

Relationship of vitamin D receptor gene polymorphisms with susceptibility, surgical outcome and prognosis of hallux valgus in a Chinese Han population



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ABSTRACT

Background: This study aimed to identify the relationship between the vitamin D receptor (VDR) BsmI gene polymorphism and risk factors, surgical outcome and prognosis of hallux valgus (HV).

Methods: A case-control study was performed on a cohort of 236 HV patients and 236 controls in a Chinese Han population. Detection of the VDR BsmI/G2A polymorphism was performed using restriction fragment length polymorphism–polymerase chain reaction.

Results: We detected a statistically significant difference in the allele distribution of the BsmI polymorphism between cases and controls ($p < 0.01$). Significant loss of hallux valgus angle (HVA) and intermetatarsal angle (IMA) correction was only noted in patients with the bb genotype during the 2-year follow-up period ($p < 0.01$). The average American Orthopaedic Foot and Ankle Society (AOFAS) scores at the 2-year follow-up were decreased in both groups when compared with those at the 6 month follow-up, and 1.45 points more decrease in patients with the bb genotype was observed as compared to those with the BB and Bb genotypes ($p < 0.0001$). The average visual analogue scales (VAS) also had the tendency with more pains in the bb genotype group ($p < 0.0001$). Furthermore, larger numbers of transfer metatarsalgia were found in patients with the bb genotype upon 2-year follow-up ($p = 0.049$).

Conclusions: We report the first candidate gene polymorphism associated with susceptibility, surgical outcome and prognosis of HV in a Chinese Han population. Moreover, development of genetically-based method to predict the surgical outcome accurately and individualized therapy for HV are warranted.

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1. Introduction

Hallux valgus (HV), progressive bunion formation occurring in several stages, is characterized by lateral deviation of the big toe (hallux) and medial deviation of the first metatarsal (metatarsus primus varus). In its later stages, hallux valgus involves progressive subluxation of the first metatarsophalangeal (MTP) joint and transfer metatarsalgia [1,2]. According to a recent study involving patients in America, Germany, Russia, Spain, and China, the incidence of HV is 23% in adults aged 18–65 years and 35.7% among those over 65 [3]. Sim-Fook and Hodgson examined 200 Chinese patients in Hong Kong and observed hallux valgus in 1.9% of barefooters and 30% of shoe-wearers [4]. At present, the incidence of hallux valgus is higher in China, likely due to race, ethnicity and genetic susceptibility. With progression of the disease, mobility is

restricted and quality of life decreases. Although over 100 different osteotomies have been described for the operative treatment of hallux valgus deformity, current mainstream techniques include chevron osteotomy [5], scarf osteotomy [6], ligidus arthrodesis [7], basal osteotomy [8] and hybrid osteotomy (above-mentioned procedures combined with Akin osteotomy) [9]. However, cases of recurrence and associated complications are fairly common, the causes of which remain unknown.

Hallux valgus is generally thought to be associated with age, gender, and footwear choice [1]. Furthermore, recent studies have reported that genetic factors play a critical role in the development of hallux valgus. Pedigree studies have revealed that 63–90% of individuals with HV have a family history of the condition [10]. More recently, HV was found to be highly heritable in the Framingham Foot Study (involving 1370 Caucasian participants of European descent from 429 families) [11] and the Korean Healthy Twin Study (involving 1265 East Asian participants and 206 twin pairs) [12]. The tendency to develop hallux valgus is inherited and maybe associated with several SNPs (Single Nucleotide

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Polymorphisms) [13,14]. However, to the best of our knowledge, no case-control studies have reported the association of a candidate gene polymorphism with hallux valgus.

The actions of vitamin D are mediated via its nuclear receptor, the vitamin D receptor (VDR). VDR is located on chromosome 12 (12q13.11), and most studies have focused on several polymorphisms situated near the 3' end of VDR [15]. The BsmI polymorphism is located in the non-coding region of the VDR gene, which can affect protein levels and coding regions. BsmI has been shown to be in strong linkage disequilibrium with other mutations [16].

