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Original Article

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Associations of *COL2A1* Gene Polymorphisms and Ankylosing Spondylitis in the Korean Population

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Study Design: Case-control comparison study.
Objectives: The aim of this study was to investigate whether single nucleotide polymorphisms (SNPs) of *COL2A1* affect the development of ankylosing spondylitis (AS).
Summary of Literature Review: Many factors have been reported to be involved in the etiology of AS. Human leukocyte antigen (HLA)-B27 has been established as a genetic factor involved in the development of AS; however, it has been reported in recent studies that various genetic polymorphisms may be related to the development of AS. The collagen, type II, alpha 1 gene (*COL2A1*) plays a role in cartilage formation and maintaining the vitreous humor in the eye. Several previous studies have investigated the associations of *COL2A1* with spinal degenerative diseases, but no case-control comparative study has yet investigated the effect of *COL2A1* variants on the development of AS.
Materials and Methods: The study was planned with 96 AS patients in the study group and 330 healthy individuals in the control group. We searched the gene region of the COL2A1 gene in the NCBI SNP database (http://www.ncbi.nlm.nih.gov/snp), and 3 SNPs (rs3803183, rs2070739 and rs1793949) were found using sequencing to be significantly different between the AS and control groups. Multiple logistic regression models for genetic analysis were applied
Results: Three SNPs (rs3803183, rs2070739 and rs1793949) of *COL2A1* showed significant associations with AS patients compared to control subjects ($p<0.05$).
Conclusions: SNPs of *COL2A1* may be associated with the development of AS in the Korean population.

Key words: Ankylosing spondylitis, Collagen type II alpha 1 gene, Single nucleotide polymorphisms, AS in the Korean population

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease and an autoimmune disease. In AS, it has been considered that immune-mediated inflammation is major pathophysiologic process in the inflammation of spinal and axial joint enthesis.

There have been previous study results strongly suggest that AS has a strong genetic component. First, human leukocyte antigen (HLA)-B27 subtypes have been implicated in many studies.[1] HLA-B27 is mostly positive in AS and related spondyloarthropathies, however, 10% of AS patients do not have the genotypes and only 10% of the carriers develop the disease.[2]

The collagen, type II, alpha 1 gene (COL2A1) is located on chromosome 12q13.11.[3] Type II collagen is a homotrimer consisted of three identical alpha chains. The triple helical domain of the α-chains contains a repeating triplet sequence (Gly-X-Y) with glycine occupying every third position in the

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protein sequence allowing the formation of the triple helix.[4] COL2A1 is a responsible gene for type II collagen, and it is major constituent of joint and enthesis.[5] Additionally, citrullinated type II collagen is associated with inflammatory degradation of collagen, and autoantibodies to them are specifically produced and deposited in the inflamed articular synovium as immune complex, in rheumatoid arthritis patients.[6]

Such results may give light to the reason that polymorphisms in the collagen genes may affect susceptibility to the inflammatory arthritis. However, there was no previous study of COL2A1, which is a major collagen in joint and cartilage, in the aspect of development or clinical features of AS. The purpose of this study was to investigate the association between COL2A1 polymorphisms and AS in Korean populations.

Materials and Methods

1. Study Population

A total of ninety six Korean AS patients were participated in this study. The diagnosis of AS was done according to patient history and radiographic workups. They were 85 male (mean age, 43.6±11.3) and 11 female (mean age, 51.5±15.6) patients. We used Modified New York criteria for diagnosis of AS. All patients with AS showed thoracolumbar and lumbosacral spinal fusions with kyphotic deformities. 90 cases (93.8%) were performed corrective surgeries of the spine. Age-matched three-hundred thirty healthy individuals were participated as a control group. They were consisted of 165 male (mean age, 47.3±10.5) and 165 female (mean age, 46.7±10.1), and confirmed that they have no spinal diseases, glucose intolerance, diabetes, obesity, or any severe disorders (Table 1). Informed consents were obtained from all subjects in both groups. We received an approval for this study from the Ethics Committee of the Medical Research Institute.

Table 1. General characteristics of study participants.

	n	Mean age	SD
Controls			
Male	165	47.3	10.5
Female	165	46.7	10.1
AS			
Male	85	43.6	11.3
Female	11	51.5	15.6

AS: ankylosing spondylitis, SD: standard deviation.

