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Impact of Vitamin D Receptor Genotypes on Taiwan Hallux Valgus

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Abstract. *Background/Aim: Hallux valgus (HV) is the most prevalent deformity affecting the forefoot; however, its genetic etiology remains unclear. In the literature, vitamin D receptor (VDR) genotypes have been reported to be associated with the risk of skeletal malformations accompanied by inflammation. This study aimed to examine the hypothesis that VDR genotypes are associated with the risk of HV. Materials and Methods: The VDR rs731236, rs1544410, rs2228570 and rs7975232 genotypes of 150 HV patients and 600 non-HV subjects were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology and examined regarding their associations with HV risk. Results: The results showed that none of the genetic frequency distributions of VDR rs731236, rs1544410, rs2228570, or rs7975232 were significant between the HV cases and non-HV controls (p for trend=0.4055, 0.2170, 0.7220, 0.5509, respectively). Additionally, allelic frequency analysis showed that none of the allelic frequencies of VDR rs731236, rs1544410, rs2228570, or rs7975232 were significantly distributed (p=0.2285, 0.1572, 0.9278, and 0.5547, respectively). Furthermore, stratified analysis showed that no correlation was observed between VDR rs731236 and different age groups (either younger or older than 51) or sex (p=0.3953 and p=0.9576). Moreover, no correlation was found between VDR rs731236 genotype and the risk of HV in individuals within subgroups of height, weight, or body mass index (BMI) (p=0.8317, 0.5346, and p=0.8783, respectively). Conclusion: VDR rs731236, rs1544410, rs2228570, and rs7975232 may not serve as indicators for a higher risk of HV.*

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Hallux valgus (HV), commonly known as a bunion, has since long been recognized as one of the most prevalent chronic foot complaints worldwide (1). It is characterized by medial pain in the big toe and difficulties with footwear (2, 3). Despite extensive research, the precise underlying causes of HV remain incompletely understood. HV is more commonly observed in women than in men, with a reported ratio as high as 15:1 in certain studies. Tight-fitting shoes and high heels have been identified as contributing factors to this condition (4). The prevalence of HV is approximately 23.0% among adults aged 18 to 65 years and increases to 35.7% in adults over 65 years of age (5). When focusing on adult females, the occurrence of HV deformity can be as high as 30.0%, with a higher prevalence in women compared to men (5). In its later stages, HV involves progressive

subluxation of the first metatarsophalangeal joint and bunion inflammation (2). Few studies have investigated the potential impact of genetic variations on HV etiology from an epidemiological perspective. For instance, a typical genome-wide association study reported that HV risk was significantly associated with rs9675316 (chr17q23-q24 near *AXIN2*) for males and with rs7996797 (chr13q14.1-q14.2 near *ESD*) for females (6). Another genome-wide association study proposed that *MYH13* genotypes were associated with the risk of HV (7). In recent years, candidate-gene-based studies for HV have significantly grown, but a clinically practicable marker remains unavailable to date.

Vitamin D and its receptors are pivotal in bone metabolism and the prevention of bone diseases (8-10). The *vitamin D receptor (VDR),* located on human chromosome 12, plays a crucial role in numerous biological processes (11, 12). Among the polymorphic sites within the VDR gene, rs731236, rs1544410, rs2228570, and rs7975232 have been extensively studied, particularly for their association with bone diseases, such as osteoarthritis (13, 14), rickets (15-17), spondylitis (18-20), and Gaucher disease (21-23). In 2018 and 2019, Tao and his colleagues have announced that *VDR* rs731236 and rs1544410 could serve as novel markers in HV (24, 25).

Considering the characteristics of HV and the pivotal role of the *VDR* gene and protein in bone metabolism and immune regulation, we hypothesized that genotypes of *VDR* genotypes might contribute to determining individual susceptibility to HV. Therefore, in the present study, we aimed to examine the association between *VDR* rs731236, rs1544410, rs2228570, and rs7975232 genotypes and HV risk in a Taiwanese population, comprising 150 HV cases and 600 non-HV controls.

