Association of *ADAMTS12* polymorphisms with rheumatoid arthritis

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Abstract. a disintegrin and metalloproteinase (ADAM) with thrombospondin type 1 motif 12 (ADAMTS12) is a degradative enzyme that interacts with the degradable fragments of cartilage oligomeric matrix protein, which is a prominent non-collagenous matrix component in articular cartilage. ADAMTS12 has been observed in the cartilage, synovial fluid and serum of arthritic patients, and may play an important role in the pathogenesis of arthritis. In the present study, we investigated whether genetic polymorphisms of *ADAMTS12* are associated with rheumatoid arthritis (RA). To observe the association between *ADAMTS12* and RA, we genotyped three single nucleotide polymorphisms (SNPs) (rs1364044, intron C/T; rs10461703, intron C/T; rs25754, missense Thr1495Ile) of *ADAMTS12* using a direct sequencing method in 303 RA patients and 495 control subjects. Multiple logistic regression models were performed to analyze the genetic data. SNPStats and SNPAnalyzer Pro programs were used to estimate the odds ratios, 95% confidence intervals and p-values. Bonferroni's correction (p^c) was conducted to obtain a defined result. Of the three SNPs, the genotype frequency of rs10461703 was associated with the development of RA (p^c=0.0024 in the co-dominant model; p^c=0.0009 in the dominant model; p^c=0.0006 in the log-additive model). The allele frequency of rs10461703 also showed a significant difference between RA and controls (p^c<0.0001). The C allele frequency of rs10461703 was lower in the RA group (36.6%) compared to the control group (45.7%), whereas the T allele frequency of rs10461703 in the RA group (63.4%) was higher compared to that in the control group (54.3%). The other two SNPs (rs1364044 and rs25754) were not associated with the development of RA. However, we did not find any association between the three tested SNPs and RA patients according to clinical features, including erythrocyte sedimentation rate, C-reactive protein level, rheumatoid factor (+ and -) and bone erosion (+ and -). Our results suggest that *ADAMTS12* may be a susceptibility gene for RA development.

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Introduction

Several members of the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family are known to have significant functions in arthritis. ADAMTS1, ADAMTS4, ADAMTS5 and ADAMTS8 degrade the cartilage proteoglycan aggrecan, and they play a key role in aggrecan loss in arthritis (1-6). Cartilage oligomeric matrix protein (COMP) is a prominent non-collagenous component of cartilage. It accounts for approximately 1% of the wet weight of articular tissue (7,8). COMP fragments are detected in the cartilage, synovial fluid and serum of osteoarthritis (OA) and rheumatoid arthritis (RA) patients (9). Månsson *et al* suggested that COMP levels may be used to assess the presence and progression of arthritis (10). ADAMTS12 is a new COMP-degrading enzyme that may play an important role in COMP degradation in the initiation and progression of arthritis (11). ADAMTS12 is also expressed at higher levels in tissues of OA and RA patients (11,12). The *ADAMTS12* gene is located on chromosome 5q35 and spans approximately 365 kb. The chromosome 5q region has been suggested to contain susceptibility loci for autoimmune or inflammatory diseases, such as Crohn's disease, asthma and RA (13-18). Despite the potential importance of *ADAMTS12* on RA pathogenesis, there have been no published studies on the relationship between the genetic variants of *ADAMTS12* and RA. Our aim was to investigate whether single nucleotide polymorphisms (SNPs) of *ADAMTS12* are associated with RA in the Korean population.

Materials and methods

Subjects. A case-control study was conducted to determine the genetic association between *ADAMTS12* SNPs and RA. Three hundred and three unrelated patients with RA were enrolled from two rheumatic centers (Soonchunhyang

University Hospital and Kyung Hee University Hospital). Each patient was diagnosed by a rheumatologist according to the ACR 1987 Rheumatoid Arthritis diagnostic criteria (19). Four hundred and ninety-five control subjects were recruited among participants who participated in a general health check-up program. Participants with RA, OA and other severe diseases were excluded. This study was carried out according to the Declaration of Helsinki guidelines, and written informed consent was obtained from each subject. The study was approved by the ethics review committee of the Medical Research Institute, School of Medicine, Kyung Hee University, Seoul, Republic of Korea.

Demographic data were obtained from the patient medical records or by interviews at the time of enrollment. Biochemical data were measured, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF). Patients with bone erosion were classified by radiographic findings.

