ORIGINAL ARTICLE

Association of Vitamin D Receptor Gene *BsmI* (rs1544410) Polymorphism with Bone Speed of Sound, Serum Vitamin D Concentration and Isokinetic Muscular Performance in Malay Teenage Females

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ABSTRACT

Introduction: This study was carried out to examine the association of Vitamin D receptor (*VDR*) gene *BsmI* (rs1544410) polymorphism with bone speed of sound, serum vitamin D concentration, and muscular peak torque and power in teenage female athletes and non-athletes of Malay origin. **Materials and methods:** Sixty young female athletes and non-athletes were recruited for this study. Deoxyribonucleic acid (DNA) was derived from the blood and genotyping of *VDR* gene *BsmI* polymorphism was carried out. Bone speed of sound (SOS), serum vitamin D concentration, and muscular peak torque (an indicator of muscular strength) and power were also measured. **Results:** Athletes with bb genotype had significantly greater ($p<0.05$) bone SOS in the arm, whilst those with Bb genotype had significantly greater ($p<0.05$) bone SOS in the leg, when compared to athletes with BB genotype respectively. Non-athletes with BB genotype were found to have significantly higher ($p<0.01$) flexion peak torque per body weight and isokinetic extension in the leg compared to those with Bb genotype. In addition, the non-athletes with BB and Bb genotype exhibited significantly higher arm isokinetic flexion peak torque ($p<0.05$) when compared to non-athletes with bb genotype. No significant associations were observed between *BsmI* genotypes with serum vitamin D concentration in athletes group and non-athletes group respectively. **Conclusion:** *VDR BsmI* bb and Bb genotypes seems to be associated with better bone health status in Malay teenage female athletes. In addition, *VDR BsmI* BB and Bb genotype may also be associated with higher muscular strength in Malay teenage female non-athletes.
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Keywords: Bone speed of sound, Isokinetic muscular peak torque, Malay athletes, Polymorphism, *Vitamin-D receptor (VDR)* gene

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INTRODUCTION

Genetic factors are important particularly in the selection or talent identification of elite athletes based on their athletic or physical performance. Genetic factors have been reported to influence approximately 66% of the variance in athletic performance. The remaining difference could be attributed to factors associated with the environment (1). Genetics have been shown to have a significant impact on various aspects of athletic performance, such as muscular power, endurance, strength, muscle fiber size and composition, coordination and flexibility (2). It is generally known and accepted that gene variants which may impact one's ability to perform physically in one population might not have the same impact in another population, and genotype as well as phenotype variation do exist in different ethnicities and population (3, 4, 5).

One of the essential nutrients for the human body is vitamin D, and its effect is mediated by vitamin D receptor (*VDR*) (6). Vitamin D in the body can be obtained from any diet intake or reaction generated from available ultraviolet (UV) sunlight. Vitamin D3 is yielded as a consequence of exposure of the skin to UV light, i.e. via photolysis of 7- dehydrocholesterol (7-9). Then, it is activated by sequential hydroxylation in the kidney and liver. In the liver, the activated vitamin D3 undergoes the first 25-hydroxylation to generate

25-hydroxyvitamin D3 (8). This molecule disseminates and binds to transport proteins of vitamin D that are used to determine vitamin D status. The next phase of hydroxylation occurs mainly in the kidney to produce 1α, 25-dihydroxyvitamin D3. This molecule binds to the *VDR* and subsequently controls the transcription of target genes related to the homeostasis of calcium (8,10).

Vitamin D is essential for various biological functions like cell proliferation, cell differentiation and calcium homeostasis (11). It is also been reported to be a prime regulatory factor in calcium homeostasis as well as bone metabolism (12-14). Vitamin D hormone is bound to receptors in its target cells, regulating the synthesis of various types of proteins engaged in the transportation and use of calcium. Vitamin D and its receptor are also vital for typical development of skeletal muscle and in enhancing muscular performance (15).

The receptor for vitamin D actions comprised of two domains, i.e. a domain that connects to DNA and a domain that connects to a hormone. These domains pair up with a similar protein, 9-cis retinoic acid receptor (RXR), and together they bind to the DNA (16). The *VDR* gene contains 8 introns and 9 exons and is found on chromosome 12 (12q13.11). A genome-wide analysis has identified more than 100 types of single nucleotide polymorphisms (SNPs) in the *VDR* gene (17, 18). The common SNPs in the *VDR* gene are characterized by their specific genomic positions: *BsmI* (rs1544410) is located in intron 8, FokI (rs2228570) in the 5' untranslated region (UTR), TaqI (rs731236) in exon 9, and ApaI (rs7975232) in intron 8 of the *VDR* gene (19).

