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Research Article

Association between cSNPs of BMP2 Gene and Degenerative Lumbar Scoliosis in Korean Population

Hyung-Ki Kim[1], Hwayoung Lee[1], Jun-Tack Kwon[1], Ki Tack Kim[2], Hak-Jae Kim[1,3]*

[1]Department of Clinical Pharmacology, Soonchunhyang University, Republic of Korea

[2]Department of Orthopedic Surgery, Kyung Hee University East West Neomedical Center, Republic of Korea

[3]Soonchunhyang Medical Research Institute, Soonchunhyang University, Cheonan, Republic of Korea

***Corresponding author:** Hak-Jae Kim, Department of Clinical Pharmacology, College of Medicine, Soonchunhyang University, Republic of Korea, Tel: +82 41 570 2478; Fax: +82 41 575 2406; Email: hak3962@sch.ac.kr

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Abstract

Background: Bone morphogenetic proteins (BMPs) are involved in cartilage and bone formation. However, the association between single nucleotide polymorphisms (SNPs) of *BMP* genes and degenerative lumbar scoliosis (DLS) has not been investigated yet. The aim of this study was to determine whether coding SNPs (cSNPs) of *BMP* genes (*BMP2*, *3*, *4*, *5*, *6*, and *10*) are associated with DLS in Korean population.

Methods: Seven cSNPs in *BMP* genes were selected and genotyped for 66 patients with DLS and 127 healthy controls using direct sequencing.

Results: Of the SNPs examined, two cSNPs of *BMP2* gene showed weak associations with DLS in the codominant (rs235768, Arg190Ser, missense, OR = 2.28, 95% CI = 1.19 – 4.36, p = 0.03) and dominant models (rs235768, OR = 1.99, 95% CI = 1.07 – 3.72, p = 0.03; rs1049007, Ser87Ser, synonymous, OR = 1.93, 95% CI = 1.039 – 3.62, p = 0.04).

Conclusion: *BMP2* may be a susceptible gene for DLS in Korean population.

Introduction

Lumbar scoliosis is a three-dimensional deformity of spine associated with structural alterations of vertebral bodies. Lumbar scoliosis in adult stage could be from deformity developed at growing age or de novo degenerative deformity after skeletal maturity [1-6]. Degenerative lumbar scoliosis (DLS), "de novo" lumbar scoliosis, usually occurs after the fourth or fifth decade in patients without history of scoliosis. The curve is composed of a few vertebral bodies with its apex in the intervertebral space, most frequently at the L2 - L3 or the L3 - L4 level [7-9]. The causes of DLS development are various. Degeneration of the spinal column is the most common cause. Neuromuscular disorders, metabolic abnormalities (osteoporosis), leg length discrepancy, long-standing pelvic obliquity, and outcomes of prior surgical interventions are other causes [10]. Several genetic variations have been linked to lumbar spine degeneration or osteoporosis [11, 12]. Intra genic polymorphisms of vitamin D receptor gene were reported to be associated with lumbar spine degeneration and bone density [11]. Gómez et al. (2007) reported that estrogen receptor alpha gene polymorphisms were associated with osteoporosis [12].

Bone morphogenetic proteins (BMPs) are phylogenetically conserved signaling growth factors belonging to the transforming growth factor beta super family [13-15]. BMPs also play important roles in the pathophysiology of several diseases, including osteoporosis [16], arthritis [17], pulmonary hypertension [17, 18], and kidney diseases [19]. Previous studies have reported that *BMPs* (*BMP2*, *BMP6*, *BMP7*, and *BMP15*) are associated with several diseases such as ossification of the posterior longitudinal ligament (OPLL), a vascular necrosis, and ovarian failure [20-26]. Wang et al. (2008) reported a positive association between *BMP2* polymorphisms [Ser37Ala (T/G) and Ser87Ser (A/G)] and OPLL of the cervical spine.

Despite the potentially important role of BMPs in the development of DLS, the association between genetic variations of *BMPs* and DLS has not been reported. Therefore, the objective of this study was to determine whether coding single nucleotide polymorphisms (cSNPs) of *BMP* family genes (*BMP2*, *3*, *4*, *5*, *6*, and *10*) are associated with DLS in Korean population.