Materials and Methods

Recruitment of HV cases and non-HV controls. Data collection for the study was conducted at the China Medical University Hospital, a medical center situated in central Taiwan. A total of 150 unrelated individuals diagnosed with HV were enrolled as cases between 2020 and 2024. To evaluate HV, a laminated foot diagram featuring two intersecting lines set at 15 degrees was employed (26). Participants stood on the diagram, positioning the medial edge of one foot against one line and aligning their first metatarsophalangeal joint with the apex of the two lines. HV was deemed present if the angle of the great toe exceeded 15 degrees on either foot. For the control group, four controls per HV case were chosen from the Health Examination Center of China Medical University Hospital. Controls were sex- (exactly the same) and age-matched (within ±5 years) to each patient. Importantly, non-HV controls had no familial relationship with each other and all of them were Taiwanese citizens. During pre-screening and matching, individuals with incomplete demographic data regarding age, sex, height, weight, and family history of HV were excluded. Additionally, potential control candidates displaying symptoms, such as osteoarthritis, osteoporosis, or osteopenia were further excluded. A total of 600 non-HV control subjects were included for genotyping experiments and subsequent data analysis. Written informed consent was obtained from each participant, and 3-5 ml of venous blood was collected for genotyping experiments under the supervision and guidance of the Institutional Review Board of China Medical University Hospital (CMUH109-REC3-091). All clinical investigations and records adhered to the principles outlined in the Declaration of Helsinki. Table I provides a summary of the selected demographic and clinical characteristics of all study participants.

Table I. *Subject characteristics and spatiotemporal parameters of the hallux valgus and control groups.*

	Controls (n=600)	Cases (n=150)	*p*-Value
Age, years	50.50±14.02	51.33±20.17	0.8030
Sex			1.0000
Males, n	120 (20.0%)	30 (20.0%)	
Females, n	480 (80.0%)	120 (80.0%)	
Height, m	1.60±0.09	1.60±0.09	0.2249
Mass, kg	61.40±9.92	61.01±11.39	0.2714
Body mass index	23.79±2.66	23.62±4.20	0.5494

Age, height, mass, and body mass index were analyzed by unpaired Student's *t*-test; sex is analyzed by Chi-square test with Yates' correction; statistical significance is set as *p*-Value less than 0.05.

DNA preparation and storage. In this study, DNA extraction was carried out on peripheral blood leukocytes obtained from each participant. The QIAamp blood mini kit (Qiagen, Valencia, CA, USA) was utilized for DNA extraction, following standard laboratory protocols (27, 28). The extracted DNA samples were then stored at –80˚C for long-term preservation. Additionally, the DNA samples underwent simultaneous dilution, aliquoting, and preparation as a working stock for genotyping purposes, adhering to established protocols (29-31). The working stock DNA samples were stored at -20˚C until further analysis.

Determination of vitamin D receptor genotypes among Taiwanese HV population. Blood samples (2 ml each) were collected *via* atraumatic venipuncture into trisodium citrate tubes. Genomic DNA was then extracted from leukocytes. The four polymorphic sites of the *VDR* gene (rs731236, rs1544410, rs2228570, and rs7975232) were genotyped using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) methodology. Specific primers and restriction enzymes were selected and designed at the Terry Fox Cancer Research Laboratory. Information regarding the polymorphic sites, forward and reverse primer sequences, corresponding restriction enzymes, and resulting DNA fragments has been summarized in Table II.

In summary, the PCR cycling conditions were as follows: an initial denaturation step at 95˚C for 5 min, followed by 35 cycles of denaturation at 95˚C for 30 s, annealing at 54˚C for 30 s, elongation at 72˚C for 1 min, and a final extension at 72˚C for 7 min. Following the PCR procedures, the PCR products underwent enzymatic digestion (New England Biolabs, Beverly, MA, USA) according to the manufacturer's instructions. Subsequently, the digested products were visualized *via* agarose gel electrophoresis using ethidium bromide staining under UV light. All genotypic analyses were

Table II. *Summary the polymorphic sites, paired primer sequences, restriction enzymes and DNA fragments after enzyme digestions for vitamin D receptor polymorphic sites.*

Polymorphic sites	Primer sequences (5'→3')	Restriction enzymes	Genetic variants	DNA fragments, bp
rs731236	Forward: TTGGCATAGAGCAGGTGGCT	*Taq* I	A	261
	Reverse: ATCACCGGTCAGCAGTCATA		G	173+88
rs1544410	Forward: GACCTCATCACCGACATCAT	*Bsm* I	T	596
	Reverse: GAAGCTGAACTTGCATGAGG		C	343+253
rs2228570	Forward: CCGCATGTTCCATGGACATT	*BtsC* I	G	501
	Reverse: AGCTGATTCCAAGCCATGCT		A	264+237
rs7975232	Forward: TTGGCATAGAGCAGGTGGCT	*Hae* I	A	261
	Reverse: ATCACCGGTCAGCAGTCATA		C	168+93

independently repeated by at least two researchers listed as authors and acknowledged in a blinded manner. The results of the genotyping were found to be 100% concordant with each other.