VDR plays an important role in skeletomuscular metabolism and bone remodeling, and VDR mutations can result in skeletal deformity. Obermayerpietsch et al. provided the first evidence that the VDR gene may be involved in differences in bone mass density and bone metabolism in cases of ankylosing spondylitis [17]. Consistent evidence has emerged for the association of knee and multi-joint osteoarthritis (OA) with variations in the VDR receptor [18]. In the foot, the acquired deformity is frequently manifested by hallux valgus and can lead to recurrence of postoperative complications. In 2011, a molecular-genetic analysis of 35 unrelated normal and 47 patients with slow bone consolidation after osteotomy for hallux valgus found that the spectrum of polymorphic variants of the VDR gene were related to nonunion [19]. However, the association between the prognosis and other complications of HV with VDR gene polymorphism has not been reported in the literature.

We conducted a case-control study combined with polymerase chain reaction (PCR) assays to analyze the relationship between VDR gene polymorphism and susceptibility, surgical outcome, and prognosis in cases of hallux valgus. Our findings offer a theoretical basis for the pathogenesis, diagnosis, treatment and prognosis of hallux valgus.

2. Patients and methods

This case-control study includes 472 participants (236 patients and 236 controls), recruited from the Foot and Ankle Clinic of Nanjing First hospital, Nanjing Medical University (NJMU). All subjects were ethnically Han Chinese and completed a clinical examination during 2014–2016. Their medical records were all reviewed, and data, including age, sex, surgical procedures, radiographic parameters and follow-up results, were analyzed. The study protocol included three visits (preoperation, 6 months postoperation, and 2 years postoperation). This study was approved by Foot and Ankle Research, Nanjing First Hospital. The protocol was approved by the ethics committee of Nanjing Medical University. Written informed consent was obtained from all participants before enrollment in the study.

2.1. Assessment of hallux valgus

HV was considered to be present if the examiner determined that the lateral deviation of the hallux with respect to the first metatarsal was 15° or more [20]. Controls were considered not to have HV if this criterion was not met.

2.2. Inclusion and exclusion criteria

Inclusion criteria for this study were the presence of symptomatic bunions with radiographic, fully closed growth plates in the foot; normal function of the lower extremities; and failed conservative care for at least 6 months prior to surgery. The study employed a control group of 236 healthy subjects with healthy, asymptomatic feet upon physical examination.

The exclusion criteria for both groups include previous operations on the symptomatic foot; pregnancy or lactation; bone mineral density abnormalities (e.g., radiographically detected bone cysts in the first ray and manifested osteoporosis); neurological pathologies; and participation in other studies 30 days before the start of this study and during the participation in this study.

2.3. Radiographic parameters

All patients in the study group had weight-bearing anteroposterior radiographs of the affected foot taken pre- and postoperatively [21,22]. The parameters measured, as described previously, from these radiographs included the hallux valgus angle (HVA), intermetatarsal angle (IMA), distal articular set angle (DASA), and proximal articular set angle (PASA) (Fig. 1).

2.4. Surgical procedures

All cases were performed by one senior surgeon. The Chevron, Scarf, Basal osteotomies and the Lapidus arthrodesis were performed as the conventional procedures [5–8,23,24]. The hybrid procedure, if indicated, combined the above osteotomies and an Akin osteotomy to correct DASA [9,25]. Transfer metatarsalgia of the lesser toes were treated either by flexor-to-extensor tendon transfer if the dorsal extension deformity of the MTP joint was flexible or by Weil osteotomy if the dorsal extension deformity of the MTP joint was rigid. Cross-over toe deformity was treated by extensor digital brevis tendon transfer or Weil osteotomy. The interphalangeal flexion deformity was treated by resection arthroplasty.

2.5. DNA extraction and genotyping

Peripheral blood was collected from each participant in an EDTA-treated tube. Genomic DNA was extracted from the peripheral blood of all study subjects using a High Pure PCR Template Preparation kit (KGA1343, KeyGEN BioTECH, China).

The BsmI/T2C/rs1544410 polymorphism of the VDR gene was detected by restriction fragment length polymorphism–polymerase chain reaction (RFLP–PCR) according to the protocol of Horst-Sikorska et al. [26] Using a DNA ladder of 100 base pairs (bp) as a reference, we identified the BsmI polymorphism genotypes:



Fig. 1. Pre-operative radiograph demonstrating the angles measured. (A) Hallux valgus angle (HVA). (B) Distal articular set angle (DASA). (C) Proximal articular set angle (PASA). (D) Intermetatarsal angle (IMA).