Methods

Subjects

All patients with DLS were from Kyung Hee University East-West Neo-Medical Center, Seoul, Republic of Korea and National Medical Center, Seoul, Republic of Korea. The DLS group included 66 patients with mean age of 69.1 ± 7.7 years (7 male, 65.4 ± 8.1 years; 59 female, 69.6 ± 7.6 years). The control group was recruited after it was confirmed in a general health check-up program that they had no clinical evidence of DLS or any other disorders. A total of 127 healthy controls with mean age of 68.1 ± 8.6 years (17 male, 71.6 ± 8.3 years; 110 female, 67.5 ± 8.6 years) were recruited. All case-control subjects used in this study were surveyed through the same center. Each patient was diagnosed by a special spine surgeon. All patients fulfilled physical examination and radiographic criteria (Cobb's angle over 10 degrees) [27]. Informed consent was obtained from all individuals according to the Declaration of Helsinki guidelines [28]. The study was approved by the ethics review committee of the Medical Research Institute, Kyung Hee University Medical Center, Seoul, Republic of Korea.

SNP Genotyping

First, we searched for cSNPs of *BMP* genes originally known as "*BMP*" (*BMP2/3/4/5/6/8/10/15*) in GenBank database (http://www.ncbi.nlm.nih.gov/gene). The SNPs of procollagen C-proteinase (*PCP*, same as *BMP1*), osteogenic protein 1 (*OP1*, same as *BMP7*), and

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Table 1: Sequences of primers.

SNP/gene		Sequence(5′→3′)	Product Size (bp)	Annealing temperature (˚C)
rs235768	Forward	TTATCACCTCAGCAGAGCTTCA	375	58
BMP2	Reverse	GGCCAAAAGTTACTAGCAATGG		
rs1049007	Forward	GACGAGGTCCTGAGCGAGTTCG	339	58
BMP2	Reverse	TACAGAAGCAAGAGTGGAAACG		
rs3733549	Forward	AGTTGTCCAGTGTCTGGAGGAT	351	58
BMP3	Reverse	TCCCTGTAAGCTTGATACCACA		
rs17563	Forward	CAGTAGGTTTCCCCTGCATAAG	361	58
BMP4	Reverse	TCCAGTAGTCGTGTGATGAGGT		
rs3734444	Forward	GAGGATGTTGTGCTCAGAAATG	399	58
BMP5	Reverse	AGCATAAAGAGAGGTGCAGAGG		
rs17557	Forward	GAAAGGAGTGCTTTGATTCTGC	433	58
BMP6	Reverse	ACAAGGCTTTCTGGAAACACAG		
rs2231344	Forward	GGTGTCTGGGGAGATATATGGA	326	58
BMP10	Reverse	CAGGTCCACTGGAAAAGCTATC		

Table 2: Genotype and allele frequencies of the *BMP* gene SNPs in degenerative lumbar scoliosis (DLS) and controls.

