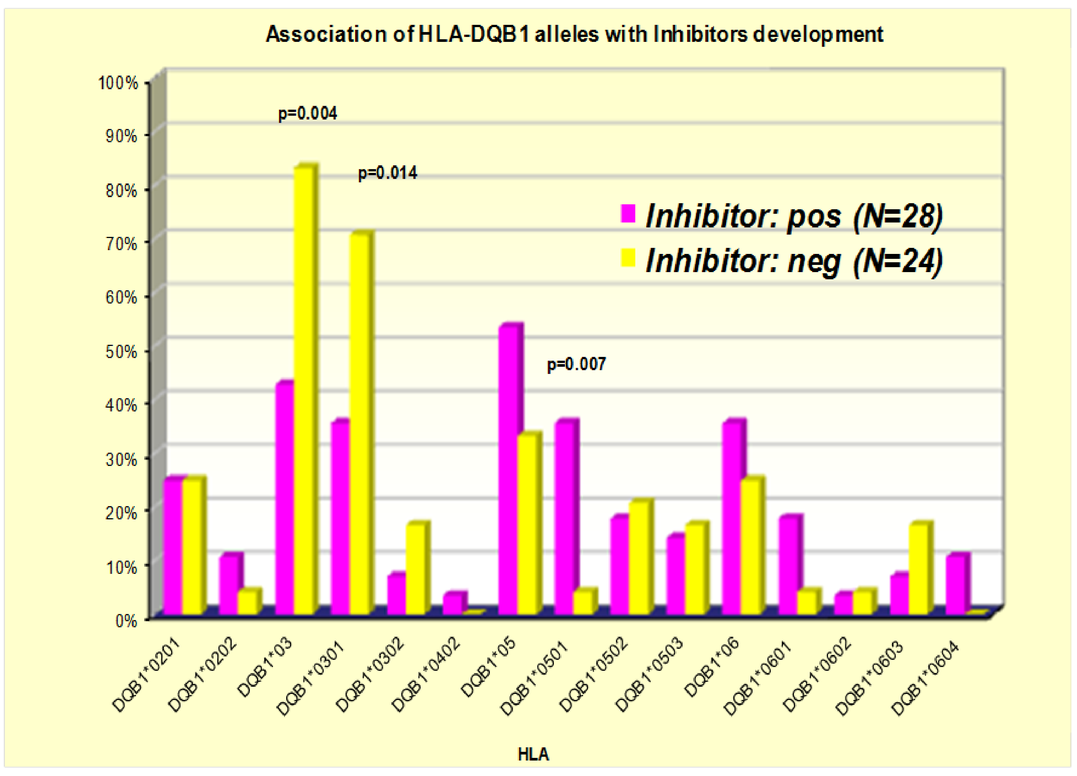
RESULTS

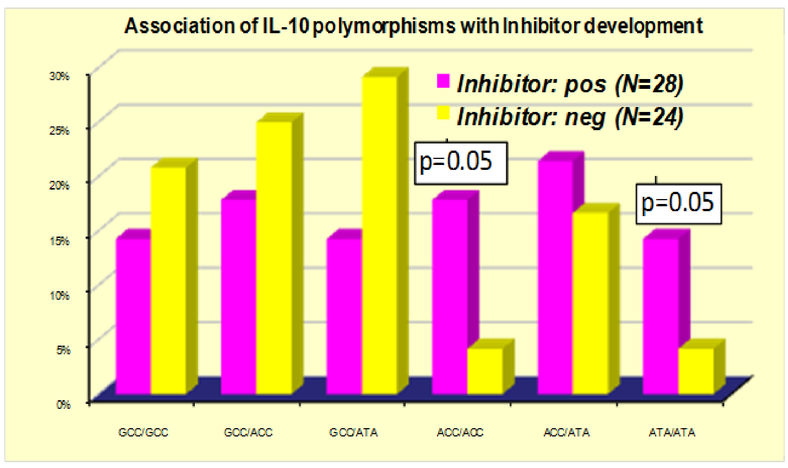
Twenty-eight children had developed inhibitors (Group I), while 24 had not (Group II). Analysis of HLA frequencies showed statistically significant differences between the two groups (Table 1).

