P-118

The Polymorphisms Study between HLA-DQB Genes and Ankylosing Spondylitis in Korean Population

Eo Jin Park M.D.[1], Jong Ha Lee M.D[2], Min Kyun Sohn M.D.[2], Seung Don Yoo M.D.[1], Dong Hwan Yun M.D.[2], Dong Hwan Kim M.D.[1], Jinmann Chon M.D.[2], Seung Ah Lee M.D.[1], Sung Joon Chung M.D.[1], Yun Soo Soh M.D.[2], Myung Chul Yoo M.D.[2], Ga Yang Shim MD.[2], Min Gyun Kim M.D.[1]

Department of Physical Medicine and Rehabilitation, College of Medicine, Kyung Hee University at Gangdong

Department of Physical Medicine and Rehabilitation, College of Medicine, Kyung Hee University

BACKGROUND

Ankylosing spondylitis (AS) is a chronic immune mediated inflammatory disease. It is considered an inherited disease, as over 90% of the risk of its development relies on genes. More than 100 genetic variants associated with AS account for no more than 30% of the heritability. Despite being associated with several environmental and genetic factors, the genetics and pathogenesis are poorly understood. In particular, there are several studies on the association between human leukocyte antigen (HLA)-DQB and AS, but studies on HLA-DQB polymorphism are lacking.

OBJECTIVE

This study investigated whether polymorphisms in the HLA-DQB1 and 2 genes contribute to the development of ankylosing spondylitis.

METHOD

Ninety-six patients with ankylosing spondylitis and 330 healthy controls were enrolled in this study. Four single nucleotide polymorphisms (SNPs) (rs1049225, rs1140320, rs1049072, and rs9274579) in HLA-DQB1 and six SNPs (rs7756516, rs3213485, rs2301271, rs34988824, rs1573649, and rs1573646) in HLA-DQB2 were selected and analyzed. The frequencies of genotypes and alleles of the phenotypes were evaluated.

RESULTS

Three of the four SNPs, rs1049225, rs1140320, and rs9274579 in HLA-DQB1 and all six SNPs, rs7756516, rs3213485, rs1573649, s1573646, rs2301271 and rs34988824 in HLA-DQB2, were significantly associated with AS. Analysis of haplotypes revealed that the TAT, TGT, TGC, GAGAG, GGGAG, and AAGAA haplotypes in HLA-DQB1, and the CTAC, TCAGAAGG, and CGCAGGTA haplotypes in HLA-DQB2 were associated with AS.

Table 1. Genotype Analysis of rs1049225, rs1140320, rs9274579 in HLA-DQB1 Gene.

SNPs /Location /Function	Genotype	Control n (%)	AS n (%)	Models	OR (95% CI)	P value
rs1049225	G/G	220 (66.70)	80 (83.30)	Dominant	0.36 (0.20-0.67)	**0.0006**
/3'UTR	A/G	95 (28.80)	16 (16.70)	Recessive	0.00 (0.00-NA)	**0.003**
/Unknown	A/A	15 (4.50)	0 (0.00)	Log-additive	0.47 (0.25-0.86)	**0.0001**
rs1140320	G/G	101 (31.10)	29 (30.20)	Dominant	0.88 (0.51-1.49)	0.63
/CDS	A/G	164 (50.50)	61 (63.50)	Recessive	0.28 (0.11-0.68)	**0.0017**
/Nonsynonymous	A/A	60 (18.50)	6 (6.20)	Log-additive	1.53 (0.93-2.52)	**0.048**
rs9274579	G/G	220 (68.50)	80 (83.30)	Dominant	0.41 (0.22-0.76)	**0.0027**
/Promoter	A/G	95 (29.60)	16 (16.70)	Recessive	0.00 (0.00-NA)	0.12
/Unknown	A/A	6 (1.90)	0 (0.00)	Log-additive	0.44 (0.24-0.81)	**0.0018**

Note: HLA-DQB1, human leukocyte antigen-DQB1; SNP, single nucleotide polymorphism; AS, Ankylosing spondylitis; UTR, untranslated region; OR, odds ratio; CI, confidence interval.

Table 2. Genotype Analysis of rs1049225, rs1140320, rs9274579 in HLA-DQB2 Gene.