gene	SNP	Genotype	DLS		Control		Model	OR (95% CI)	p
			Freq	%	Freq	%			
BMP2	rs235768	T/T	36	54.5	90	70.9	codominant	2.28 (1.19-4.36)	**0.03**
	(Arg190Ser)	T/A	28	42.4	30	23.6	dominant	1.99 (1.07-3.72)	**0.03**
		A/A	2	3.0	7	5.5	recessive	0.52 (0.10-2.63)	0.40
BMP2	rs1049007	G/G	37	56.1	91	71.7	codominant	1.57 (0.92-2.67)	0.10
	(Ser87Ser)	G/A	27	40.9	31	24.4	dominant	1.93 (1.03-3.62)	**0.04**
		A/A	2	3.0	5	3.9	recessive	0.78 (0.15-4.17)	0.77
BMP3	rs3733549	G/G	44	66.7	94	74.0	codominant	1.40 (0.76-2.58)	0.29
	(Arg192Gln)	G/A	21	31.8	32	25.2	dominant	1.40 (0.73-2.70)	0.31
		A/A	1	1.5	1	0.8	recessive	1.95 (0.12-32.05)	0.64
BMP4	rs17563	T/T	34	51.5	78	61.4	codominant	1.40 (0.86-2.28)	0.18
	(Val152Ala)	T/C	27	40.9	43	33.9	dominant	1.46 (0.80-2.68)	0.22
		C/C	5	7.6	6	4.7	recessive	1.74 (0.51-6.00)	0.39
BMP5	rs3734444	T/T	49	74.2	86	67.7	codominant	0.77 (0.42-1.42)	0.40
	(Ser37Ser)	T/C	16	24.2	38	29.9	dominant	0.76 (0.39-1.49)	0.42
		C/C	1	1.5	3	2.4	recessive	0.61 (0.06-6.01)	0.66
BMP6	rs17557	C/C	37	62.7	77	61.1	codominant	0.83 (0.48-1.45)	0.51
	(Val368Val)	C/G	21	35.6	42	33.3	dominant	0.90 (0.48-1.72)	0.76
		G/G	1	1.7	7	5.6	recessive	0.31 (0.04-2.64)	0.23
BMP10	rs2231344	T/T	51	77.3	102	80.3	codominant	1.15 (0.57-2.31)	0.60
	(Asp242Asp)	T/C	15	22.7	24	18.9	dominant	1.20 (0.58-2.48)	0.62
		C/C	0	0	1	0.8	recessive	0.00 (0.00-NA)	0.41

Freq, frequency; OR, odds ratio; CI, confidence intervals; NA, not applicable; p, p value. Bold characters represent statistically significant values and its rs number of SNP.

GDF2/5/6/7/11 (same as *BMP9/14/13/12/11*) genes were excluded from this study. Related information of cSNP sequences was obtained from the SNP database (dbSNP #130) of the National Center for Biotechnology Information (NCBI). The SNPs with unknown heterozygosity and minor allele frequency (below 5%) were excluded. Finally, rs235768 (*BMP2*), rs1049007 (*BMP2*), rs3733549 (*BMP3*), rs17563 (*BMP4*), rs3734444 (*BMP5*), rs17557 (*BMP6*), and rs2231344 (*BMP10*) were selected.

Genomic DNA was extracted from blood samples collected in EDTA using a commercially available Qiagen DNA Extraction kit (Qiagen, Tokyo, Japan). Genomic DNA was amplified using the gene-specific primers for each SNP (Table 1). PCR products were sequenced

Table 3: The haplotype frequencies of the *BMP* gene SNPs in degenerative lumbar scoliosis (DLS) patients and healthy controls.

Haplotype	Type	DLS		Freq	Control		Freq	Models	OR(95% CI)	p
		Freq	%		Freq	%				
TGGTTCT	HH	5	7.6	0.24	12	9.4	0.26	codominant	0.90(0.57-1.43)	0.67
	H-	22	33.3		43	33.9		dominant	0.91(0.50-1.66)	0.75
	--	39	59.1		72	56.7		recessive	0.79(0.26-2.33)	0.66
TGGTTGT	HH	0	0.0	0.11	2	1.6	0.15	codominant	0.68(0.35-1.34)	0.26
	H-	14	21.2		33	26.0		dominant	0.71(0.35-1.44)	0.34
	--	52	78.8		92	72.4		recessive	0.00(0.00--)	0.99
AAGTTCT	HH	1	1.5	0.15	0	0.0	0.11	codominant	1.57(0.81-3.02)	0.18
	H-	18	27.3		27	21.3		dominant	1.50(0.76-2.96)	0.25
	--	47	71.2		100	78.7		recessive	NA	0.99
TGGCTCT	HH	2	3.0	0.17	2	1.6	0.09	codominant	1.93(1.04-3.59)	**0.04**
	H-	18	27.3		19	15.0		dominant	2.19(1.09-4.43)	**0.03**
	--	46	69.7		106	83.5		recessive	1.95(0.27-14.19)	0.51
TGATTCT	HH	0	0.0	0.08	0	0.0	0.06	codominant	1.39(0.60-3.19)	0.44
	H-	11	16.7		16	12.6		dominant	1.39(0.60-3.19)	0.44
	--	55	83.3		111	87.4		recessive	NA	NA
TGGTTCC	HH	0	0.0	0.03	1	0.8	0.07	codominant	0.42(0.14-1.26)	0.12
	H-	4	6.1		16	12.6		dominant	0.42(0.13-1.30)	0.13
	--	62	93.9		110	86.6		recessive	NA	0.99

