

# HLA alleles, especially amino-acid signatures of HLA-DPB1 might contribute to the molecular pathogenesis of early-onset AITD.

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**Background:** Major histocompatibility complex region have been suggested to play a solid role in the development of AITD. In this study, we investigate the association of human leukocyte antigen (HLA) alleles and amino acids variants of HLA with early onset autoimmune thyroid disease (AITD).

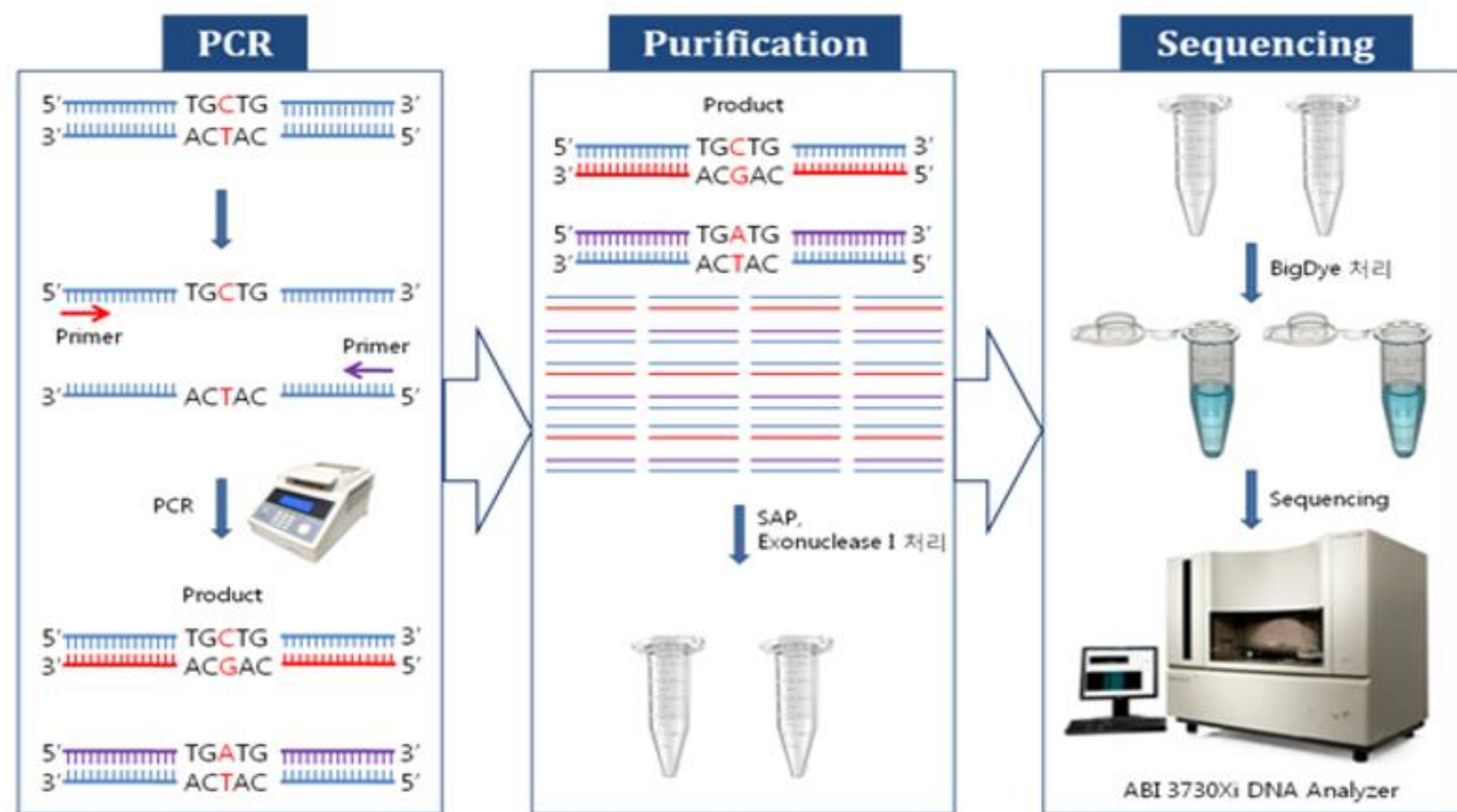
**Subjects:**

**Normal control group:** 142 healthy Koreans

**AITD patients group:** 102 Korean children [40 HD and 62 GD]

The study was approved by catholic university IRB, with written informed consent from all samples.