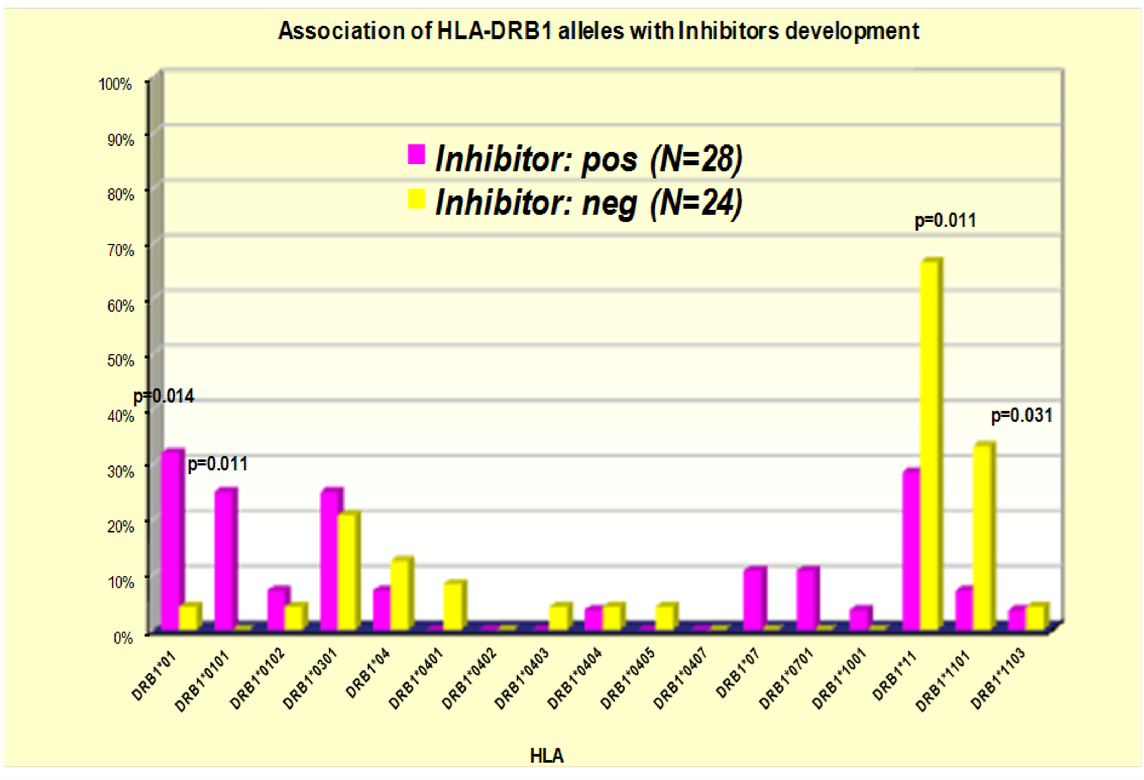
HLA Alleles	Patients with inhibitor (N=28)	Patients without inhibitor (N=24)	P <0.05	OR (95% CI)
HLA alleles with increased prevalence in Group I vs Group II				
DRB1*01	32.1%	4.2%	0.014	10.9 (1.3-93.9)
DRB1*01:01	25.0%	0%	0.011	-
DQB1*05:01	35.7%	4.2%	0.005	12.8 (1.5-109.3)
HLA alleles with significantly lower frequencies in Group I vs Group II				
DRB1*11	28.6%	66.7%	0.011	0.2 (1.5-16.3)
DRB1*11:01	7.1%	33.3%	0.031	0.15 (1.1-34.5)
DQB1*03	42.9%	83.3%	0.004	0.15 (1.8-24.7)
DQB1*03:01	35.7%	70.8%	0.014	0.22 (1.4-14.1)