SNPs /Location /Function	Genotype	Control n (%)	AS n (%)	Models	OR (95% CI)	P value
rs7756516	T/T	181 (54.9)	65 (67.7)	Dominant	0.50 (0.30-0.83)	**0.0064**
/3'UTR	C/T	124 (37.6)	29 (30.2)	Recessive	0.24 (0.06-1.09)	**0.029**
/Unknown	C/C	25 (7.6)	2 (2.1)	Log-additive	0.63 (0.37-1.05)	**0.0022**
rs3213485	C/C	183 (55.50)	65 (67.70)	Dominant	0.51 (0.31-0.85)	**0.0089**
/Intron	C/T	122 (37.00)	29 (30.20)	Recessive	0.24 (0.06-1.09)	**0.029**
/Unknown	T/T	25 (7.60)	2 (2.10)	Log-additive	0.64 (0.38-1.08)	**0.003**
rs1573649	A/A	142 (43.20)	55 (57.30)	Dominant	0.53 (0.32-0.86)	**0.01**
/5'UTR	A/G	145 (44.10)	36 (37.50)	Recessive	0.38 (0.14-1.01)	**0.035**
/Unknown	G/G	42 (12.80)	5 (5.20)	Log-additive	0.57 (0.38-0.84)	**0.0036**
rs1573646	G/G	142 (43.20)	55 (57.30)	Dominant	0.53 (0.32-0.86)	**0.01**
/Promoter	G/T	146 (44.40)	36 (37.50)	Recessive	0.40 (0.15-1.07)	**0.048**
/Unknown	T/T	41 (12.50)	5 (5.20)	Log-additive	0.69 (0.42-1.14)	**0.0044**
rs2301271	G/G	196 (59.40)	66 (68.80)	Dominant	0.56 (0.33-0.93)	**0.024**
/Intron	A/G	113 (34.20)	28 (29.20)	Recessive	0.33 (0.07-1.49)	0.10
/Unknown	A/A	21 (6.40)	2 (2.10)	Log-additive	0.65 (0.39-1.10)	**0.013**
rs34988824	C/C	246(74.80)	68 (70.80)	Dominant	1.34 (0.78-2.30)	0.30
/Intron	C/G	79 (24.00)	21 (21.90)	Recessive	10.31 (2.51-42.33)	**0.0008**
/Unknown	G/G	4 (1.20)	7 (7.30)	Log-additive	0.92 (0.51-1.64)	**0.045**

Note: HLA-DQB2, human leukocyte antigen-DQB2; SNP, single nucleotide polymorphism; AS, Ankylosing spondylitis; UTR, untranslated region; OR, odds ratio; CI, confidence interval.

Table 3. Haplotype Analysis of HLA-DQB1 Polymorphisms in Control Subjects and Patients with AS

Haplotype	Frequency	Control		AS		Chi square	P value
		+	-	+	-		
GGT	0.563	369	291	111	81	0.219	0.6398
TAT	0.165	125	535	16	176	12.114	**0.0005**
TGT	0.144	74	586	49	143	24.653	**<0.001**
TGC	0.127	92	568	16	176	4.223	**0.0399**
GAACG	0.323	220	439	55	137	1.509	0.2193
GAGCG	0.240	148	511	56	136	3.562	0.0591
GAGAG	0.188	104	511	55	137	15.887	**<0.001**
GGGAG	0.093	69	591	10	182	4.866	**0.0274**
AAGAA	0.081	63	597	6	186	8.238	**0.0041**
GAGAA	0.075	54	605	10	182	1.918	0.1661

Note: HLA-DQB1, human leukocyte antigen-DQB1; AS, Ankylosing spondylitis; Haplotypes comprised of rs1063355, rs1049225, rs28688207, rs1110314, rs12722107, rs1049072, rs9274552, and rs9274579 in HLA-DQB1. The bold number indicates a significant association.

Table 4. Haplotype Analysis of HLA-DQB2 Polymorphisms in Control Subjects and Patients with AS

Haplotype	Frequency	Control		AS		Chi square	P value
		+	-	+	-		
TCGC	0.615	399	260	124	68	1.022	0.3121
CTAC	0.219	155	505	32	160	4.036	**0.0445**
TCGG	0.142	86	573	35	157	3.219	0.0728
CTGC	0.020	16	644	1	191	2.756	0.0969
TCAGAAGG	0.676	430	230	146	46	8.054	**0.0045**
CGCAGGTA	0.198	141	519	28	164	4.300	**0.0381**
TCAGAGTA	0.083	58	602	13	179	0.792	0.3735
TCAGAGTG	0.042	31	629	5	187	1.610	0.2045

Note: HLA-DQB2, human leukocyte antigen-DQB2; AS, Ankylosing spondylitis; Haplotypes comprised of rs7756516, rs7774954, rs3213485, rs2301271, rs34988824, Affx-28505362, rs762815, rs7768538, rs7453920, rs2051549, and rs1573649 in HLA-DQB2. The bold number indicates a significant association.

CONCLUSION

The results of this study suggest that HLA-DQB1 and HLA-DQB2 polymorphisms are associated with the development of AS.