VDR BsmI BB genotype has been reported to be associated with poor density of bone mineral in premenopausal black and white females (20). Nevertheless, another study reported that there was no correlation between *VDR* genotypes and bone mineral density and in prepubertal American girls of Mexican descent (21). *VDR* genotype has been shown to be correlated with muscular strength in Swedish premenopausal females (22) and elderly men (23). *VDR* genotype was also found to be connected to fat-free mass in older males (24). Geusens et al. (25) reported that in elderly, the existence of the *BsmI* single nucleotide polymorphism (SNP) in the *VDR* gene was associated with muscle strength of the quadriceps (25).

The frequencies of SNPs vary in different ethnicities (26). Regarding research studies which investigated genetic variants and athletic performance in Malaysia, Li et al. (3) revealed a correlation between *ACE* gene polymorphisms and strength and power of muscles in Malay university level female athletes and non-athletes. Other studies in Malaysia have investigated the association between gene variants and athleticism, including a research on the *Alpha-Actinin-3 (ACTN3) R/X* gene polymorphism and its impact on physical performance among the multi-ethnic Malaysians (4), and another study on the *Angiotensin Converting Enzyme (ACE) I/D* gene polymorphism in well-trained Malaysian athletes (5). However, to the best of our understanding, studies to investigate the association between *VDR* gene polymorphism, bone speed of sound, blood vitamin D level and isokinetic muscular strength and power among Malay female athletes and non-athletes were not existent. In addition, no studies have been carried out to look into the presence and distribution of *VDR* gene polymorphism in Malay young athletes and non-athletes. Hence, this current study investigated the frequency distribution of *VDR* gene *BsmI* polymorphism in Malay teenage female athletes and non-athletes, and the correlation of *VDR* gene *BsmI* polymorphism with bone speed of sound, serum vitamin D concentration and isokinetic muscular performance in this population.

MATERIALS AND METHODS

Study Participants

Sixty young females were recruited. They were matched by age and thereafter assigned into two groups, i.e. athletes group (n = 30) and non-athletes group (n = 30). The inclusion criteria of the participants in the athletes group were females who were representing Kelantan state of Malaysia and participating in either netball, volleyball and hockey competitions at national level during the study period. The inclusion criteria of the participants in non-athletes group were females who did not play sports and exercised less than twice per week. All the participants were Malays who had been residents of Malaysian peninsula for at least three generations and had no family history of racial mixing. Written informed consents were then obtained from all the participants. This study was sanctioned by the Human Research Ethics Committee of Universiti Sains Malaysia (USM) (Code: USM/JEPeM/16020073). The sample size of this study was determined by considering a study power of 80%, 95% confidence interval, i.e. alpha at 0.05 with two study groups (25). The number of samples that was obtained from the calculation was 60, Therefore, a total of 60 participants were recruited in this study.

Anthropometric and Physiological Characteristics Measurements

Participant's body mass (kg) and body height (m) were determined using a stadiometer (Seca 220, Hamburg, Germany). The readings for height and body mass were reported to the nearest 0.01 m and 0.1 kg, respectively. Participant's body composition and basal metabolic rate were determined using a body composition measuring device (Tanita, TBF-140, Japan). The data provided by the analyzer were percent body fat, basal metabolic rate and fat-free mass.

Serum Vitamin D Concentration Analysis and Ultrasound Measurements of Bone Speed of Sound

Three mL of venous blood sample was taken from the participants after a 12-hour of overnight fasting. Serum

vitamin D concentration which reflects participants' vitamin D status was analyzed using 25-Hydroxy Vitamin Ds EIA kit (IDS, Israel) and the procedures as suggested by the manufacturer were followed. Participant's bone speed of sound (SOS, $m.s^{-1}$), a measure of density of bone minerals and bone health status, was determined by using a bone sonometer (Sunlight Mini OmniTM, Petah Tikva, Israel) on the radius of both arms, dominant and non-dominant, and on the tibia of both legs.

Measurements of isokinetic muscular performance

The participants' isokinetic knee and shoulder extension and flexion peak torque and power were determined via an isokinetic dynamometer (BIODEX Multi-Joint System 3 Pro, New York). Muscular peak torque (an indicator of muscular strength) and power of dominant and non-dominant legs and arms during isokinetic knee and shoulder extension and flexion were assessed at 3 velocities ($60o.s^{-1}$, $180o.s^{-1}$, and $300o.s^{-1}$). The participants performed 5 sub-maximal repetitions at an angular velocity of $60os^{-1}$. Meanwhile, at velocities of $180os^{-1}$ and $300o.s^{-1}$, the sub-maximal repetitions were set for 10 repetitions, both during flexion and extension. At each speed setting, the participants were allowed to rest for 20 seconds to prevent any possible muscle fatigue. Verbal encouragement was also given in an attempt to achieve maximal effort level from the participants.