2. Single nucleotide polymorphism (SNP) selection and genotyping

For the selection among COL2A1 gene SNPs, we searched for SNPs on exon of the COL2A1 gene in the SNP database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP, BUILD 138) and SNPs investigated in previous study. SNPs with <10% minor allele frequency (MAF), <0.1 heterozygosity, unknown heterozygosity, and unknown genotype frequencies in Asian populations were excluded. Among the exonic SNPs of the COL2A1 gene, we had finally selected two exonic SNPs (rs3803183, Thr9Ser and rs2070739, Gly1405Ser) and one SNP (rs1793949, intron).

Peripheral blood samples from each subject were collected in Ethylenediaminetetraacetic acid (EDTA)-coated tubes and stored in a −20°C freezer. Genomic DNA was prepared from peripheral blood using a genomic DNA isolation reagent kit (High Pure PCR template preparation kit; Roche, City, State, USA) and SNP genotyping was determined by direct sequencing. Polymerase chain reactions (PCRs) were performed using the primers for two exonic SNPs (rs3803183, sense primer: 5'-GGGAGAAGACGCAGAGCGCTGCT-3', anti-sense primer: 5'-AAC TCTTCTTGGTGAACTTCTG-3'; rs2070739, sense primer: 5'- TGCTGCCCCAGTACCCTT-GAG-3', anti-sense primer: 5'- CTGACAGCTGCCGC-GGGCCAAC-3'; rs1793949, sense primer: 5'- TCCCAGT-CAGGGCCCTGGAGAA-3', anti-sense primer: 5'-TTCTCCAGGGCCCTGACTGGGA-3'). The PCR products were sequenced using an ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, CA, USA). Sequencing data were analyzed using SeqMan II software (DNASTAR, Madison, WI, USA).

3. Statistical analysis

The multiple logistic regression models for genetic analysis (codominant1, major allele homozygotes vs. heterozygotes; codominant2, major allele homozygotes vs. minor allele homozygotes; dominant, major allele homozygotes vs. heterozygotes and minor allele homozygotes; recessive, major allele homozygotes and heterozygotes vs. minor allele homozygotes;

Table 2. The Hardy-Weinberg equilibrium (HWE) of genotype of COL2A1 SNPs in control subjects and ankylosing spondylitis (AS) patients.

SNPs	All subjects	Control	AS
rs3803183	0.54	1.00	0.30
Thr9Ser			
rs2070739	0.20	0.91	0.06
Gly1405Ser			
rs1793949	0.48	0.22	0.63
Intron			

and log-additive, major allele homozygotes vs. heterozygotes vs. minor allele homozygotes) were applied to obtain estimated odd ratios (ORs), 95% confidence intervals (CIs), and corresponding P values with age and gender were controlled for covariables.[7] Hardy-Weinberg equilibrium for all SNPs was assessed with SNPStats. Genotype distributions of three SNPs in this study were in Hardy-Weinberg equilibrium in control subjects (rs3803183, Thr9Ser, p=1.00; rs2070739, Gly1405Ser, p=0.91; rs1793949, intron, p=0.22) (Table 2). The haplotype estimation and linkage disequilibrium (LD) block calculation of tested SNPs were done with the Haploview 4.2 software.[8] In the statistical tests, the significance level was set at the p-value <0.05.

Results

The SNP rs3803183 of COL2A1 showed significant differences between AS patients and control subjects [codominant model 2 (A/A versus T/T), OR=2.03, 95% CI=1.02-4.02, p=0.044]. Also, SNP rs2070739 showed significant association between AS patients and control subjects [codominant model 2 (G/G versus A/A), OR=2.83, 95% CI=1.47-5.46, p=0.002; recessive model (G/G versus G/A and A/A), OR=2.50, 95% CI=1.46-4.28, p=0.001; log-additive model (G/G versus G/A versus A/A), OR=1.70, 95% CI=1.21-2.37, p=0.0017, respectively] (Table 3). In allele distribution analysis, allele of rs2070739 was associated with AS (OR=1.76, 95% CI=1.27-2.43, p= 0.001) (Table 3).

And SNP rs1793949 showed significant association between AS patients and control subjects [codominant model 1 (C/C versus C/T), OR=0.48, 95% CI=0.28-0.81, p=0.006; codominant model 2 (C/C versus T/T), OR=0.31, 95% CI=0.14-0.71, p=0.006; dominant model (C/C and C/T versus T/T), OR=0.43, 95% CI=0.26-0.71, p=0.0009; recessive model (C/C versus C/T and T/T), OR=0.46, 95% CI=0.21-1.00, p=0.039; log-additive model (C/C versus C/T versus T/T), OR=0.53, 95% CI=0.36-0.77, p=0.0006, respectively]. In allele distribution analysis, allele of rs1793949 was associated with AS (OR=0.54, 95% CI=0.38-0.77, p=0.001) (Table 3).