BB = 358 bp (GG); Bb = 358 bp and 193 bp (GA); and bb = 193 bp and 165 bp lengths (AA); A was the mutation allele. Therefore, the participants were divided into three genotype groups according to the polymorphism: BB group carrying BB genotype; Bb group carrying Bb genotype; and bb group carrying bb genotype.

2.6. Clinical evaluation

Two independent health care professionals assessed the patients preoperatively and at 6 months and 2 years postoperatively for transfer metatarsalgia and clinical outcome scores. X-ray examinations were applied and radiological measurement of above-mentioned parameters were performed at every visit. The outcome scores included visual analogue score (VAS) for pain and the American Orthopaedic Foot and Ankle Society (AOFAS) hallux score for function [27,28]. Postoperative complications were also recorded.

2.7. Statistical analysis

The data analysis was performed using the Statistical Package of Social Science (SPSS, version 17.0; SPSS, Chicago, IL, USA) program and Graphpad Prism 6 Software (GraphPad Software, Inc., San Diego, CA, USA). A Student's t-test was used to compare average pre- and postoperative measurements for age and each angle measured (HVA, IMA, DASA and PASA). Chi-square statistics and one-way analysis of variance (ANOVA) were used to analyze genotype, operative technique and complications. Fisher's exact test was used to analyze gender and alleles. Statistical significance was set at the 0.05 level.

3. Results

3.1. General features and genotyping analysis

Frequencies of the examined VDR (BsmI) alleles in the patient and control groups were shown in Table 1. Two hundred and twenty-six cases of female patients with hallux valgus were enrolled in the patient group, with a mean age of (60.3 ± 8.9) years old. The control group consisted of 187 healthy females with an average age of (56.9 ± 13.7) years old. No significant differences were found in the age and gender distribution between the HV group and control group ($p > 0.05$). In the patient group, the frequency of the VDR BsmI bb genotype (32%) was significantly higher than in the control group (11%), and the frequency of the VDR BsmI b allele (54%) was significantly higher than in the control group (30%) ($p < 0.01$). Statistical analyses showed that the genotype distributions of the BsmI polymorphism in the patient and control groups were in the Hardy–Weinberg equilibrium.

Table 1
Frequencies of selected VDR SNPs in the study population.

		Patients	Controls	<i>p</i>
Age		60.3 ± 8.9	56.9 ± 13.7	0.16
Female n (%)		226 (95.8)	187 (79.2)	0.38
Genotypes	BB	56 (24)	120 (51)	0.00**
	Bb	104 (44)	90 (38)	
	bb	76 (32)	26 (11)	
	b	216 (46)	330(70)	
Alleles	B	256 (54)	142(30)	0.00**
	b	216 (46)	330(70)	
HWB	χ^2	2.97	2.06	–
	<i>p</i>	0.08	0.15	

* $p < 0.05$ (not consistent with HWE).

** $p < 0.01$.

3.2. Relationship between gene polymorphism and surgical procedures

The distribution of the BsmI genotype relative to the five surgical procedures was summarized in Table 2. Surgical procedures included Chevron, Scarf, Lapidus, basal and hybrid osteotomy. No statistically significant correlation was found between BsmI genotype and the choices of surgical procedures (p : 0.14, 0.12, 0.12, 0.08 and 0.06, respectively).

