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

Hyung-Ki Kim1, Hwayoung Lee1, Jun-Tack Kwon1, Ki Tack Kim1, Hak-Jae Kim2*

1Department of Clinical Pharmacology, Soochunhyang University, Republic of Korea
2Department of Orthopedic Surgery, Kyung Hee University East West Neomedical Center, Republic of Korea

*Corresponding author: Hak-Jae Kim, Department of Clinical Pharmacology, College of Medicine, Soochunhyang University, Republic of Korea

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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
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.

<p>| Table 1: Sequences of primers. |</p>
<table>
<thead>
<tr>
<th>SNP/gene</th>
<th>Sequence(5’→3’)</th>
<th>Product Size (bp)</th>
<th>Annealing temperature (˚C)</th>
</tr>
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<tbody>
<tr>
<td>rs235768</td>
<td>Forward TTATCACCTCAGCAGGCTTCA</td>
<td>375</td>
<td>58</td>
</tr>
<tr>
<td>BMP2</td>
<td>Reverse GCCAAAAAGTTACTAGGAATGG</td>
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<td></td>
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<tr>
<td>rs1049007</td>
<td>Forward GACGAGGTCCTGAGCGAGTTCG</td>
<td>339</td>
<td>58</td>
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<td></td>
<td></td>
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<tr>
<td>rs3733549</td>
<td>Forward AGTTGTCCAGTGCTGAGGAT</td>
<td>351</td>
<td>58</td>
</tr>
<tr>
<td>BMP3</td>
<td>Reverse TCCCTGAACTGTGATACCACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs17563</td>
<td>Forward CAGTAGGTTTCCCCCTGATAAG</td>
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<td>58</td>
</tr>
<tr>
<td>BMP4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>rs3734444</td>
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<td>399</td>
<td>58</td>
</tr>
<tr>
<td>BMP5</td>
<td>Reverse AGCATAAGAGGAGGTGAGG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs17557</td>
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<td></td>
</tr>
<tr>
<td>BMP6</td>
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<td></td>
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<tr>
<td>rs2231344</td>
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<td>58</td>
</tr>
<tr>
<td>BMP10</td>
<td>Reverse CAGGTCCACTGGAAAGCTATC</td>
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<td></td>
</tr>
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<p>| Table 2: Genotype and allele frequencies of the BMP gene SNPs in degenerative lumbar scoliosis (DLS) and controls. |
|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>gene</th>
<th>SNP</th>
<th>Genotype</th>
<th>DLS</th>
<th>Control</th>
<th>Model</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
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<td>70.9</td>
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</tr>
<tr>
<td></td>
<td>(Arg190Ser)</td>
<td>T/A</td>
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<td>42.4</td>
<td>30</td>
<td>23.6</td>
<td>dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/A</td>
<td>2</td>
<td>3.0</td>
<td>7</td>
<td>5.5</td>
<td>recessive</td>
</tr>
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<td>rs1049007</td>
<td>G/G</td>
<td>37</td>
<td>56.1</td>
<td>91</td>
<td>71.7</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Ser87Ser)</td>
<td>G/A</td>
<td>27</td>
<td>40.9</td>
<td>31</td>
<td>24.4</td>
<td>dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/A</td>
<td>2</td>
<td>3.0</td>
<td>5</td>
<td>3.9</td>
<td>recessive</td>
</tr>
<tr>
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<td>rs3733549</td>
<td>G/G</td>
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<td>66.7</td>
<td>94</td>
<td>74.0</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Arg192Gln)</td>
<td>G/A</td>
<td>21</td>
<td>31.8</td>
<td>32</td>
<td>25.2</td>
<td>dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/A</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
<td>0.8</td>
<td>recessive</td>
</tr>
<tr>
<td>BMP4</td>
<td>rs17563</td>
<td>T/T</td>
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<td>78</td>
<td>61.4</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Val152Ala)</td>
<td>T/C</td>
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<td>40.9</td>
<td>43</td>
<td>33.9</td>
<td>dominant</td>
</tr>
<tr>
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<td></td>
<td>C/C</td>
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<td>7.6</td>
<td>6</td>
<td>4.7</td>
<td>recessive</td>
</tr>
<tr>
<td>BMP5</td>
<td>rs3734444</td>
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<td>74.2</td>
<td>86</td>
<td>67.7</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Ser37Ser)</td>
<td>T/C</td>
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<td>24.2</td>
<td>38</td>
<td>29.9</td>
<td>dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C/C</td>
<td>5</td>
<td>7.6</td>
<td>6</td>
<td>4.7</td>
<td>recessive</td>
</tr>
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<td>BMP6</td>
<td>rs17557</td>
<td>C/C</td>
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<td>62.7</td>
<td>77</td>
<td>61.1</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Val368Val)</td>
<td>C/G</td>
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<td>35.6</td>
<td>42</td>
<td>33.3</td>
<td>dominant</td>
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<tr>
<td></td>
<td></td>
<td>G/G</td>
<td>1</td>
<td>1.7</td>
<td>7</td>
<td>5.6</td>
<td>recessive</td>
</tr>
<tr>
<td>BMP10</td>
<td>rs2231344</td>
<td>T/T</td>
<td>51</td>
<td>77.3</td>
<td>102</td>
<td>80.3</td>
<td>codominant</td>
</tr>
<tr>
<td></td>
<td>(Asp242Asp)</td>
<td>T/C</td>
<td>15</td>
<td>22.7</td>
<td>24</td>
<td>18.9</td>
<td>dominant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C/C</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.8</td>
<td>recessive</td>
</tr>
</tbody>
</table>