Table 4 shows the genotype and allele distributions of three SNPs in the subgroup of AS patients who undergone surgical treatment for severe deformities (AS-S), and the control group. The genetic analysis between those AS patients who undergone surgery (AS-S) and control subjects was performed by logistic regression analysis with adjusting age and sex. A SNP rs3803183 was not significantly associated with AS-S patients. However, the other SNPs rs2070739 [codominant model 2 (G/G versus A/A), OR=2.63, 95% CI=1.34-5.15, p=0.0048; recessive model (G/G versus G/A and A/A), OR=2.29, 95% CI=1.31-3.99, p=0.0049; log-additive model (G/G versus G/A versus A/A), OR=1.67, 95% CI=1.20-2.33, p=0.0049; allele distribution, OR=1.67, 95% CI=1.20-2.33, p=0.0024, respectively] (Table 4) and rs1793949 [codominant model 2 (G/G versus A/A), OR=0.49, 95% CI=0.29-0.84, p=0.011; recessive model (G/G versus G/A and A/A), OR=0.45, 95% CI=0.27-0.75, p=0.0021; log-additive model (G/G versus G/A versus A/A), OR=0.55, 95% CI=0.38-0.81, p=0.0017; allele distribution, OR=0.56, 95% CI=0.40-0.81, p=0.0016, respectively] (Table 4) were significantly associated with AS-S. The tendency of significant models and odd ratios of the controls and AS-S were similar to the Table 3.

Three SNPs (rs3803183, Thr9Ser, rs2070739, Gly1405Ser, and rs1793949, intron) of COL2A1 were analyzed for LD and haplotypes using Haploview 4.2. The LD block was composed of rs2070739 and rs1793949 (D'=0.99 and r squared=0.541). There were three haplotypes in LD block (haplotype AC, frequency=0.45; GT, frequency=0.40; GC, frequency=0.15) (Table 5). Distributions of theses haplotypes (AC and GT) in LD block were associated with AS (haplotype AC, chi square=11.27, p=0.0008; haplotype GT, chi square=12.68, p=0.0004) (Table 5).

Table 3. The genotype and allele distribution of COL2A1 SNPs in control subjects and ankylosing spondylitis (AS) patients.

SNP	Genotype/ allele	Control	AS	Models	OR (95% CI)	p
		n (%)	n (%)			
rs3803183	A/A	129 (39.1)	32 (33.3)	Codominant 1	1.19 (0.69-2.05)	0.54
Thr9Ser	A/T	155 (47.0)	42 (43.8)	Codominant 2	2.03 (1.02-4.02)	0.044
	T/T	46 (13.9)	22 (22.9)	Dominant	1.38 (0.83-2.30)	0.21
				Recessive	1.84 (1.00-3.40)	0.05
				Log-additive	1.39 (0.99-1.95)	0.06
	A	413 (62.6)	106 (55.2)		1	
	T	247 (37.4)	86 (44.8)		1.36 (0.98-1.88)	0.07
rs2070739	G/G	110 (33.5)	23 (24.0)	Codominant 1	1.24 (0.68-2.26)	0.49
Gly1405Ser	G/A	159 (48.5)	38 (39.6)	Codominant 2	2.83 (1.47-5.46)	0.002
	A/A	59 (18.0)	35 (36.5)	Dominant	1.69 (0.98-2.94)	0.056
				Recessive	2.50 (1.46-4.28)	0.001
				Log-additive	1.70 (1.21-2.37)	0.0017
	G	379 (57.8)	84 (43.8)		1	
	A	277 (42.2)	108 (56.2)		1.76 (1.27-2.43)	0.001
rs1793949	C/C	100 (30.5)	49 (51.0)	Codominant 1	0.48 (0.28-0.81)	0.006
Intron	C/T	173 (52.7)	38 (39.6)	Codominant 2	0.31 (0.14-0.71)	0.006
	T/T	55 (16.8)	9 (9.4)	Dominant	0.43 (0.26-0.71)	0.0009
				Recessive	0.46 (0.21-1.00)	0.039
				Log-additive	0.53 (0.36-0.77)	0.0006
	C	373 (56.9)	136 (70.8)		1	
	T	283 (43.1)	56 (29.2)		0.54 (0.38-0.77)	0.001

SNP:single nucleotide polymorphisms, OR: odd ratio, CI: confidence interval.