Genotyping of *VDR BsmI* gene polymorphism

Using an extraction kit (Gene All, Korea) DNA was extracted from the blood. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used for genotyping the *VDR BsmI* gene.

The primer pair used for amplification were: 5'-AACTTGCATGAGGAGGAGCATGTC-3' (forward) and 5'-GGAGAGGAGCCTGTGTCCCATTTG-3' (reverse). The PCR amplification process was carried out in a total of 25 µL of reaction mixture which contained 100 ng/µL of genomic DNA in final concentration of 1X PCR buffer, 0.2 µM of deoxyribonucleotide triphosphate (dNTPs), 2.0 mM magnesium chloride ($MgCl_2$), 10pmol of each specific primers, 1.25 U of Taq DNA polymerase, Dimethyl sulfide (DMSO4) and double distilled water (ddH_2O). The PCR comprised of 35 cycles of denaturation (95°C for 30 seconds), primer annealing (60°C for 30 seconds) and elongation (72°C for 30 seconds), and a final extension (72°C for 5 minutes). The PCR reaction products were separated on a 2% agarose gel and determined under UV light.

Restriction digestion was performed by firstly adding 5.7 µL ddH_2O, 1.0 µL 10X of Buffer R (assay buffer), 0.3 µL of the restriction enzyme (Mva 12691) and 3 µL PCR product into a sterile tube. After an hour of incubation at 37°C (rs1544410), the digested DNA was separated and visualized on 2% agarose gel. Following genotyping, the genotypes were categorized into groups of (i) homozygous wild type (*B/B*): 474bp and 339bp, (ii) heterozygous (*B/b*): 813bp, 474bp and (iii) 339bp and homozygous variant (*b/b*): 813bp.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 22.0. was used for statistical analysis. Chi-square test was used to compare genotype and alleles frequencies between groups, and to test for the presence Hardy-Weinberg equilibrium among genotypes. The study data was found to be normally distributed before conducting the parametric test to answer the hypothesis. One-way analysis of variance (ANOVA) was used to compare among groups with different genotypes. Independent t-test was carried out to compare all the measured parameters between athletes and non-athletes groups with the same genotype. Results are reported as means ± SD (standard deviation), unless otherwise stated. The accepted threshold for significance was set at $p<0.05$. Genotype distribution in the non-athlete group met the Hardy-Weinberg Equilibrium (HWE) ($p>0.05$), while the athlete group did not ($p<0.05$). This deviation in the athlete group may suggest that certain genotypes confer a fitness advantage, leading natural selection to shift genotype frequencies away from the expected Hardy-Weinberg ratios.

RESULTS

Genotype and Allele Frequencies of *VDR* Polymorphism

Thirty athletes (mean age: 16.00±0.00 years) and thirty non-athletes (mean age: 15.90±0.10 years) were recruited for this study. In non-athletes group, the frequency of BB, Bb and bb genotypes were 18 (60%), 10 (33.33%), and 2 (6.67%) respectively. The frequency of B allele was 46, and the frequency of b allele was 14. In the athletes group, the frequencies of BB, Bb *and* bb genotypes were 26 (86.67%), 2 (6.67%), and 2 (6.67%) respectively, and the frequency of B and b alleles were 54 and 6 respectively. Figure 1 shows a 2% agarose gel with PCR analysis results for the *VDR* gene, while Figure 2 shows a 2% agarose gel with PCR-RFLP analysis results for the *VDR* gene.

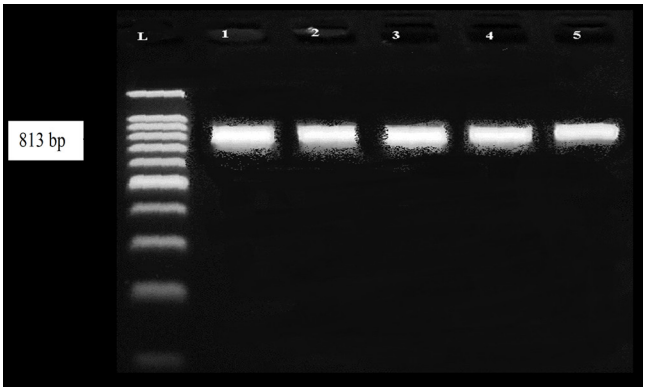

Figure 1: A 2% agarose gel showing VDR gene PCR analysis. Abbreviations: L 100 bpDNA ladder; Lane 1-5 are sample test