**Methods :**



## RESULTS

**Table 1. Characteristic of 102 AITD patients**

Characteristic	
Sex (F/M)	83/19
Age (years) at diagnosis	11.3 ± 3.2
Age (years) at enrollment	13.7 ± 3.5
HD/GD	40 / 62
HD condition at diagnosis	
Euthyroid state	9(22.5%)
Subclinical hypothyroid state	14(35%)
Overt hypothyroid state	12(30%)
Hyperthyroid state	5(12.5%)
Class of TAO	
0~1 No sign~ only sign	70
2 soft tissue involvement	7
3 Proptosis	21
4 Extraocular muscle involvement	3
5 Corneal involvement	1
6 Sight loss	0

AITD, autoimmune thyroid diseases; HD, Hashimoto's disease; GD, Graves' disease; TAO=32, thyroid associated ophthalmopathy

**Table 2. Frequencies of HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 alleles significantly associated with GD or HD in Korean children with AITD (P < 0.01)**

Locus	alleles	Controls n=142 (%)	AITD n=102 (%)	GD n=62 (%)	Controls vs GD p-value OR	HD n=40 (%)	Controls vs HD p-value OR	GD vs HD p-value
A	02:07	8 (5.6)	21 (20.6)	11 (17.7)	0.006 3.6	10 (25.0) <sup>a</sup>	0.0003 5.6	
B	46:01	16 (11.3)	31 (30.4)	21 (33.9) <sup>b</sup>	0.0001 4.0	10 (25.0)		
B	15:02	0 (0.0)	4 (3.9)	1 (1.6)		3 (7.5)	0.009 15.1	
B	44:03	19 (13.4)	2 (2.0)	1 (1.6)	0.005 0.1	1 (2.5)		
C	01:02	48 (33.8)	54 (52.9)	34 (54.8)	0.005 2.4	20 (50.0)		
C	06:02	18 (12.7)	1 (1.0)	0 (0.0)	0.004 0.1	1 (2.5)		
DRB1	08:03	20 (14.1)	31 (30.4)	19 (30.6)	0.006 2.7	12 (30.0)		
DRB1	14:03	2 (1.4)	6 (5.9)	6 (9.7)	0.0095 7.5	0 (0.0)		
DRB1	07:01	19 (13.4)	2 (2.0)	1 (1.6)	0.005 0.1	1 (2.5)		
DRB1	13:02	23 (16.2)	4 (3.9)	2 (3.2)	0.005 0.2	2 (5.0)		
DRB1	15:01	21 (14.8)	11 (10.8)	11 (17.7)		0 (0.0)		0.009
DQB1	02:02	17 (12.0)	1 (1.0)	1 (1.6)	0.009 0.1	0 (0.0)		
DQB1	06:04	16 (11.3)	0 (0.0)	0 (0.0)	0.009 0.1	0 (0.0)		
DQB1	05:01	26 (18.3)	5 (4.9)	4 (6.5)		1 (2.5)	0.006 0.1	
DQB1	06:02	21 (14.8)	11 (10.8)	11 (17.7)		0 (0.0)		0.009
DPB1	02:02	8 (5.6)	25 (24.5)	13 (21.0) <sup>c</sup>	0.0009 4.4	12 (30.0) <sup>d</sup>	0.00001 7.2	
DPB1	05:01	88 (62.0)	74 (72.5)	54 (87.1) <sup>e,f</sup>	0.0003 4.1	20 (50.0)		0.00004
DPB1	04:01	22 (15.5)	7 (6.9)	1 (1.6) <sup>g</sup>	0.002 0.1	6 (15.0)		

AITD, autoimmune diseases; GD, Graves' disease; HD, Hashimoto's disease; OR, Odds ratio.  
 Control vs. GD : <sup>a</sup> P< 0.004; <sup>b</sup> P< 0.013; <sup>c</sup> P< 0.005; <sup>d</sup> P< 0.005; <sup>e</sup> P< 0.005; <sup>f</sup> P< 0.022.  
 Control vs. HD : <sup>a</sup> P< 0.005; <sup>d</sup> P< 0.0002.  
 GD vs. HD : <sup>f</sup> P< 0.0006

### CONCLUSION-I

Our results suggests that HLA alleles, especially amino-acid signatures of HLA-DP β-chain might contribute to the molecular pathogenesis of early-onset AITD.