3.3. Relationship between gene polymorphism and prognosis

Correlations between radiographic parameters both pre- and postoperatively and the three SNP groups were analyzed in Fig. 2. The weighted mean HVA decreased from 20.32° preoperatively to 10.85° at 6 months postoperatively (weighted mean and variance: 20.32 ± 15.25 vs. 10.85 ± 7.86, $p < 0.001$) and 11.79° at 2 years postoperatively (weighted mean and variance: 20.32 ± 15.25 vs. 11.79 ± 8.33, $p < 0.001$). The weighted mean IMA decreased from 10.24° preoperatively to 6.94° at 6 months postoperatively (weighted mean and variance: 10.24 ± 9.69 vs. 6.94 ± 6.44, $p < 0.001$) and 7.79° at 2 years postoperatively (weighted mean and variance: 10.24 ± 9.69 vs. 7.96 ± 4.28, $p < 0.001$). Similarly, the weighted mean DASA decreased from 15.31° preoperatively to 7.70° at 6 months postoperatively (weighted mean and variance: 15.31 ± 7.67 vs. 7.70 ± 4.57, $p < 0.001$) and 8.23° at 2 years postoperatively (weighted mean and variance: 15.31 ± 7.67 vs. 8.23 ± 3.94, $p < 0.001$). The weighted mean PASA decreased from 10.67° preoperatively to 6.25° at 6 months postoperatively (weighted mean and variance: 10.67 ± 7.38 vs. 6.25 ± 6.11, $p < 0.001$) and 6.97° at 2 years postoperatively (weighted mean and variance: 10.67 ± 7.38 vs. 6.97 ± 4.21, $p < 0.001$). Overall, HVA, IMA, DASA and PASA were corrected significantly after surgery, but some degrees of correction loss was observed during the 2-year follow-up period. The relationship between the correction loss and gene polymorphism was analysed. A tendency to greater loss of HVA correction was noted in the bb group upon 2-year follow-up when compared to the BB+Bb group (2.20 ± 0.09 vs. 0.4 ± 0.14, $p < 0.001$). Similarly, a tendency to greater loss of IMA correction was noted in the bb group upon 2-year follow-up as compared to the BB+Bb group (1.70 ± 0.12 vs. 0.72 ± 0.13, $p = 0.007$). But no similar trend was found in terms of DASA and PASA correction as the loss of DASA and PASA correction between bb and BB+Bb group did not differ significantly ($p > 0.05$).

Clinically, all patients recovered uneventfully after the surgery and had complete resolution of bunions at the final follow-up. The slight limitation in the motion range of the first MTP joint (total range <75°) was noted in 22 cases due to unaggressive rehabilitation, but none of these patients had a subjective feeling of stiffness. Nine cases of prominent implants was treated by implant removal. There were no overcorrection, non-union, mal-unions or disappointed patients at the final follow-up, except for 13 cases of transfer metatarsalgia with pain under the lesser metatarsal head. Among these patients, only one patient had lesser metatarsal surgery and got a favorable outcome. All osteotomy

Table 2
BsmI genotype distribution relationship with operative techniques of HV (cases).

		BsmI (cases)			Total (n)	χ^2	<i>p</i>
		BB	Bb	bb			
Therapy	Chevron	5	13	8	26	3.91	0.14
	Scarf	7	13	5	25	4.31	0.12
	Lapidus	5	13	7	25	4.31	0.12
	Basal osteotomy	6	14	6	26	5.11	0.08
	Hybrid	33	51	50	134	5.66	0.06