SNP genotyping. We searched *ADAMTS12* SNPs using the NCBI websites (www.ensembl.org, www.ncbi.nlm.nih.gov/SNP and www.hapmap.org). SNPs with >5% minor allele frequency (MAF), >10% heterozygosity and genotype frequencies in the Asian population were included. Among four exonic *ADAMTS12* SNPs with >5% MAF and >10% heterozygosity, a missense SNP rs16891281 (Ser1591Pro) shows a monomorphic genotype in Asians and a synonymous SNP rs61748199 (Leu499Leu) represents no genotypic data in Asians. Therefore, two missense SNPs (rs3813474, Trp1177Arg; rs25754, Thr1495Ile) were selected. Of the intronic SNPs, two SNPs (rs1364044 and rs10461703) were added using the aggressive tagging option of the Tagger program (www.broad.mit.edu/mpg/tagger). Finally, we assessed four SNPs in this study. DNA was isolated from peripheral blood using the GenEx™ B DNA purification kit (GeneAll Biotechnology, Seoul, Korea). Genomic DNA was amplified by polymerase chain reaction (PCR) using primers for each SNP: rs3813474 (sense, 5'-GGA GGC CTT GTA GCT ACA ACA AC-3' and anti-sense, 5'-GGA AGT TTC AGG TGG TTA CGG TT-3'); rs25754 (sense, 5'-GGA TTG GAG GTG TTC TAC TGG TGT-3' and anti-sense: 5'-TCC ATG TTG GAT GAC ATC AGT GTG-3'); rs1364044 (sense, 5'-TTC CAA ATC CTC CCA TTG TTA CTG CC-3' and anti-sense, 5'-GGA TTG CAA AGG CGA GAT GTG ATG TG-3') and rs10461703 (sense, 5'-TTG GTT TTC CAC CTG GCA TGT GTG TG-3' and anti-sense, 5'-GAG AAT ATG TCC TCA CAG CTT GCC AC-3'). The PCR products were genotyped using the direct sequencing method employing an ABI Prism 3730XL automatic sequencer (PE Applied Biosystems, Foster City, CA, USA). The sequence data was analyzed using SeqManII software (DNAStar Inc., Madison, WI, USA).

Statistical analysis. Hardy-Weinberg equilibrium (HWE) was assessed by SNPStats (http://bioinfo.iconcologia.net/index.php). Haploview version 4.2 was used for the linkage disequilibrium (LD) block (Daly Lab Inc., Cambridge, MA, USA). SNPStats and SNPAnalyzer Pro (Istech Inc., Goyang, Korea) were also used to evaluate the odds ratios (ORs), 95% confidence intervals (CIs) and p-values. Multiple logistic regression analysis adjusted for age and gender as covariables was performed. Bonferroni's correction was applied by multiplying the p-values by the number of SNPs and haplotypes.

Table I. Clinical and demographic features of the RA and control subjects.

	RA (n=303)	Control (n=495)
Age (years, mean ± SD)	49.75±12.96	43.66±13.01
Gender (male/female)	58/245	213/282
Disease duration (years, mean ± SD)	4.66±4.45	
ESR (mm/h, mean ± SD)	41.78±29.67	
CRP (mg/dl, mean ± SD)	2.27±4.86	
Subgroups		
ESR (≥30/<30 mm/h)	184/119	
CRP (≥0.5/<0.5 mg/dl)	210/93	
RF (+/-)	265/38	
Bone erosion (+/-)	142/161	

RA, rheumatoid arthritis; SD, standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor. RA patients with inappropriate clinical data were excluded.

Results

Clinical and demographic features of the study subjects. Table I presents the clinical and demographic features of the RA and control subjects. The mean ages (±SD) of RA patients and control subjects were 49.75 (±12.96) and 43.66 (±13.01) years, respectively. There were 58 male and 245 female (total n=303) RA patients and 213 male and 282 female (total n=495) control subjects. RA patients were classified into clinical subgroups according to ESR levels (>30 and <30 mm/h), CRP levels (>0.5 and <0.5 mg/dl), rheumatoid factor (RF; present and absent) and bone erosion (present and absent). The numbers of RA patients with ESR level >30 and <30 mm/h were 184 (60.7%) and 119 (39.3%), respectively. The patients with a CRP value >0.5 and <0.5 mg/dl were 210 (69.3%) and 93 (30.7%), respectively. The patients with a RF present and absent were 265 (87.5%) and 38 (12.5%), respectively. The patients with a bone erosion present and absent were 142 (46.9%) and 161 (53.1%), respectively.

Genetic association of ADAMTS12 SNPs in RA. The genotype distributions of three SNPs (rs1364044, rs10461703 and rs25754) was within HWE (p>0.05), whereas one SNP (rs3813474) was not (p<0.05; data not shown). Therefore, rs3813474 was excluded in the analysis of genetic data. As a result, the genotypic frequency of rs10461703 was statistically associated with RA in the codominant model [OR=1.70 (2.14), 95% CI 1.21-2.40 (1.36-3.37), p=0.0008, p^c=0.0024], the dominant model (OR=1.82, 95% CI 1.32-2.50, p=0.0003, p^c=0.0009) and the log-additive model (OR=1.51, 95% CI 1.21-1.88, p=0.0002, p^c=0.0006). The allele frequency of rs10461703 was also associated with RA (OR=0.69, 95% CI 0.56-0.85,

Table II. Genotype and allele frequencies of *ADAMTS12* SNPs in RA and control subjects.

