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ORIGINAL ARTICLE

Bone Morphogenetic Protein 6 Polymorphisms are Associated With Systemic Lupus Erythematosus Susceptibility in the Korean Population

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ABSTRACT

Objectives: This study aims to investigate whether bone morphogenetic protein 6 (BMP6) single-nucleotide polymorphism (SNP) is associated with susceptibility to systematic lupus erythematosus (SLE).

Patients and methods: We analyzed the genotype and allele frequencies of BMP6 SNPs using genomic deoxyribonucleic acid (DNA) isolated from 119 SLE patients (9 males, 110 females; mean age 36.4 years; range 19 to 59 years) and 509 healthy controls (323 males, 186 females; mean age 42.1 years; range 19 to 61 years). Genomic DNA was extracted from peripheral blood leukocytes using a standard phenol-chloroform method or by using a genomic DNA extraction kit. Erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody levels of SLE patients were recorded.

Results: Our results showed that the genotype frequencies of rs17557 and rs9505273 for BMP6 in SLE patients significantly differed from those of the control group (p=0.01 and p=0.04, respectively). The genotype frequencies of the rs17557 and rs9505273 for BMP6 in female SLE patients were also significantly different from those in female healthy controls (p=0.04 and p=0.03, respectively). We also revealed that the distribution of the main haplotypes of BMP6 SNPs in SLE patients was significantly different from their distribution in healthy controls.

Conclusion: These results suggested that SNPs in BMP6 might be associated with susceptibility to SLE and that haplotypes of BMP6 polymorphisms might represent useful genetic markers for SLE.

Keywords: Bone morphogenetic protein 6; haplotype; polymorphism; systematic lupus erythematosus.

Systematic lupus erythematosus (SLE) is a chronic inflammatory and complex autoimmune disease caused by a combination of multiple genetic, hormonal, and environmental factors.[1,2] SLE is accompanied by the presence of multiple autoantibodies, including an antinuclear antibody (ANA).[3] SLE is a rare non-organ-specific disorder that occurs in 10 to 50 individuals per 100,000.[4] Additionally, SLE occurs more frequently in females, with a ratio of 9:1 between females and males.[5]

Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-beta superfamily and widely considered as crucial molecules involved in cell proliferation, differentiation, apoptosis, and migration in various tissues.[6,7] BMP6 (also known as vegetal related growth factor or vegetal related growth factor 1), is detected in various types of cancers and cancer cell lines and associated with cancer-cell growth, migration, and drug resistance.[8] Human BMP6 is located in chromosome region 6p23 to 6p24 and consists of seven exons (NM_001718.5; NP_001709.1). BMP6 is expressed in arthritic synovium of rheumatoid arthritis (RA) patients and strongly upregulated by proinflammatory

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cytokines.[9] We previously identified several candidate genes, including gamma-aminobutyric acid receptor pi subunit (GABRP), epithelial stromal interaction 1 (EPSTI1), and BMP6, associated with SLE and RA in our pilot study using a customized 3K single-nucleotide polymorphism (SNP) chip, which revealed that polymorphisms in GABRP and EPSTI1 might be associated with susceptibility to SLE, and that haplotypes of GABRP and EPSTI1 SNPs are useful genetic markers for SLE.[10,11] Therefore, in this study, we aimed to investigate whether BMP6 SNP is associated with susceptibility to SLE.

PATIENTS AND METHODS

We obtained genomic deoxyribonucleic acid (DNA) samples from 119 SLE patients (9 males, 110 females; mean age 36.4 years; range 19 to 59 years) and 509 healthy controls (323 males, 186 females; mean age 42.1 years; range 19 to 61 years) between February 2009 and December 2011 at Chonnam University Hospital and Wonkang University Hospital, respectively. DNA samples were provided by the Biobank of Wonkwang University Hospital (Iksan, Korea), a member of the National Biobank of Korea and supported by the Ministry of Health and Welfare. The study protocol was approved by the Wonkwang University Hospital Ethics Committee (WKUH1155). A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Genomic DNA was extracted from peripheral blood leukocytes using a standard phenol-chloroform method or by using a genomic DNA extraction kit (iNtRON Biotechnology, Seongnam, Korea) according to manufacturer instructions. SLE patients were recruited from the outpatient clinic at Chonnam National University Hospital (Gwangju, Korea). SLE was diagnosed according to the criteria of the American College of Rheumatology.[5] Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ANA levels in SLE patients were determined in a routine laboratory at Chonnam National University Hospital. Controls were recruited from the general population and had received comprehensive medical testing at Wonkwang University Hospital. All study participants were Korean, and the healthy controls ethnically matched individuals in the SLE-patient group.