Statistical analysis. The continuous variable, age, was expressed as the mean±standard deviation. To compare the distribution of age between the case and control groups, the unpaired Student's *t*-test was employed. For all other comparisons among dichotomous variables, such as assessing the associations between *VDR* polymorphisms and the risk of HV, Pearson's chi-square test with Yates' correction (when all n≥5) or Fisher's exact test (when any n<5) was utilized. Odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were calculated for each individual to evaluate the associations. The significance level (alpha) was set at 0.05, and all tests were two-tailed; any *p*-value less than 0.05 was considered statistically significant.

Results

Analysis of basic characteristics between the HV and non-HV control groups. The frequency distributions of age, sex, height, weight, and BMI were compared between the 150 HV patients and the 600 non-HV control subjects (Table I). During the matching process, the control subjects were meticulously matched with the HV patients in terms of age (within±5 years) and sex. Statistical analysis revealed no significant differences in these variables between the two groups ($p>0.05$) (Table I). Furthermore, there were no significant differences observed in the distributions of height, weight, or BMI between the HV patients and the non-HV control subjects (all $p>0.05$) (Table I).

Association of VDR genotypes with HV risk. The genotypic analysis for *VDR* rs731236, rs1544410, rs2228570, and rs7975232 among the 150 HV patients and the 600 non-HV control subjects is presented in Table III. Firstly, the genotypic distribution of all *VDR* polymorphic sites in the control group was found to be in accordance with the Hardy-Weinberg equilibrium ($p=0.1538$, $p=0.0957$, $p=0.7101$, and $p=0.2262$, respectively). Secondly, non-significant differences in the genotypic frequency distributions of *VDR* rs731236, rs1544410, rs2228570, and rs7975232 were observed between the HV cases and non-HV controls (p for trend=0.4055, 0.2170, 0.7220, and 0.5509, respectively) (Table III). In detail, the heterozygous AG or homozygous GG genotypes of *VDR* rs731236 did not show any significant association with HV risk (OR=1.25 and 2.09, 95%CI=0.76-2.06 and 95%CI=0.52-8.47, $p=0.4468$ and $p=0.5282$, respectively). Furthermore, in the recessive model, the comparison of individuals carrying the GG genotype with those carrying the AA or AG genotype revealed a 2.02-fold odds ratio for HV (95%CI=0.50-8.17, $p=0.3937$, Table III). In the dominant model, individuals carrying the AG or GG genotypes exhibited a non-significantly altered risk of HV (OR=1.18, 95%CI=0.73-1.88, $p=0.5821$) compared to those with the AA genotype (Table III). Similarly, no differential distributions of *VDR* rs1544410, rs2228570, or rs7975232 genotypes were observed among the subjects in any of the models examined (Table III).

Association of VDR allelic frequencies with HV risk. To further corroborate the preliminary findings presented in Table III, we conducted allelic frequency analysis to evaluate the contribution of *VDR* polymorphic sites to HV risk. The results are displayed in Table IV. The distribution of variant alleles for *VDR* rs731236, rs1544410, rs2228570, or rs7975232 showed no significant association ($p=0.2285$, $p=0.1572$, $p=0.9278$, and $p=0.5547$, respectively, Table IV). Specifically, individuals carrying the variant G allele at *VDR* rs731236 exhibited a 1.34-fold odds ratio (95%CI=0.87-2.06) for HV compared to those carrying the wild-type A allele (Table IV). Similarly, individuals carrying the variant T allele at *VDR* rs1544410 had a 1.40-fold odds ratio (95%CI=0.91-2.17) for HV compared to those carrying the wild-type C allele (Table IV). Likewise, individuals carrying the variant A allele at *VDR* rs2228570 showed a 1.02-fold odds ratio (95%CI=0.79-1.31) for HV compared to those carrying the wild-type G allele (Table IV). Furthermore, individuals carrying the variant A allele at *VDR* rs7975232 demonstrated a 1.10-fold odds ratio (95% CI=0.83-1.45) for HV compared to those carrying the wild-type C allele (Table IV).