SNP	Genotype/ allele	RA		Control		Model	OR	95% CI		p-value	p^c
		Freq.	%	Freq.	%			LCL	UCL		
rs1364044	C/C	98	33.2	187	39.8	Co-dominant 1	0.80	0.57	1.14	0.3900	1.0000
	C/T	141	47.8	204	43.4	Co-dominant 2	0.78	0.50	1.23		
	T/T	56	19.0	79	16.8	Dominant	0.80	0.58	1.11	0.1700	0.5100
						Recessive	0.88	0.59	1.32	0.5400	1.0000
						Over-dominant	0.87	0.64	1.19	0.4000	1.0000
						Log-additive	0.87	0.70	1.08	0.2100	0.6300
	C	337	57.1	578	61.5						
	T	253	42.9	362	38.5		1.20	0.97	1.48	0.0900	0.2700
rs10461703	T/T	122	41.5	145	29.3	Co-dominant 1	1.70	1.21	2.40	0.0008	**0.0024**
	T/C	129	43.9	248	50.1	Co-dominant 2	2.14	1.36	3.37		
	C/C	43	14.6	102	20.6	Dominant	1.82	1.32	2.50	0.0003	**0.0009**
						Recessive	1.57	1.05	2.37	0.0270	0.0800
						Over-dominant	1.32	0.97	1.79	0.0750	0.2300
						Log-additive	1.51	1.21	1.88	0.0002	**0.0006**
	T	373	63.4	538	54.3						
	C	215	36.6	452	45.7		0.69	0.56	0.85	<0.0001	**<0.0001**
rs25754	T/T	171	58.0	272	58.2	Co-dominant 1	1.06	0.76	1.47	0.8600	1.0000
	T/C	106	35.9	166	35.5	Co-dominant 2	0.88	0.46	1.70		
	C/C	18	6.1	29	6.2	Dominant	1.03	0.75	1.41	0.8500	1.0000
		8				Recessive	0.86	0.45	1.64	0.6600	1.0000
						Over-dominant	1.07	0.77	1.48	0.6800	1.0000
						Log-additive	1.00	0.77	1.29	0.9800	1.0000
	T	448	75.9	710	76.0						
	C	142	24.1	224	24.0		1.01	0.79	1.23	0.9700	1.0000

SNP, single nucleotide polymorphism; RA, rheumatoid arthritis; Freq., frequency; OR, odds ratio; CI, confidence intervals; LCL, lower confidence limit; UCL, upper confidence limit; p^c, p-value corrected by the Bonferroni's method. Total numbers of genotypes and alleles in each SNP are different, since the unclear or missing genotype data were excluded.

Table III. Genotype frequencies of *ADAMTS12* SNPs in each population.

SNP	Genotype	Korean	European	Chinese	Japanese	Sub-Saharan African
rs1364044	C/C	0.398	0.517	0.489	0.386	0.400
	C/T	0.434	0.383	0.422	0.455	0.500
	T/T	0.168	0.100	0.089	0.159	0.100
rs10461703	T/T	0.293	0.217	0.200	0.156	0.650
	T/C	0.501	0.550	0.556	0.578	0.267
	C/C	0.206	0.233	0.244	0.267	0.083
rs25754	T/T	0.582	0.233	0.578	0.556	0.467
	T/A	0.355	0.500	0.378	0.422	0.400
	A/A	0.062	0.267	0.044	0.022	0.133

SNP, single nucleotide polymorphism.

$p<0.0001$, $p^c<0.0001$). The C allele frequency of rs10461703 was lower in the RA group (36.6%) than in the control group (45.7%). The other two SNPs (rs1364044 and rs25754) were not associated with the development of RA (Table II).

Next, we accessed the relationship between the three examined SNPs and clinical features of RA patients, including ESR, CRP, RF (+ and -) and bone erosion (+ and -). However, no significant differences were found in these markers (data

not shown). The human SNP database (www.ncbi.nlm.nih.gov/SNP, dbSNP Build 132) has the genotype frequencies for rs25754 (T/T:T/A:A/A, European 0.233:0.500:0.267; Chinese 0.578:0.378:0.044; Japanese 0.556:0.422:0.022; Sub-Saharan African 0.467:0.400:0.133), rs10461703 (T/T:T/C:C/C, European 0.217:0.550:0.233; Chinese 0.200:0.556:0.244; Japanese 0.156:0.578:0.267; Sub-Saharan African 0.650:0.267:0.083) and rs1364044 (C/C:C/T:T/T, European 0.517:0.383:0.100; Chinese 0.489:0.422:0.089; Japanese 0.386:0.455:0.159; Sub-Saharan African 0.400:0.500:0.100) (Table III). The genotype distributions of rs1364004 in the control group that were analyzed in our study are similar to those of the Asian population, especially the Japanese population. With respect to rs10461703, the frequencies were similar to those of Europeans, but differences between the populations were not shown. The frequencies of rs25754 in the control group were similar to the Chinese population.