Freq, frequency; OR, odds ratio; CI, confidence intervals; NA, not applicable; p, p value. Bold characters represent statistically significant values and its structure of haplotype.

using ABI PRISM 3730XL analyzer (PE Applied Biosystems, Foster City, California, USA). Sequence data were analyzed using SeqManII software (DNASTAR Inc., Madison, WI, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed by SNP stats in both controls and cases [29]. For linkage disequilibrium (LD) block, Haploview version 3.32 was used [30]. Haplotypes and their frequencies was inferred using expectation-maximization (EM) algorithm [31]. Multiple logistic regression model was used to calculate odds ratios (OR), 95% confidence interval, and corresponding p values. While controlling age and gender as co variables, SNP stats, Hap Analyzer version 1.0 [32], and Helixtree (Golden Helix Inc., MT, USA) were used to analyze association of SNPs and haplotypes with DLS.

Results

Of the seven SNPs of *BMP* genes examined, all SNPs were polymorphic. The genotype distributions of all seven SNPs (rs235768, rs1049007, rs3733549, rs17563, rs3734444, rs17557, and rs2231344) were in HWE ($p > 0.05$). Of the SNPs examined, two SNPs (rs235768 and rs1049007) of *BMP2* gene were weakly associated with DLS in the co dominant (rs235768, Arg190Ser, missense, OR = 2.28, 95% CI = 1.19 - 4.36, p = 0.03) and dominant model (rs235768, OR = 1.99, 95% CI = 1.07 - 3.72, p = 0.03; rs1049007, Ser87Ser, synonymous, OR = 1.93, 95% CI = 1.039 - 3.62, p = 0.04).

A haplotype-based association analysis was performed for different combinations of SNPs within *BMP* genes between the DLS group and the control group. The haplotypes were constructed with cSNPs of BMP genes selected for this study [rs235768 (*BMP2*, A/G), rs1049007 (*BMP2*, A/G), rs3733549 (*BMP3*, A/G), rs17563 (*BMP4*, A/G), rs3734444 (*BMP5*, A/G), rs17557 (*BMP6*, G/A), and rs2231344 (*BMP10*, T/C)]. The order of SNPs in the haplotypes was: rs235768, rs1049007, rs3733549, rs17563, rs3734444, rs17557, and rs2231344. Haplotype (TGGCTCT) showed weak association with DLS. The haplotype was associated with DLS in the co dominant (OR = 1.93, 95% CI = 1.04 - 3.59, p = 0.04, Table 2) and dominant model (OR = 2.19, 95% CI = 1.09 - 4.43, p = 0.03, Table 3). Therefore, the TGGCTCT of BMP *genes* may be a susceptible factor of DLS.

To compare our genotypic results with different ethnic populations, we searched the human SNP database (www.ncbi.nlm.nih.gov/SNP, dbSNP Build 130). Database representing genotype frequencies for the SNPs analyzed in this manuscript is shown in Table 4. The genotype distributions of the control group of all SNPs analyzed in our study are similar to those of Asian population, especially Japanese population (Table 4).

Discussion

Several researches have suggested genetic associations between *BMP* genes and some diseases [26-32]. The association between several SNPs of *BMP2* and *BMP4* genes and genetic hemochromatosis was investigated in the study. A SNP of *BMP2* gene observed in this study (rs235756) was reported to be associated with hemochromatosis penetrance [26]. Wang et al. (2008) reported that SNP of *BMP2* gene (rs1049007 analyzed in our study) was significantly associated with the occurrence of OPLL in the cervical spine [27]. The association of a single SNP of *BMP6* gene (rs3812163) was suggested to have a potential role of *BMP6* in the development of a vascular necrosis in

Table 4: Genotype frequencies of the SNPs of *BMP* genes in each population.