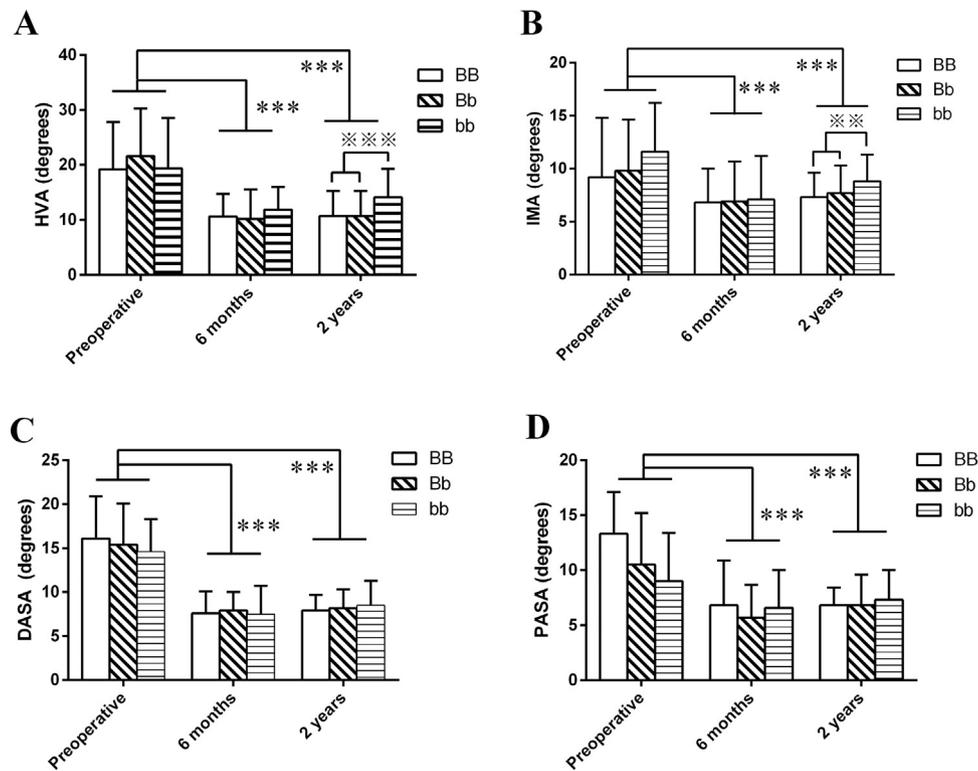


Fig. 2. Evolution of radiographic parameters preoperatively, 6 months and 2 years postoperatively. HVA: hallux valgus angle, IMA: intermetatarsal angle, PASA: proximal articular set angle, DASA: distal articular set angle. *** $p < 0.0001$ (weighted mean and variance, preoperation vs. 6 months or preoperation vs. 2 years). ** $p < 0.01$ and *** $p < 0.0001$ (correction loss, bb vs. BB + Bb).

sites healed successfully. The AOFAS scores and complications both pre- and postoperatively is shown in Fig. 3. The weighted mean and variance of the AOFAS score was 53.75 ± 23.54 preoperatively, 91.84 ± 6.83 at 6 months and 90.81 ± 3.70 at 2 years after surgery, indicating significant improvement after surgery ($p < 0.0001$). Interestingly, the decline of AOFAS scores at 2 year follow-up seemed to be genetically dependent as the values differed significantly between the different genotype groups. The difference in AOFAS scores between the 2-year and 6-month follow-up was 1.45 points lower in the bb group compared to the BB + Bb group (difference between 2-year and 6-month follow-up: bb -2.00 ± 0.29 vs. BB + Bb -0.55 ± 0.36 , $p < 0.0001$). The weighted mean and variance of the VAS scale was 5.96 ± 4.00 preoperatively, 3.23 ± 3.09 at 6 months and 1.60 ± 1.40 at 2 years after surgery, indicating significant improvement after surgery ($p < 0.0001$). The deterioration of VAS scale between the 6-month and 2-year follow-up differed significantly between the different genotype groups as 0.93 points more deterioration of VAS scale was found in the bb group as compared to the BB + Bb group (difference between 2-year and 6-month follow-ups: bb -1.00 ± 0.48 vs. BB + Bb -1.93 ± 0.74 , $p < 0.0001$). The discrepancy of VAS scales between the different genotypes seemed to be contributed by the increasing number of transfer metatarsalgia in the bb group upon 2-year follow-up as compared to the BB + Bb group (10 cases versus 3 cases, $p = 0.049$). Nevertheless, most patients with transfer metatarsalgia showed improvement at the 2-year follow up (119 versus 13 cases, $p < 0.0001$). Therefore, the prognosis of surgical treatment of HV seemed to be genetically dependent, irrespective of the surgical procedures applied.

4. Discussion

Hallux valgus (HV) is a common pathology leading to pain and deformation of the first metatarsophalangeal joint (MTP1) [29]. A

recent meta-analysis regarding the epidemiological changes of hallux valgus reported that the global prevalence reaches up to 23% in those aged between 18- to 65-year [3]. Even prior to the understanding of hallux valgus pathology, the age, gender and footwear have been implicated as etiologies [1]. But it has been increasingly caused by genetic predisposition [10–12]. Heredity is likely to be a major predisposing factor in some patients, with up to 56–90% of patients demonstrating familial tendency [10]. We therefore examined heredity by adjusting age and gender to minimize the potential confounding factors. Two genome-wide association studies of hallux valgus have been described. One conducted in a North Carolina county reported that thirteen SNPs within the MYH13 gene locus were associated with HV [14]. The other was conducted in Caucasian and African Americans, and it was found that SNPs near the AXIN2 gene in men, as well as the ESD gene in women, were associated with HV [13]. Thus, it has been demonstrated that HV-related SNPs vary by region, which might be partially attributed to ethnicity. In the Chinese population, Lam Sim-Fook and Hodgson examined 200 people for the incidence of hallux valgus [4]. In recent years, the incidence of HV has increased in the Chinese Han population due to genetic susceptibility and population growth. To our knowledge, our study is the first report in the literature aimed at assessing the relationship between hallux valgus and vitamin D receptor gene polymorphisms in a Chinese Han population.