Discussion

AS has long been known to be a highly familial and heritable disease. Previous studies were reported regarding twin study and genetic evidence on AS. These studies were suggested that genetic factor plays an important role for susceptibility to AS. Until now, HLA-B27 is only one of many genes associated with AS.[9] Recently, several studies were reported candidate genes associated with AS, such as Interleukin 1 receptor antagonist (IL-1RN),[10] Endoplasmic reticulum aminopeptidase 1 (ERAP1),[11] and Interleukin 23 (IL-23).[12]

Mutations in COL2A1 cause defects in the protein structure, and it will alter the tensile characteristics of cartilage and the type 2 collagenopathies. They consist of achondrogenesis, several heritable chondrodysplasias, early onset familial osteoarthritis, SED congenita, Langer-Saldinoachondrogenesis, Kniest dysplasia, Stickler syndrome type I, and spondyloepimetaphyseal dysplasia Strudwick type that phenotypically range from severe lethal dwarfism at birth to relatively mild conditions with precocious osteoarthritis and little or no skeletal growth

Table 4. The genotype and allele distribution of COL2A1 SNPs in control subjects and ankylosing spondylitis (AS) patients who undergone surgical treatment.

SNP	Genotype/ allele	Control	AS surgery	Models	OR (95% CI)	p
		n (%)	n (%)			
rs3803183	A/A	129 (39.1)	31 (34.4)	Codominant 1	1.20 (0.69-2.08)	0.52
Thr9Ser	A/T	155 (47.0)	41 (45.6)	Codominant 2	1.72 (0.84-3.52)	0.14
	T/T	46 (13.9)	18 (20.0)	Dominant	1.32 (0.79-2.21)	0.29
				Recessive	1.56 (0.82-2.96)	0.19
				Log-additive	1.29 (0.91-1.83)	0.15
	A	413 (62.6)	103 (57.2)		1	
	T	247 (37.4)	77 (42.8)		1.25 (0.89-1.75)	0.19
rs2070739	C/C	110 (33.5)	22 (24.4)	Codominant 1	1.26 (0.68-2.32)	0.46
Gly1405Ser	C/T	159 (48.5)	37 (41.1)	Codominant 2	2.63 (1.34-5.15)	0.0048
	T/T	59 (18.0)	31 (34.4)	Dominant	1.65 (0.94-2.90)	0.07
				Recessive	2.29 (1.31-3.99)	0.0039
				Log-additive	1.63 (1.15-2.29)	0.0049
	C	379 (57.8)	81 (45.0)		1	
	T	277 (42.2)	99 (55.0)		1.67 (1.20-2.33)	0.0024
rs1793949	A/A	100 (30.5)	45 (50.0)	Codominant 1	0.49 (0.29-0.84)	0.011
Intron	A/G	173 (52.7)	36 (40.0)	Codominant 2	0.34 (0.15-0.78)	0.38
	G/G	55 (16.8)	9 (10.0)	Dominant	0.45 (0.27-0.75)	0.0021
				Recessive	0.49 (0.23-1.08)	0.06
				Log-additive	0.55 (0.38-0.81)	0.0017
	A	373 (56.9)	126 (70.0)		1	
	G	283 (43.1)	54 (30.0)		0.56 (0.40-0.81)	0.0016

SNP: single nucleotide polymorphisms, OR: odd ratio, CI:confidence interval.

Table 5. Haplotype association between COL2A1 SNPs in linkage disequilibrium (LD) blocks and ankylosing spondylitis (AS)

Haplotype	Frequency	AS		Control		Chi Square	p
		+	-	+	-		
AC	0.45	106.9	85.1	277.2	382.8	11.27	0.0008
GT	0.40	54.9	137.1	283.2	376.8	12.68	0.0004
GC	0.15	29.1	162.9	98.3	561.7	0.01	0.94

abnormality.[13] In addition, defects in processing chondrocalcin, a calcium binding protein that is the C-propeptide of this collagen molecule, are also associated with chondrodysplasia.