**Table 3. Amino acid variants of HLA-DRB1, -DQB1 and -DPB1 showing higher significant associations with GD or with HD compared to those of HLA genotype in Korean children (P < 0.001).**

Locus	No.	Variant	Controls n=142 (%)	AITD n=102 (%)	GD n=62 (%)	p-value	OR	Controls vs GD	HD	Controls vs HD	GD vs HD
DRB1	57	Ser	36 (25.4)	50 (49.0)	32 (51.6)	0.0003	3.1	18 (45.0)			
DRB1	74	Leu	30 (21.1)	43 (42.2)	28 (45.2)	0.0005	3.1	15 (37.5)			
DQB1	57	Asp	113 (79.6)	100 (98.0)	61 (98.4)	0.0005	15.7	39 (97.5)			
DPB1	35	Leu	95 (66.9)	89 (87.3)	61 (98.4)	0.000001	30.2	28 (70.0)			0.00003
DPB1	55	Glu	95 (66.9)	89 (87.3)	61 (98.4)	0.000001	30.2	28 (70.0)			0.00003
DPB1	56	Ala	112 (78.9)	93 (91.2)	61 (98.4)	0.0004	16.3	32 (80.0)			

AITD, autoimmune diseases; GD, Graves' disease; HD, Hashimoto's disease; OR, Odds ratio.

**Table 4. Frequencies of HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 haplotypes significantly associated with GD or with HD in Korean children with AITD (P < 0.05).**

Haplotypes	Controls n=142(%)	AITD n=102(%)	GD n=62(%)	Controls vs GD p-value OR	HD n=40(%)	Controls vs HD p-value OR	GD vs HD p-value
<b>Class I (A, B, C)</b>							
02:07-46:01-01:02	7 (4.9)	17 (16.7)	10 (16.1)	0.008 3.7	7 (17.5)	0.008 4.1	
02:06-46:01-01:02	3 (2.1)	10 (9.8)	8 (12.9)	0.002 6.9	2 (5.0)		
24:02-46:01-01:02	3 (2.1)	10 (9.8)	7 (11.3)	0.005 5.9	3 (7.5)		
24:02-15:02-08:01	0 (0.0)	3 (2.9)	0 (0.0)		3 (7.5)	0.009 15.1	
<b>Class II (DRB1, DQB1, DPB1)</b>							
08:03-06:01-02:02	1 (0.7)	15 (14.7)	11 (17.7)	0.000002 30.4	4 (10.0)	0.001 15.7	
08:03-06:01-05:01	14 (9.9)	17 (16.7)	13 (21.0)	0.031 2.4	4 (10.0)		
08:03-04:01-05:01	0 (0.0)	5 (4.9)	2 (3.2)		3 (7.5)	0.009 15.1	
08:03-06:01-02:01	5 (3.5)	10 (9.8)	4 (6.5)		6 (15.0)	0.007 4.8	
09:01-03:03-02:02	3 (2.1)	6 (5.9)	2 (3.2)		4 (10.0)	0.022 5.1	
11:01-03:01-02:02	2 (1.4)	5 (4.9)	2 (3.2)		3 (7.5)	0.037 5.7	
15:01-06:02-05:01	12 (8.5)	11 (10.8)	11 (17.7)		0 (0.0)		0.009
<b>Class I and II (A, B, C, DRB1, DQB1, DPB1)</b>							
02:07-46:01-01:02-08:03-06:01-05:01	4 (2.8)	7 (6.9)	6 (9.7)	0.037 3.7	1 (2.5)		
02:07-46:01-01:02-09:01-03:03-05:01	0 (0.0)	4 (3.9)	1 (1.6)		3 (7.5)	0.009 15.1	

AITD, autoimmune diseases; GD, Graves' disease; HD, Hashimoto's disease; OR, Odds ratio.