Haplotype association of ADAMTS12 SNPs in Koreans with RA. In order to evaluate the haplotype of the polymorphisms within the *ADAMTS12* gene, the haplotypes were analyzed by Haploview, SNPanalyzer and SNPstats. A LD block including two SNPs (rs25754 and rs3813474) was constructed using the Gabriel method. However, the haplotype was not analyzed for the association study since a SNP (rs3813474) of the block was not in HWE ($p<0.05$).

Sample power. The power of the sample size was calculated using a genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc). When we estimated the sample power ($\alpha=0.05$, risk 2-fold, no. of case 80% power), our case-control study was sufficiently powerful to determine a positive association. In this study, we had 0.9896 for rs1364044 (n=130), 0.9169 for rs10461703 (n=212) and 0.9896 for rs25754 (n=130).

Discussion

Loss of articular cartilage caused by extracellular matrix breakdown is the hallmark of arthritis. Degradative fragments of COMP have been observed in arthritic patients (1). ADAMTS12, a member of the ADAMTS family, has been associated with COMP degradation *in vitro*, and is significantly overexpressed in the cartilage and synovium of patients with RA (7). Recent studies have demonstrated the importance of COMP degradation by ADAMTS12. In particular, the size of COMP fragments generated by ADAMTS12 is similar to that of COMP-degradative fragments seen in arthritic patients (20). In addition, antibodies against ADAMTS12 significantly inhibit tumor necrosis factor-induced and interleukin-1β-induced COMP degradation in cartilage explants. Furthermore, suppression of ADAMTS12 expression using the RNAi method in human chondrocytes markedly prevents COMP degradation (21). COMP degradation mediated by ADAMTS7 and ADAMTS12 is inhibited by α-2-macroglobulin (22). The chromosomal location of the *ADAMTS12* gene has been suggested to contain susceptibility loci for autoimmune or inflammatory diseases, such as Crohn's disease, asthma and RA (13-18).

A few studies have been published on the role of *ADAMTS12* SNPs. Morrison *et al* reported that an intronic SNP rs6868223 of *ADAMTS12* was associated with mortality of heart failure patients of African descent (23). Sun *et al* showed that the rs2548035 intronic SNP was related to aggressive prostate cancer in a Swedish population (24). Li *et al* revealed that the rs1423300 intronic SNP was strongly associated with an adverse drug response to gemcitabine (25).

Despite the fact that the *ADAMTS12* gene has received attention as being involved in autoimmune diseases, such as RA, the relationship between RA and *ADAMTS12* SNPs remains obscure. The results in this study suggest that *ADAMTS12* gene variations may be involved in the pathogenesis of RA. In agreement with previous reports, an intronic SNP rs10461703 showed significant association with alleles and genotypes with RA after Bonferroni's correction (corrected $p=0.0024$ in the codominant model, corrected $p=0.0015$ in the dominant model, corrected $p=0.001$ in the log additive model, corrected $p<0.0001$). These facts indicate that there is a potential genetic association between the *ADAMTS12* gene and RA. In this study, we selected two missense SNPs (rs3813474, Trp1177Arg; rs25754, Thr1495Ile) for the association study. Of the SNPs, rs25754 is located in the mRNA sequence of thrombospondin type 1 (8th domain) of ADMTS12. The polymorphism induces a change from threonine at 1475 of the amino acid sequence to isoleucine. The change may or may not result in structural changes of the ADAMTS12 protein and thus may induce different functions of the protein. Moreover, rs3813474 is located in the spacer 2 region of the *ADMTS12* gene. The polymorphism induces a change from tryptophan at 1157 of the amino acid sequence to arginine. The SNPs were not associated with RA and its biological and/or clinical significance still need to be elucidated. To confirm the genotype frequencies and the association between the *ADAMTS12* gene and RA, replication studies with an adequate sample size or an association study with different SNPs that were not analyzed in this study may be required. Further genetic or biological studies also will help in understanding the precise mechanism of pathogenesis in patients with RA.

In conclusion, we detected a significant association between *ADAMTS12* SNPs and rheumatoid arthritis. These findings suggest that the *ADAMTS12* genotype may modify the clinical presentation of RA, and this represents another step toward a molecular classification of the genetics of RA.

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