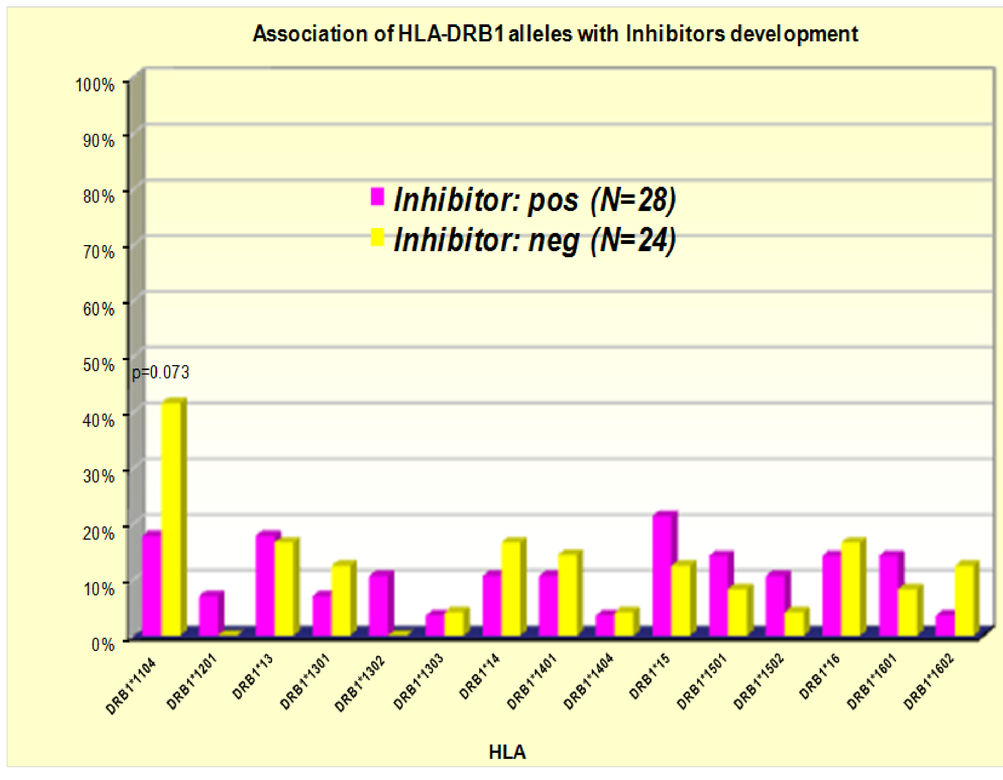
Table 1

The differences between the two groups regarding the polymorphisms of cytokines were not statistically significant in all but in homozygosity of the haplotypes ACC and ATA for IL-10 -1082G>A, -819C>T and -592C>A polymorphisms where a higher prevalence for Inh development was detected (p=0.05, OR=4.7). No statistically increased intron-22 inversion frequencies were found in Group I as compared to Group II: 15/28 (53.5%) vs 9/24 (37.5%) respectively.









CONCLUSION

The findings of this study demonstrate very high frequencies of -DRB1*01,-DRB1*01:01,-DQB1*05:01 and of the haplotype DRB1*01/DQB1*05:01 which are possibly predisposing factors for Inh development. On the other hand, the very low frequencies of DRB1*11, -DQB1*03:01 and the haplotype DRB1*11/DQB1*03:01 indicate that these factors could be protective for Inh formation in Greek HA patients. Regarding cytokines polymorphisms, a significant association with Inh formation was only shown with the haplotypes ACC/ACC and ATA/ATA of IL-10. Intron-22 inversion did not present correlation with FVIII Inh development. Therefore, significant evidence for the role of HLA molecules in Inh formation in the Greek population is provided..

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