There was only few study reported association between AS and COL2A1. In recent studies, there were several studies between COL2A1 polymorphisms and specific diseases. Metlapally et al.[14] investigated association between COL1A1 and COL2A1 genes and myopia susceptibility. And Xu et al.[15] studied relationships between two COL2A1 polymorphisms (T2088C and G4006A) and osteoarthritis (OA) in Han Chinese women. They suggested that the AA genotype, A allele and T-A may increase the risk of OA in the Han Chinese women while T-G may protect these women from OA.[15] There are a hereditary arthro-ophthalmopathies associated with retinal detachment, named Stickler syndromes.[16] Most of the COL2A1 missense mutations are single-nucleotide substitutions that change codons for the glycine residues to codons for other bulkier amino acids. Many studies reported that COL2A1 is associated with Stickler syndrome,[17,18] especially accompanied with vitreous anomaly.[16,19] Stickler syndromes have similarity in common with AS, because both disease shows that ophthalmopathy may co-exist with spinal arthropathy.[20,21]

In addition, ossification of the posterior longitudinal ligament (OPLL) may be a related disease with AS, as inflamed joints may be more susceptible for pathologic ossifications.[22,23] COL6A1, the collagen, type VI, alpha 1 gene, plays a role in maintaining the integrity of various tissues and which is associated with muscular dystrophies,[24] is also associated with OPLL.[25,26] Moreover, there was a study of the frequency of OPLL with AS patients reported that OPLL may not be significantly associated with AS disease course.[27]

In this study, we evaluated whether two exon SNPs (rs3803183, Thr9Ser and rs2070739, Gly1405Ser) and intron SNP (rs1793949, intron) of COL2A1 gene were associated with AS in Korean population. Our results also showed that COL2A1 polymorphisms were associated with susceptibility of AS. In addition, patients who undergone surgical treatment were analyzed as a clinical factor. In this study, patients who did not undergone surgery were too small numbered, therefore statistical analysis was only done in AS-S versus controls. However, which can support that severely deformed AS patients may be associated with COL2A1 SNPs. Especially, a missense SNP rs2070739 and an intronic SNP rs1793949 are associated with AS in AS-S group when compared to controls (Table 4), and only the two SNPs were associated to the AS development in AC or GT haplotypes (Table 5).

Conclusions

We investigated whether two exon SNPs and intron SNP of COL2A1 are related to AS in Korean population. We found significant associations between AS patients and control subjects. The genotype distributions of exon SNP (rs2070739) and intron SNP (rs1793949) were showed significant differences between AS patients and control subjects. Haplotypes (haplotype TG and haplotype CA) were also associated with AS. These results indicate that COL2A1 gene may be related to the susceptibility of AS in Korean population.

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한국인에서의 *COL2A1* 유전자 다형성과 강직성 척추염의 연관성

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목적: 본 연구의 목적은 COL2A1의 단일 뉴클레오티드 다형성(SNP)이 AS의 발생에 영향을 줄 수 있는지 여부를 조사하는 것이다.
선행 연구문헌의 요약: 강직성 척추염(AS)의 병인에 관여하는 많은 요인들은 밝혀져있다. 인간 백혈구 항원(HLA) -B27은 강직성 척추염의 발생에 관여하는 유전적 인자로 알려져 있지만, 최근의 연구에서 다양한 유전자 다형성이 AS의 발생과 관련 될 수 있다고보고 되었다. 콜라겐, 유형 Ⅱ, 알파 1 유전자(COL2A1)는 연골 형성 및 안구 유리체 유지의 역할을 한다. 척추 퇴행성 질환과 연관한 COL2A1에 대한 많은 연구가 있었지만, AS의 발생에 대한 COL2A1의 유전적 영향에 대한 사례-대조 비교 연구는 없었다.
대상 및 방법: 96명의 강직성 척추염 환자를 연구 군으로 정하고 330명의 건강한 사람을 대조 군으로 정하여 연구를 계획하였다. 우리는 SNP NCBI 데이터베이스(http://www.ncbi.nlm.nih.gov/snp)에서 COL2A1 유전자의 유전자 영역을 검색하였고, 시퀀싱을 이용하여 3개의 SNP(rs3803183, rs2070739, rs1793949) 를 비교 분석 하였다. 유전자 분석을 위해 다중 로지스틱 회귀 분석 모델을 적용하였다.
결과: COL2A1의 3개의 SNP (rs3803183, rs2070739, rs1793949)와 AS의 연관성은 통계적으로 유의 하였다($p < 0.05$).
결론: COL2A1의 SNP가 한국인에서 AS의 발생과 관련 될 수 있음을 시사한다.

색인 단어: 강직성 척추염, 콜라겐 유형 Ⅱ 알파 1 유전자, 단일 뉴클레오티드 다형성, 한국인에서 AS의 발생
약칭 제목: COL2A1 유전자 다형성과 강직성 척추염의 연관성

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