The assay reagents for rs1107495, rs9505273, rs17557, rs76699422, and rs1044104 in the BMP6 gene were designed by Applied Biosystems (Applied Biosystems, Foster City, CA, USA). Global minor-allele frequency were as follows: rs1107495, G=0.2670/1337 (1000 Genomes; http://www.internationalgenome.org) and G=0.1827/5319 (Trans-Omics for Precision Medicine [TOPMED]; https://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed/); rs9505273, C=0.2638/1321 (1000 Genomes) and C=0.29621/8624 (TOPMED); rs17557, G=0.4024/2015 (1000 Genomes), G=0.4419/12866 (TOPMED), C=0.4824/6274 (GO-ESP; http://evs.gs.washington.edu/EVS/), and C=0.4637/56251 (ExAC; http://exac.broadinstitute.org); and rs1044104, G=0.4411/2209 (1000 Genomes) and G=0.3782/11012 (TOPMED). The reagents consisted of a 40× mix of unlabeled polymerase chain reaction (PCR) primers and TaqMan

Table 1. Primer sequences used for genotype analysis

Applications	Primers	Primer sequence (5' → 3')	Regions
TaqMan analysis	BMP6-TF1	CCTTTTAAATGATGGTAAAAGAGAA	rs1107495
	BMP6-TR1	GCTTCAGATCGGGGTATTGGTCAGA	
	BMP6-TF2	TGGAATGACTGATGTGTGCTTTGGGAGATA	rs9505273
	BMP6-TR2	TCCTGGCTGCAGTGTGGAAGAGGCCTGAAA	
	BMP6-TF3	CATGGTGGCTTTCTTCAAAGTGAGTGAGGT	rs17557
	BMP6-TR3	CACGTGCGCACCACCAGGTCAGCCTCCAGC	
	BMP6-TF4	TCAGAAGAAGGCTGGCTGGAATTTGACATC	rs76699422
	BMP6-TR4	CGGCCACTAGCAATCTGTGGGTTGTGACTC	
	BMP6-TF5	AGAACCGTTCTGGTAAAGAAGAGGTGAGCA	rs1044104
	BMP6-TR5	TGCCTTCACGTGTTACACGGTTACACACCC	

minor groove binder probes (Table 1) labeled with FAM (fluorescein) and VIC fluorescent dyes, respectively.[12] The reaction in 10 μL was optimized to work with 0.125 μL 40× reagent, 5 μL 2× TaqMan genotyping master mix (Applied Biosystems, Foster City, CA, USA), and 2 μL (50 ng) of genomic DNA. The PCR conditions were as follows: one cycle at 95°C for 15 minutes, followed by 40 cycles at 95°C for 15 seconds and 60°C for 45 seconds. PCR was performed on an ABI Plus system, and samples were read and analyzed using the ABI Plus software (Applied Biosystems, Foster City, CA, USA).

Statistical analysis

Patients and healthy controls were compared using case-control association analysis. Chi square tests were employed to estimate the Hardy-Weinberg equilibrium (HWE). Pair-wise comparison of bi-allelic loci was employed for analyses of linkage disequilibrium. Haplotype frequencies of BMP6 for multiple loci were estimated using the expectation maximization algorithm with SNPAlyze software (Dynacom, Yokohama, Japan). Logistic regression analyses (SPSS v11.5; SPSS Inc., Chicago, IL, USA) were used to calculate the odds ratios (with 95% confidence intervals). Analysis of variance was applied to define the ESR, as well as CRP and ANA levels, of each genotype from individual SLE patients. A p value <0.05 was considered statistically significant.