Table III. *Distribution of vitamin D receptor genotypes among the controls and patients with hallux valgus.*

Genotype	Frequency, n (%)		OR (95%CI)	*p*-Value[a]
	Cases (n=150)	Controls (n=600)		
rs731236				
AA	123 (82.0)	514 (85.7)	1.00 (Reference)	
AG	24 (16.0)	80 (13.3)	1.25 (0.76-2.06)	0.4468
GG	3 (2.0)	6 (1.0)	2.09 (0.52-8.47)	0.5282
p_{trend}				0.4055
p_{HWE}				0.1538
Carrier comparison				
AA+AG	147 (98.0)	594 (99.0)	1.00 (Reference)	
GG	3 (2.0)	6 (1.0)	2.02 (0.50-8.17)	0.3937
AA	123 (82.0)	514 (85.7)	1.00 (Reference)	
AG+GG	27 (18.0)	96 (14.3)	1.18 (0.73-1.88)	0.5821
rs1544410				
CC	124 (82.7)	518 (86.3)	1.00 (Reference)	
CT	22 (14.7)	76 (12.7)	1.21 (0.72-2.02)	0.5552
TT	4 (2.6)	6 (1.0)	2.78 (0.77-10.02)	0.1128
p_{trend}				0.2170
p_{HWE}				0.0957
Carrier comparison				
CC+CT	146 (97.4)	594 (99.0)	1.00 (Reference)	
TT	4 (2.6)	6 (1.0)	2.71 (0.76-9.74)	0.1195
CC	124 (82.7)	518 (86.3)	1.00 (Reference)	
CT+TT	26 (17.3)	82 (13.7)	1.32 (0.82-2.15)	0.3106
rs2228570				
GG	40 (26.7)	174 (29.0)	1.00 (Reference)	
AG	79 (52.7)	294 (49.0)	1.17 (0.76-1.79)	0.5385
AA	31 (20.6)	132 (22.0)	1.02 (0.61-1.72)	0.9359
p_{trend}				0.7220
p_{HWE}				0.7101
Carrier comparison				
GG+AG	119 (79.4)	468 (78.0)	1.00 (Reference)	
AA	31 (20.6)	132 (22.0)	0.92 (0.59-1.43)	0.8076
GG	40 (26.7)	174 (29.0)	1.00 (Reference)	
AG+AA	110 (73.3)	426 (71.0)	1.12 (0.75-1.68)	0.6420
rs7975232				
CC	79 (52.7)	322 (53.7)	1.00 (Reference)	
AC	54 (36.0)	227 (37.8)	0.97 (0.66-1.43)	0.9532
AA	17 (11.3)	51 (8.5)	1.36 (0.74-2.48)	0.4015
p_{trend}				0.5509
p_{HWE}				0.2262
Carrier comparison				
CC+AC	133 (88.7)	549 (91.5)	1.00 (Reference)	
AA	17 (11.3)	51 (8.5)	1.38 (0.77-2.46)	0.3565
CC	79 (52.7)	322 (53.7)	1.00 (Reference)	
AC+AA	71 (47.3)	278 (46.3)	1.04 (0.73-1.49)	0.8981

OR: Odds ratio; CI: confidence interval. [a]Based on Chi-square test with Yates' correction (all n≥5) or Fisher's exact test (any n<5). p_{trend}, *p*-Value for trend analysis; p_{HWE} *p*-Value for Hardy-Weinberg Equilibrium; statistical significance is set as *p*-value less than 0.05.

Interaction analysis of VDR genotypes and demographic factors. We aimed to investigate the impacts of *VDR* genotypes and demographic factors on HV risk. Firstly, subgroup analysis based on age was conducted to assess the distribution of *VDR* rs731236 genotypes among HV patients older and younger than 51 years of age. The results showed no significant difference in genotype distribution between the two age groups (OR=1.58, 95%CI=0.68-3.67, *p*=0.3953, Table V). Secondly, the distribution of *VDR* rs731236 genotypes based on sex was examined, and no significant difference was observed among

Table IV. *Allelic frequencies for vitamin D receptor genotypes among the controls and patients with hallux valgus.*