Many studies have shown that vitamin D receptor gene polymorphisms regulate bone metabolism and bone remodeling, which in severe cases can manifest as skeletal deformities. Tamura et al. performed a study using genome-wide single nucleotide polymorphism array to demonstrate that hereditary 1,25-dihydroxyvitamin D-resistant rickets (HVDRR) is an autosomal recessive disease caused by biallelic mutations in the vitamin D receptor (VDR) gene [30]. A literature review confirmed that VDR gene is a candidate gene for OA susceptibility [18]. VDR functioning

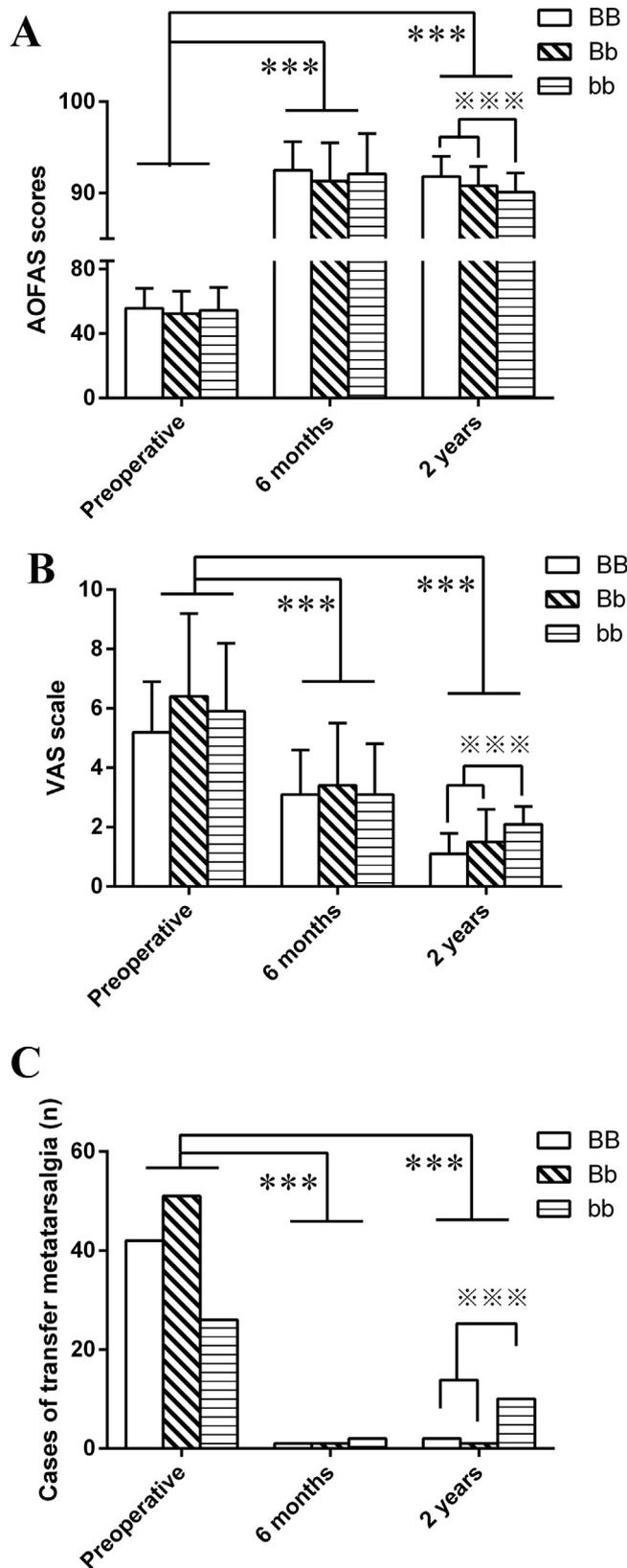


Fig. 3. Evolution of scores and complications preoperatively, 6 months and 2 years postoperatively. AOFAS: American Orthopaedic Foot and Ankle Society score for hallux, VAS: visual analogue scale. *** $p < 0.0001$ (weighted mean and variance, preoperation vs. 6 months or 2 years). ※※※ $p < 0.0001$ (difference between 2-year and 6-month followup, bb vs. BB + Bb).