RESULTS

The BMP6 gene was identified as a candidate gene associated with SLE in our previous pilot study using a customized 3K SNP chip. We selected five SNPs, including rs1107495, rs9505273, rs17557 (Val368Val), rs76699422 (Thr311Pro), and rs1044104, in human BMP6 for large-sample genotyping based on their locations. All genotype frequencies were in HWE (data not shown). A SNP, rs76699422, from the National Center for Biotechnology Information SNP database, was also genotypically analyzed; however, analysis of 204 samples revealed only an AA genotype (data not shown), indicating that rs76699422 might represent a very rare polymorphism or monomorphism in the Korean population. The genotype and allele frequencies of rs1107495 and rs1044104 were not significantly different

Table 2. Genotype and allele analyses of bone morphogenetic protein 6 gene polymorphisms in systematic lupus erythematosus patients and healthy controls

Position*	Genotype/Allele	Healthy controls		SLE patients		Odds ratio† (95% CI)		p‡
		n	%	n	%			
rs1107495	GG	142	28.5	26	21.8	1.00		
	GA	234	46.9	69	58.0	0.66	0.40-1.10	0.09
	AA	123	24.6	24	20.2	1.61	0.98-2.65	
	G	518	51.9	121	50.8	1.00		
	A	480	48.1	117	49.2	1.04	0.79-1.39	0.77
rs9505273	CC	171	33.6	52	44.1	1.00		
	CT	246	48.3	57	48.3	0.42	0.20-0.89	**0.01**
	TT	92	18.1	9	7.6	0.76	0.50-1.16	
	C	588	57.8	161	68.2	1.00		
	T	430	42.2	75	31.8	0.64	0.47-0.86	**0.003**
rs17557	CC	302	59.9	59	49.6	1.00		
	CG	171	33.9	55	46.2	1.65	1.09-2.49	**0.04**
	GG	31	6.2	5	4.2	0.83	0.31-2.21	
	C	775	76.9	173	72.7	1.00		
	G	233	23.1	65	27.3	1.25	0.91-1.72	0.18
rs1044104	CC	249	50.4	56	47.1	1.00		
	CT	196	39.7	51	42.9	0.94	0.47-1.90	0.80
	TT	49	9.9	12	10.1	1.16	0.76-1.77	
	C	694	70.2	163	68.5	1.00		
	T	294	29.8	75	31.5	1.09	0.80-1.47	0.64

SLE: Systematic lupus erythematosus; CI: Confidence interval; * Calculated from translation start site; † Logistic regression analyses were used for calculating odds ratio (95% confidence interval); ‡ Value was determined by Fisher's exact test or Chi square tests from a 2×2 contingency table.

Table 3. Genotype and allele analyses of bone morphogenetic protein 6 gene polymorphisms in female systematic lupus erythematosus patients and female healthy controls

Position*	Genotype/Allele	Healthy controls		SLE patients		Odds ratio† (95% CI)		p‡
		n	%	n	%			
rs1107495	GG	48	27.0	24	21.8	1.0		
	GA	94	52.8	62	56.4	1.32	0.73-2.37	0.33
	AA	36	20.2	24	21.8	1.33	0.65-2.72	
	G	190	53.4	110	50.0	1.0		
	A	166	46.6	110	50.0	1.15	0.82-1.60	0.43
rs9505273	CC	66	35.5	50	45.9	1.0		
	CT	91	48.9	52	47.7	0.75	0.46-1.25	**0.01**
	TT	29	15.6	7	6.4	0.32	0.13-0.79	
	C	223	59.9	152	69.7	1.0		
	T	149	40.1	66	30.3	0.65	0.46-0.93	**0.02**
rs17557	CC	118	63.4	55	50.0	1.0		
	CG	56	30.1	50	45.5	1.92	1.16-3.15	**0.008**
	GG	12	6.5	5	4.5	0.89	0.30-2.66	
	C	292	78.5	160	72.7	1.0		
	G	80	21.5	60	27.3	1.37	0.93-2.01	0.11
rs1044104	CC	96	52.2	52	47.3	1.0		
	CT	72	39.1	47	42.7	1.21	0.73-1.99	0.41
	TT	16	8.7	11	10.0	1.27	0.55-2.94	
	C	264	71.7	151	68.6	1.0		
	T	104	28.3	69	31.4	1.16	0.81-1.67	0.42

SLE: Systematic lupus erythematosus; CI: Confidence interval; * Calculated from the translation start site; † Logistic regression analyses were used for calculating OR (95% CI; confidence interval); ‡ Value was determined by Fisher's exact test or Chi square tests from a 2×2 contingency table.

between SLE patients and healthy controls; however, the genotype frequencies of rs9505273 (p=0.01) and rs17557 (p=0.04) in SLE patients significantly differed from those in the control group (Table 2). The allele frequencies of BMP6 polymorphism rs9505273 in the SLE group were also significantly different from those in the control group (p=0.003; Table 2). We further analyzed genotype and allele frequencies between female controls and female SLE patients, given that the SLE patients were predominantly female as compared with the population in control subjects. Although the genotype and allele frequencies of the rs1107495 and rs1044104 polymorphisms were not significantly different between female SLE patients and female controls, the genotype frequencies of the rs9505273 (p=0.01) and rs17557 (p=0.008) polymorphisms in female SLE patients were statistically significantly different from those of female healthy controls (Table 3).