Gene	SNP	Genotype	DLS	Control	Europe	China	Japan	Sub-Saharan African
BMP2	rs235768	T/T	0.55	0.71	0.57	0.50	0.64	1.00
	(Arg190Ser)	T/A	0.42	0.24	0.28	0.48	0.32	0.00
		A/A	0.03	0.06	0.15	0.02	0.04	0.00
BMP2	rs1049007	G/G	0.56	0.72	No data	No data	No data	No data
	(Ser87Ser)	G/A	0.41	0.24				
		A/A	0.03	0.04				
BMP3	rs3733549	G/G	0.67	0.74	0.90	0.67	0.73	0.88
	(Arg192Gln)	G/A	0.32	0.25	0.17	0.33	0.23	0.12
		A/A	0.02	0.01	0.00	0.00	0.04	0.00
BMP4	rs17563	T/T	0.52	0.61	0.15	0.44	0.67	0.65
	(Val152Ala)	T/C	0.41	0.34	0.48	0.47	0.32	0.32
		C/C	0.08	0.05	0.37	0.09	0.01	0.03
BMP5	rs3734444	T/T	0.74	0.68	0.40	0.71	0.76	0.07
	(Ser37Ser)	T/C	0.24	0.30	0.38	0.29	0.22	0.48
		C/C	0.02	0.02	0.22	0.00	0.02	0.45
BMP6	rs17557	C/C	0.63	0.61	0.15	0.47	0.71	0.05
	(Val368Val)	C/G	0.36	0.33	0.45	0.47	0.22	0.35
		G/G	0.01	0.06	0.40	0.06	0.07	0.60
BMP10	rs2231344	T/T	0.77	0.80	0.82	0.78	0.87	0.47
	(Asp242Asp)	T/C	0.23	0.19	0.18	0.20	0.13	0.35
		C/C	0.00	0.01	0.00	0.02	0.00	0.18

From database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp).

sickle cell disease patients [30]. These genetic studies on the association of SNP of *BMP* genes with many different diseases containing spine disease provided important information for our case-control study with DLS patients. We hypothesized that *BMP* gene polymorphisms might affect the susceptibility of spine diseases such as DLS. We first investigated the genetic association between cSNPs of *BMP* genes and DLS. Given the important biological and genetic functions of *BMP* genes during developmental process, we investigated whether *BMP* gene variations acted as risk factors for DLS in Korean sample. Our results suggested that *BMP* genes may have no involvement in the pathogenesis of DLS. Of all the SNPs and haplotypes analyzed, only two SNPs (rs235768 and rs1049007) showed weak associations with DLS. In addition, haplotype analysis between DLS and control subjects revealed that TGGCTCT of BMP *genes* might be a susceptible factor of DLS, indicating that there is a genetic association between cSNPs of *BMP* genes and DLS.

We compared our genotype frequencies with the human SNP database to show ethnic similarities and differences. The genotype frequencies of our study sample resembled those of Japanese and Chinese Hapmap populations (Table 4). Further studies are needed to elucidate: (i) whether another case-control study with different populations will reveal the association between SNP of *BMP* and DLS; and (ii) whether cSNPs can affect the expression of *BMP* genes. To confirm negative association between *BMP* genes and DLS, replication studies with adequate sample size or an association study with different SNPs not analyzed in this study may be required.

This study has several limitations. First, the sample size may not have been sufficient to detect the associations of smaller effects for DLS. Second, in this study, when we designed the experiment, only cSNPs of *BMP* genes were included for the association study. As a result, our selection of SNPs provided incomplete coverage of currently knows common variation in *BMP* genes. Therefore, additional studies with different SNPs, especially promoter SNPs, are needed.

Conclusion

In conclusion, we investigated possible association between SNPs of *BMP* genes and DLS. Our results suggested that cSNPs of *BMP* genes may have influence on the development of DLS in Korean population. However, additional genetic studies are needed to help us understand the precise mechanisms underlying the pathogenesis of DLS.

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