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.
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, 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>
<thead>
<tr>
<th>Haplotype Type</th>
<th>DLS Freq %</th>
<th>Control Freq %</th>
<th>Models OR(95% CI) p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGGTCT HH</td>
<td>5.0 7.6</td>
<td>22 33.3</td>
<td>codominant 0.90(0.57-1.43) 0.67</td>
</tr>
<tr>
<td>H-</td>
<td>22 33.3</td>
<td>43 33.9</td>
<td>dominant 0.91(0.50-1.66) 0.75</td>
</tr>
<tr>
<td>--</td>
<td>39 59.1</td>
<td>72 56.7</td>
<td>recessive 0.79(0.26-2.33) 0.66</td>
</tr>
<tr>
<td>TGGTTGT HH</td>
<td>0 0.0</td>
<td>2 1.6</td>
<td>codominant 0.68(0.35-1.34) 0.26</td>
</tr>
<tr>
<td>H-</td>
<td>14 21.2</td>
<td>33 26.0</td>
<td>dominant 0.71(0.35-1.44) 0.34</td>
</tr>
<tr>
<td>--</td>
<td>52 78.8</td>
<td>92 72.4</td>
<td>recessive 0.00(0.00--) 0.99</td>
</tr>
<tr>
<td>AAGTCT HH</td>
<td>1 1.5</td>
<td>0 0.0</td>
<td>codominant 1.57(0.81-3.02) 0.18</td>
</tr>
<tr>
<td>H-</td>
<td>18 27.3</td>
<td>27 21.3</td>
<td>dominant 1.50(0.76-2.96) 0.25</td>
</tr>
<tr>
<td>--</td>
<td>47 71.2</td>
<td>100 78.7</td>
<td>recessive NA 0.99</td>
</tr>
<tr>
<td>TGGCTCT HH</td>
<td>2 3.0</td>
<td>2 1.6</td>
<td>codominant 1.93(1.04-3.59) 0.04</td>
</tr>
<tr>
<td>H-</td>
<td>18 27.3</td>
<td>19 15.0</td>
<td>dominant 2.19(1.09-4.43) 0.03</td>
</tr>
<tr>
<td>--</td>
<td>46 69.7</td>
<td>106 83.5</td>
<td>recessive 1.95(0.27-14.19) 0.51</td>
</tr>
<tr>
<td>TGATCT HH</td>
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<td>0 0.0</td>
<td>codominant 1.39(0.60-3.19) 0.44</td>
</tr>
<tr>
<td>H-</td>
<td>11 16.7</td>
<td>16 12.6</td>
<td>dominant 1.39(0.60-3.19) 0.44</td>
</tr>
<tr>
<td>--</td>
<td>55 83.3</td>
<td>111 87.4</td>
<td>recessive NA 0.99</td>
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<tr>
<td>TGGTCC HH</td>
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<td>1 0.8</td>
<td>codominant 0.42(0.14-1.26) 0.12</td>
</tr>
<tr>
<td>H-</td>
<td>4 6.1</td>
<td>16 12.6</td>
<td>dominant 0.42(0.13-1.30) 0.13</td>
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<tr>
<td>--</td>
<td>62 93.9</td>
<td>110 86.6</td>
<td>recessive NA 0.99</td>
</tr>
</tbody>
</table>

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.

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

### References


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

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Genotype</th>
<th>DLS</th>
<th>Control</th>
<th>Europe</th>
<th>China</th>
<th>Japan</th>
<th>Sub-Saharan African</th>
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<tbody>
<tr>
<td>BMP2</td>
<td>rs235768</td>
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<td>0.57</td>
<td>0.50</td>
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<td>1.00</td>
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<td></td>
<td></td>
<td>(Arg190Ser)</td>
<td>T/A</td>
<td>0.42</td>
<td>0.24</td>
<td>0.28</td>
<td>0.48</td>
<td>0.32</td>
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<td></td>
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<td></td>
<td>A/A</td>
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<td>0.06</td>
<td>0.15</td>
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<td>0.67</td>
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<tr>
<td></td>
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<td>(Val152Ala)</td>
<td>T/C</td>
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