Table 4. Analyses of erythrocyte sedimentation rate, C-reactive protein, and antinuclear antibody levels among each genotype of bone morphogenetic protein 6 single-nucleotide polymorphisms in systematic lupus erythematosus patients

Position*	Genotype	ESR		p†	CRP		p†	ANA		p†
		n	Mean±SD		n	Mean±SD		n	Mean±SD	
rs1107495	GG	24	30.3±24.7	0.80	24	0.5±0.4	0.66	23	198.3±148	
	GA	63	30.9±25.2		63	0.8±2.4		60	276.7±226	1.48
	AA	23	26.9±20.3		23	0.4±0.2		24	238.4±106	
rs9505273	CC	49	35.7±27.6	0.06	49	0.5±0.5	0.68	53	289.1±238	
	CT	51	25.6±20.5		51	0.8±2.6		49	231.0±185	1.03
	TT	9	21.8±15.0		9	0.3±0.1		5	304.0±215	
rs17557	CC	53	27.8±21.0	0.51	53	0.8±2.6	0.74	49	275.1±243	
	CG	53	32.5±27.2		53	0.5±0.5		49	253.9±191	0.14
	GG	4	23.0±14.0		4	0.3±0.1		9	248.9±176	
rs1044104	CC	51	30.2±24.8	0.87	51	0.4±0.2	0.42	47	261.3±191	
	CT	50	30.3±24.6		50	0.9±2.7		50	237.6±197	2.49
	TT	9	25.9±16.1		9	0.5±0.3		9	408.9±359	

* Calculated from translation start site; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: Antinuclear antibody; SD: Standard deviation; † Values were analyzed by analysis of variance.

Table 5. Haplotype frequencies of bone morphogenetic protein 6 single-nucleotide polymorphisms in systematic lupus erythematosus patients and healthy controls

Haplotype				Frequency*			
rs1107495	rs9505273	rs17557	rs1044104	Control	SLE	Chi-square	p†
A	C	C	C	0.18	0.25	4.41	0.04
G	C	C	C	0.17	0.13	1.86	0.17
G	T	C	C	0.15	0.17	0.75	0.39
A	T	C	C	0.13	0.07	6.47	0.01
G	C	G	T	0.06	0.10	7.44	0.0064
A	C	G	T	0.05	0.07	1.90	0.17
G	C	C	T	0.05	0.01	7.39	0.0066
G	T	G	T	0.04	0.01	5.61	0.02
A	T	G	T	0.03	0.02	1.74	0.19
G	T	C	T	0.03	0.05	2.59	0.11
A	C	C	T	0.02	0.05	10.78	0.001
Other				0.14	0.07	-	-

SLE: Systematic lupus erythematosus; * Values were constructed by expectation-maximization algorithm with genotyped single-nucleotide polymorphisms; † Values were analyzed by Chi-square test.

To determine any possible correlations between BMP6 polymorphisms and the clinical features of SLE, we investigated relationships between BMP6 SNPs and total serum ESR, CRP, and ANA levels in SLE patients (Table 4). We found that the SNPs identified in the SLE patients showed no significant associations with the ESR, CRP, or ANA levels (Table 4).

We estimated the haplotype frequencies of the BMP6 SNPs (rs1107495, rs9505273, rs17557, and rs1044104) between controls and SLE patients (Table 5). Of 16 possible haplotypes, seven and eight were identified as the main haplotypes (>5%) in controls and SLE patients, respectively (Table 5), with the distribution of the major haplotype (ACCC) significantly different in SLE patients as compared with that in the controls (p=0.04). The distribution frequency of the GCGT and GCCT haplotypes in SLE patients was highly different than that in controls (p=0.0064 and p=0.0066, respectively). These results suggested that the BMP6 polymorphisms might represent important genetic markers associated with SLE susceptibility.