is influenced by gene polymorphisms, among which BsmI is one of the most frequently investigated polymorphisms and may be in linkage disequilibrium with other functional mutations as several mutations occurring in this intronic region [16]. In this study, we found that VDR BsmI gene polymorphism was a risk factor associated with HV, with bb carriers identified as the susceptible population. This may be explained by the fact that BsmI VDR gene polymorphism can serve as a genetic marker in coupling bone resorption to bone formation [31].

We found that VDR BsmI genotypes were not significantly correlated with the surgical procedures used to treat hallux valgus. This is likely because the choice of procedure is specific to the source of deformity, the patient's unique anatomy, and the patient's goals and expectations for correction [32]. The surgical procedures used to treat hallux valgus have largely focused on individualized therapeutic planning to ensure that the selected procedure is appropriate for the individual patient [33]. Two recent papers have reported that VDR is not significantly correlated with the surgical procedure selected in cases of dental implants and lumbar disc herniation [34,35]. However, an investigation of VDR, GDF5, COL1A1, THBS2 and CHST polymorphisms revealed that while VDR was not related to surgical procedures, the GT allele of Col1A1 was associated with a certain procedure of full endoscopic discectomy in the treatment of symptomatic lumbar disc herniation [35]. Thus, further studies involving larger patient cohorts are needed to verify the association between gene polymorphism and the choice of HV surgical procedures.

Although the surgical technique of HV has been improved significantly in the world, recurrence and other complications after hallux valgus surgery cannot be totally eliminated. The reason has not been clarified. Pentikainen et al. reported a radiological recurrence of the hallux valgus deformity in 64.7% of cases after proximal medial opening wedge osteotomy [36]. Another report showed that radiological recurrence of the hallux valgus deformity of 15° or more was especially common at long-term follow-up after distal chevron osteotomy [37]. Therefore, considerable inter-individual variations in prognosis could present among patients even treated by a same surgery, and this discrepancy could be contributed by individual genetic factors. In 2011, one study investigated the association between VDR polymorphism and postoperative morbidity (nonunion) after osteotomy and found that the incidence of nonunion at the osteotomy site was associated with certain VDR genotype [19]. Emerging evidence suggests that the association between VDR and prognosis merits exploration. Compared with BB+Bb patients, bb carriers had higher incidence of correction loss and transfer metatarsalgia and lower functional scores. This is probably because BsmI polymorphism led to varied degrees of soft tissue and bone metabolism and remodeling, which resulted in anatomical changes and abnormal plantar pressures that can induce pain and decrease motor function.

Genetic factors play an important role in the etiology and prognosis of hallux valgus in this Chinese Han population. Although we noted some inconsistencies, the significant influence on polymorphic sites persisted. Several limitations of our study deserve mention. (1) The study population was selected entirely from a local hospital. Broader study areas and various ethnic groups should be explored in future studies. (2) The sample sizes of the treatment groups according to the selected surgical procedures were relatively small and may therefore be subject to bias; larger samples are required. (3) The prognostic factors analyzed in the patient group were inadequate. The effects on multifactorial interaction should be taken into consideration. Further studies will require more accurate and multifaceted measures to achieve the study objectives of identifying novel methods for the early

diagnosis, individualized therapy and assessment of outcome in cases of hallux valgus.

5. Conclusions

1. The VDR BsmI gene polymorphism was associated with genetic predisposition to hallux valgus. bb carriers had an increased risk of hallux valgus. A significant positive correlation was observed between the b allele and risk of hallux valgus.
2. There were no significant correlations between VDR BsmI gene polymorphism and the surgical procedures selected.
3. The VDR BsmI gene polymorphism was correlated with the prognosis of the hallux valgus. Patients carrying the bb allele had a somewhat poorer outcome as compared with other genotype patients.

Conflicts of interest

None.

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