The Association of Factor VIII Genotypes and HLA *DRB1*15*, Tumor Necrosis Factor *-308A* and Interleukin -10-*1082G* Alleles on Inhibitor Development in Thai Patients with Hemophilia A

P-T-039

Ampaiwan Chuansumrit, M.D.[1], Werasak Sasanakul, B.Sc[1], Nongnuch Sirachainan, M.D.[1], Pakawan Wongwerawattanakoon, B.Sc.[2], Praguywan Kadegasem, B.Sc,[1] Oytip Nathalang, Ph.D.[3]

Department of [1]Pediatrics, [2]Nursing, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, [3]Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Pathumtani, Thailand

Medical topics: Inhibitors, Pathogenesis, Prevention and Treatment

INTRODUCTION

Factor VIII gene defect has a major influence on the inhibitor formation. The human leucocyte antigen (HLA) class II molecules play an essential role in presenting factor VIII peptides to CD4-positive T-helper cells. In addition, different polymorphisms in tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) were found to contribute to the inhibitor formation.

OBJECTIVE

The study aimed to investigate the association of factor VIII genotypes and HLA *DRB1*15,* tumor necrosis factor α (TNF-α) *-308A* and interleukin-10 (IL-10) *-1082G* alleles on inhibitor development in Thai patients with hemophilia A.

SUBJECTS AND METHODS

57 patients with hemophilia A (severe = 42, moderate = 15) and 50 normal controls were enrolled in the study. The patients' mean age was 14.4±8.9 years. Factor VIII gene defects were identified in patients with hemophilia A and the distribution of HLA *DRB1*15,* TNF-α *-308A* and IL-10-*1082G* alleles were determined. The association of the factor VIII genotypes and these alleles between patients with and without inhibitor was investigated.

RESULTS

The patients were divided into 2 groups: 26 patients without inhibitor and 31 patients a high inhibitor ≥5 Bethesda units (BU) (n = 22) and low inhibitor (n = 9). The factor VIII gene defect was identified in 41 patients while the remaining patients were on the ongoing process. The factor VIII gene mutations included intron 22 inversion (25 distal type, 3 proximal type), large gene deletion (n = 3), point mutations inducing stop codon (n = 7), amino acid alteration (n = 2) and frameshift mutation (n = 1) as shown in Table 1. Twenty-four out of 38 patients (63.2%) with severe gene defects of inversion, deletion and nonsense mutations exhibited inhibitor while neither three patients with missense mutations had inhibitor.

The frequencies of HLA-*DRB1*15* in hemophilia patients with and without inhibitor (25.4%), and patients with inhibitor (30.6%) were significantly higher than normal control (13.0%) (p = 0.025 and 0.008) whereas patients with inhibitor had a higher frequency than those without inhibitor (19.2%) but no statistical difference (p = 0.198).

However, the frequencies of TNF-α *-308A* alleles among patients with inhibitor (1.6%), without inhibitor (5.8%) and normal control (8.0%) were not statistically different. Similar findings were found in the frequency of IL-10-*1082G*: patients with inhibitor (3.2%), without inhibitor (7.7%) and normal controls (2.0%).

Table 1. Factor VIII mutations in Thai hemophilia A patients

Patients	Nucleotide changed	Amino acid changed
1	5953 C>T	R1966X
2	6380delA	D2108V fsX15
3	5856_7ins TA	M1934X
4	1681G>A	D542N
5	2615C>A	S855X
6	680G>A	W208X
7	6266G>A	W2070X
8	1820_21CAdel	T588fs
9	1644insT	L529L fsX6
10	1462G>C	A469P

DISCUSSION

The major molecular defects associated with the factor VIII gene of deletion, inversion and point mutations causing stop codon in the present study were observed in more of the patients with inhibitor, as previously reported.

The HLA-*DRB1*15* allele is known to exhibit the specific surface loop peptide comprising amino acids 1706-1724 of the factor VIII light chain, and is considered to be involved in the factor VIII inhibitor formation in severe hemophilia A patients who lack of endogenous factor VIII protein synthesis. Even though HLA-*DRB1*15* (17.5%), *DRB1*12* (16.9%) and *DRB1*09* (11.5%) are the most common alleles among Thai blood donors, the frequency of the *DRB1*15* allele among hemophilia with inhibitors in the present study was significantly higher than in the normal controls.

However, the frequencies of the *-308A* polymorphism in the TNF-α and *-1082G* in the IL-10 in the Thai hemophilia A with inhibitor were not higher than those without inhibitor and normal controls, as previously reported from western countries. Further study was warranted.

CONCLUSION

Factor VIII genotypes and HLA *-DRB1*15* showed the contribution to the inhibitor development among Thai hemophilia A patients while TNF-α *-308A* and IL-10-*1082G* alleles were of less importance.