Allelic type	Frequency, n (%)		OR (95%CI)	*p*-Value[a]
	Cases (n=300)	Controls (n=1,200)		
rs731236				
A	270 (90.0)	1,108 (92.3)	1.00 (Reference)	
G	30 (10.0)	92 (7.7)	1.34 (0.87-2.06)	0.2285
rs1544410				
C	270 (90.0)	1,112 (92.7)	1.00 (Reference)	
T	30 (10.0)	88 (7.3)	1.40 (0.91-2.17)	0.1572
rs2228570				
G	159 (53.0)	642 (53.5)	1.00 (Reference)	
A	141 (47.0)	558 (46.5)	1.02 (0.79-1.31)	0.9278
rs7975232				
C	212 (70.7)	871 (72.6)	1.00 (Reference)	
A	88 (29.3)	329 (27.4)	1.10 (0.83-1.45)	0.5547

CI: Confidence interval; OR: odds ratio. [a]Based on chi-square test with Yates' correction; statistical significance is set as *p*-value less than 0.05.

Table V. *Correlation between vitamin D receptor rs731236 genotype and demographic features of 150 HV patients.*

Index	Subgroup	Patients, n	*VDR* rs731236 genotype, n (%)		OR (95%CI)	*p*-Value[a]
			AA	AG+GG		
Age	≤51 Years	75	64 (52.0)	11 (40.7)	1.00 (Reference)	
	>51 Years	75	59 (48.0)	16 (59.3)	1.58 (0.68-3.67)	0.3953
Sex	Male	30	24 (19.5)	6 (22.2)	1.00 (Reference)	
	Female	120	99 (80.5)	21 (77.8)	0.85 (0.31-2.33)	0.9576
Height	≤159	75	62 (50.4)	13 (48.1)	1.00 (Reference)	
	>159	75	61 (49.6)	14 (51.9)	1.09 (0.48-2.52)	0.8317
Weight	≤59	78	62 (50.4)	16 (59.3)	1.00 (Reference)	
	>59	72	61 (49.6)	11 (40.7)	0.70 (0.30-1.63)	0.5346
BMI	≤23.34	77	64 (52.0)	13 (48.1)	1.00 (Reference)	
	>23.34	73	59 (48.0)	14 (51.9)	1.17 (0.51-2.69)	0.8783

CI: Confidence interval; OR: odds ratio; VDR: vitamin D receptor. [a]Based on Fisher's exact test with Yates' correction.

males or females (OR=0.85, 95%CI=0.31-2.33, *p*=0.9576, Table V). Thirdly, potential interactions between *VDR* rs731236 genotypes and height on HV risk were explored. The analysis revealed no significant differences in genotype distribution between individuals with a height less than or equal to 159 cm and those higher than 159 cm (OR=1.09, 95%CI=0.48-2.52, *p*=0.8317, Table V). Fourthly, interactions between *VDR* rs731236 genotypes and weight on HV risk were investigated. The analysis identified a cut-off point at 59 kg, and seven individuals met the criteria and were grouped into subgroup 1. The results indicated that *VDR* rs731236 genotypes did not have joint effects with weight in determining personal susceptibility to HV (OR=0.70, 95%CI=0.30-1.63, *p*=0.5346, Table V). Lastly, the potential interaction between *VDR* rs731236 genotypes and BMI in relation to HV risk was explored. The findings revealed no significant differences in genotype proportions among individuals with higher (>23.34) or lower (≤23.34) BMI (OR=1.17, 95%CI=0.51-2.69, *p*=0.8783, Table V). We also analyzed the *VDR* rs1544410, rs2228570, rs7975232 genotypes and demographic factors on HV risk, while no significance was found among the comparisons (data not shown).

Discussion

Vitamin D and its receptors are recognized for their beneficial effects on bone health (32-34). Existing literature suggests that the vitamin D endocrine system plays a crucial role in calcium metabolism, immune modulation, and proliferation and differentiation of various cell types including keratinocytes, osteoblasts, cancer cells, and T-cells (35-37). Among the genetic polymorphisms, *VDR* rs731236,

rs1544410, rs2228570, and rs7975232 have been extensively studied due to their significant associations with bone mineral density. However, their relationships with HV have not been thoroughly elucidated. In our current study, we found no significant difference in the proportion of individuals with the *VDR* variant genotype in the HV patient group compared to the non-HV healthy control group across the four VDR polymorphic sites (Table III). Additionally, no differential allelic distribution was observed among the four *VDR* polymorphic sites (Table IV). Furthermore, there was no variation in the percentage of individuals carrying the variant *VDR* rs731236 genotypes across different age groups, sex, heights, weights, or BMIs (Table V).