DISCUSSION

Systematic lupus erythematosus is a chronic inflammatory disease characterized by the presence of autoantibodies against nuclear autoantigens, as well as cytoplasmic and circulating proteins.[13] The disease is caused by a combination of environmental factors and multiple genetic factors. The major histocompatibility complex was the first genetic region reported as being associated with SLE,[14] and since then, multiple genes have been identified as associated with SLE susceptibility. However, a recent estimate advocates that most of the genetic variations identified thus far only explain ~8% of genetic SLE risk.[15] Over the previous decade, accumulating results from genome-wide association studies significantly expanded the list of SLE-susceptibility loci; however, the functional genetics related to SLE-associated SNPs largely remain undefined. SNPs in the signal transducer and activator of transcription 4 gene are associated with nephritis, as well as double stranded DNA autoantibodies in SLE patients,[16] with accumulating reports also signifying that these SNPs are associated with clinical features of SLE.[17-19] We previously reported that rs1044856 and rs1359184 in EPSTI1 are associated with elevated ESR and ANA levels in SLE patients, respectively,[11] and also that SNPs in the Forkhead-box J1,[20] interleukin coactosin-like 1,[21] thymic stromal lymphopoietin receptor,[22] GABRP,[10] and EPSTI1 genes[11] are associated with SLE susceptibility in the Korean population. In the present study, we evaluated the association between BMP6 polymorphisms and SLE susceptibility.

Bone morphogenetic protein 6 plays critical roles in skeletal development, bone formation, and differentiation of stem cells, such as mesenchymal stem cells.[23] The majority of BMP6-related

research has focused on the development and differentiation of osteoblasts and various stem cells; therefore, the primary genetic association and function of BMP6 in SLE remain unknown. We previously identified several candidate genes, including BMP6, associated with SLE.[10] In the present study, we analyzed the genotypes of the rs1107495, rs9505273, rs17557, rs76699422, and rs1044104 polymorphisms of BMP6 in SLE patients and healthy controls, finding that rs17557 and rs76699422 represented a synonymous SNP (Val368Val) and a missense SNP (Thr311Pro), respectively. However, our results indicated that rs76699422 was a very rare polymorphism or monomorphism in the Korean population. Furthermore, the genotype frequencies of rs17557 and rs9505273 in SLE patients were significantly different from those of the control group (Table 2), suggesting that these BMP6 polymorphisms might be associated with SLE susceptibility. Generally, synonymous variations affect messenger ribonucleic acid stability, secondary structure, and receptor synthesis and may result in potentially important pathophysiological alterations.[24,25] The results presented here advocated that rs17557 in BMP6 might be associated with SLE susceptibility, despite the absence of a mutation resulting in amino acid alteration in the encoded protein.

We further analyzed the genotype frequencies of these BMP6 SNPs by sex between healthy controls and SLE patients, because SLE occurs more frequently in females. We found that the associations described were also true when study subjects were confined to the female population (Table 3). These results supported that these BMP6 SNPs might strongly influence SLE susceptibility, and that these effects might be sex-specific. It will be of interest to test this hypothesis using a large male SLE sample set in future research. However, it is difficult to enroll male SLE patients, given the rare occurrence of SLE in males.

The ESR and CRP levels reflect the degree of inflammation in the body. There has been debate regarding the accuracy and sensitivity of the ESR and CRP levels in various conditions, such as those associated with SLE.[26,27] However, ANA levels allow detection of autoantibodies in blood serum, with ANA titers useful in the diagnosis of several autoimmune disorders, including SLE. Moreover, monitoring ANA levels aids in predicting disease progression.[28,29] In the present study, we investigated associations between BMP6 SNPs and the ESR, as well as CRP and ANA levels, as measured by analysis of variance; however, found no relevant associations (Table 4), signifying that the BMP6 SNPs did not affect the ESR, CRP, or ANA levels in SLE patients.

To examine any possible correlations between the haplotypes associated with rs1107495, rs9505273, rs17557, and rs1044104 polymorphisms and SLE susceptibility, we analyzed the haplotype frequencies of the SNPs in SLE patients and controls (Table 5). The distribution of the main haplotypes (ACCC, ATCC, GCGT, and GCCT) in BMP6 SNPs in SLE patients differed significantly from their distribution in controls (Table 5). These results put forward that these haplotypes might represent useful genetic markers for SLE. It will be of interest to validate this finding using a larger SLE sample set in future research.

The limitation of this association study was that although our results indicated that BMP6 polymorphisms might be correlated with SLE susceptibility, SLE pathogenesis cannot be explained by an association study.

In conclusion, our results suggest that BMP6 might be a candidate gene associated with SLE pathogenesis. Our results also provide a valuable resource for further functional studies of the BMP6 gene and its relationship with other autoimmune or inflammatory disorders.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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