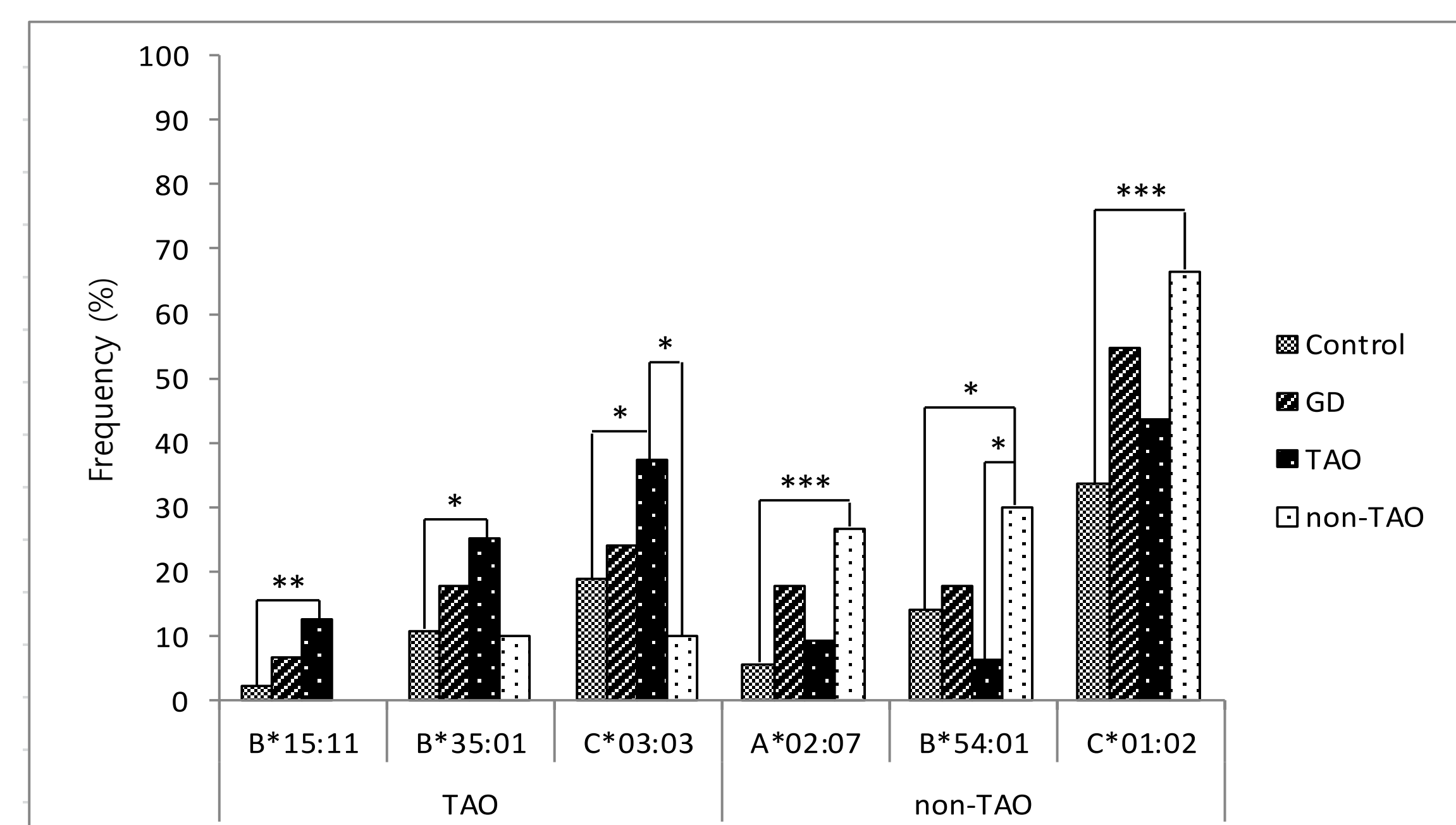


Figure 1. Distribution of HLA alleles showing differences between TAO and non-TAO (P < 0.05). HLA-C\*03:03 (TAO vs. non-TAO; 6.3% vs. 30.0%, P = 0.012) showed higher frequency in TAO than non-TAO, whereas HLA-B\*54:01 (TAO vs. non-TAO; 37.5% vs. 10.0%, P = 0.014) showed higher frequency in non-TAO than TAO. \* P < 0.05; \*\* P < 0.01; \*\*\* P < 0.001.



Figure 2. Three-dimensional ribbon models of the HLA-DPB1 proteins associated with Graves' disease risk. The protein structures of HLA-DPB1 is based on Protein Data Bank (PDB) (<https://www.rcsb.org/>) entries 3LQZ, which were prepared using UCSF (University of California, San Francisco) Chimera version 1.7. Residues at the Graves' disease risk-associated amino acid positions are highlighted as colored spheres.

### CONCLUSION-II

Especially, HLA-DPB1\*02:02 and -DPB1\*05:01, may play a pivotal role in the molecular pathogenesis of early-onset on AITD.