In 2018, Tao and his colleagues initially reported an association between *VDR* rs731236 and rs1544410 and the risk of HV in the Chinese population in Nanjing (24). They identified variant alleles as novel risk markers for HV. Their study included 200 control samples and 208 HV cases (24). Subsequently, in 2019, the same research group reported that *VDR* rs1544410 could serve as both a prognostic marker for surgical outcome and a diagnostic marker (25). The size of both the control and case groups increased from 200:208 to 236:236, respectively. Notably, the distribution of CC, CT, and TT genotypes at *VDR* rs1544410 shifted from 57, 98, and 45 in 2018 to 120, 90, and 26 in 2019, indicating that the inclusion of control subjects may significantly influence the results, particularly regarding the minor TT genotype(s). Additionally, the frequencies of the minor allele T in the control group were 47.0% (2018) and 30.0% (2019), respectively. In contrast, our study found no association of either *VDR* rs731236 or rs1544410 with HV risk in a Taiwanese population (Table III). The minor allele T frequency in our population for *VDR* rs1544410 is 92.7%, closely resembling that of the East Asian population (93.9% from 1170 samples) as reported on the NCBI website (38). Overall, their findings may need to be revised and the effects of *VDR* rs731236 and rs1544410 on HV should be validated in diverse and larger populations. As for *VDR* rs2228570 and rs7975232, the tentative conclusion of no positive association remains consistent in both Chinese and Taiwanese studies.

We have explored the potential combined influence of *VDR* genotypes with age, sex, height, weight, and BMI on HV risk (Table V). Regarding the impact of age on HV, it's undeniable that the prevalence of hallux valgus increases with age. While age may not affect perioperative, functional, or subjective outcomes following HV surgery based on questionnaire studies, elder patients should be mindful of the higher risk of recurrence following surgical correction (39). We found no combined effects of *VDR* genotypes and age on HV risk (Table V and data not shown). In 2017, Bao and his colleagues reported no significant differences in differential pediatric femoral neck levels of bone mineral density with variant *VDR* rs1544410 genotypes (40).

It is evident that females are more prone to developing HV, as reflected in our study with a female-to-male ratio of about 4:1 (Table I). In the introduction section, we noted an intriguing HV genotyping study that reported a sex-specific association with HV, with the strongest associations observed near the *AXIN2* gene for males and near the *ESD* gene for females (6). Concerning the impact of sex and *VDR* genotypes on HV, we found no combined effects of *VDR* genotypes and sex on HV risk (Table V). It was recently reported that rs1544410 and rs2228570 genotypes of the *VDR* gene may be associated with the process of decreasing bone mass density in men, contributing to aging (41). However, the detailed mechanism remains unclear in current knowledge.

Despite our diligent efforts in genotyping and analysis, this study had several limitations that warrant acknowledgment. Firstly, the absence of recorded family history of HV limited the exploration of correlations between diagnostic indices and hereditary factors. Secondly, the lack of HV sample collection prevented the investigation of differential expression of VDR mRNA and protein levels among participants, as well as the assessment of inter-individual variations in HV patients. Most importantly, the inability to measure serum vitamin D concentrations precluded the assessment of their relationship with *VDR* genotypes. Thirdly, the relatively small sample size, particularly in subgroup analyses as presented in Table V, may introduce bias and diminish the statistical power of our findings. Lastly, the complete etiology of HV has not been fully elucidated, including its association with bone mineral density, necessitating further exploration and understanding.

In conclusion, our study suggests that none of the four polymorphic sites at *VDR*, namely rs731236, rs1544410, rs2228570, and rs7975232, can serve as reliable predictive markers for HV risk. Further research is needed to elucidate the mechanisms by which vitamin D supplementation and/or bone mineral density may impact the etiology of HV.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research design: Kuo CC, Bau DT, and Tsai CH; patient and questionnaire summaries: Kuo CC, Chang HW, and Tsai CH; experimental work: Lin TC, Wang YC, Wu WT, and Tsai CW; data clearance and identification: Yang YC, Mong MC, and Hsu SW; statistical analysis: Mong MC, Wu WT, and Lin TC; manuscript writing: Kuo CC, Tsai CH, Tsai CW, and Bau DT; review and revision: Chang WS, Tsai CW and Bau DT.

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