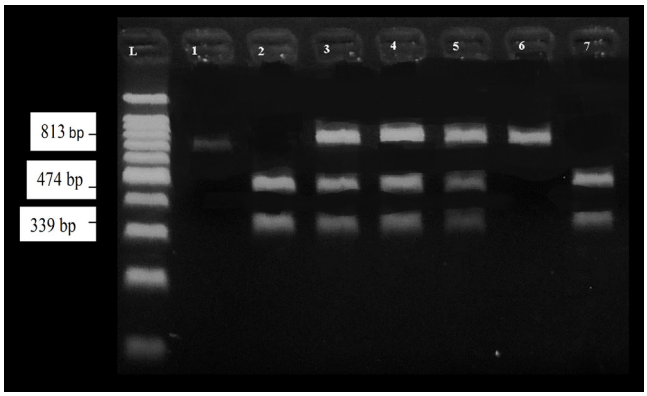

Figure 2: A 2% agarose gel showing VDR gene PCR-RFLP analysis results.
Abbreviations: L 100 bpDNA ladder; Lane 1-7 are sample test; Lane 3, 4, &5 = homozygous wildtype; Lane 2 &7 = heterozygous; Lane 1&6 = homozygous variants

The highest frequency of *BsmI* genotype observed was BB genotype in both athletes and non-athletes groups. The frequency of BB genotype was significantly higher in athletes than in non-athletes ($p<0.05$). The frequency of Bb genotype was significantly higher in non-athletes in comparison to athletes ($p<0.05$). The frequency of B allele was more than b allele in both athletes and non-athletes groups.

Anthropometric and Physiological Characteristics

Table I illustrates the results of anthropometric and physiological characteristics such as body mass, body height, body mass index (BMI), BMI z-score, BMI percentile, and BMI for age-weight status classification, body fat percentage (% BF), fat-free mass (FFM) and basal metabolic rate (BMR) according to *VDR* genotype of the athletes and non-athletes. There were no significant differences in these measured parameters between athletes and non-athletes with BB and Bb genotypes. Nevertheless, athletes with bb genotype showed significantly higher body mass ($p<0.05$) and body fat percentage ($p<0.05$) compared to non-athletes with bb genotype.

Table I: Anthropometric and physiological characteristics, serum vitamin D concentration and bone speed of sound according to *VDR* genotype in Malay female athletes and non-athletes

VDR Genotypes	Non-Athletes (n=30)			Athletes (n=30)		
	BB	**Bb**	**bb**	**BB**	**Bb**	**bb**
Number of participants	n=18	n=10	n=2	n=26	n=2	n=2
Body mass (kg)	46.84±8.64	50.85±10.52	**39.20±3.96**	50.72±9.92	50.65±0.92	**55.60±0.00***
Body height (cm)	155.64±4.86	151.37±5.74	144.75±1.77	158.41±5.93	160.00±2.83	156.00±4.24
BMI	19.31±3.30	22.23±4.80	18.65±1.48	21.82±7.05	19.80±0.99	22.90±1.27
BMI z-score	-0.39	0.51	-0.65	-0.07	-0.22	0.67
BMI percentile	34.8	69.4	25.8	47	41.2	74.8
BMI for age-weight status classification	Healthy weight	Healthy weight	Healthy weight	Healthy weight	Healthy weight	Healthy weight
%BF (%)	25.69±7.98	31.27±8.58	**24.90±3.96**	28.60±6.53	25.15±3.61	**30.05±3.18***
FFM (kg)	34.19±2.91	34.17±2.72	29.40±1.41	31.80±9.95	37.90±1.13	38.85±1.77
BMR (kJ.day^{-1})	5119.78±473.37	5214.00±159.21	4512.00±236.17	5376.58±563.68	5356.50±111.02	5750.00±104.65
Serum vitamin D concentration (Nmol/L)	35.36±7.66	36.32±4.83	37.97±16.59	34.87±8.93	37.11±11.07	37.87±9.47
Radius bone SOS of dominant arm	3965.56±114.55	3957.00±94.57	3904.00±104.65	3964.27±130.43	3949.50±64.35	4026.00±103.24
Radius bone SOS of non-dominant arm	3936.61±89.18	3952.30±89.62	3972.00±69.30	**3973.38±117.50**	3917.00±56.57	**4206.50±226.98**[a]
Tibia bone SOS of dominant leg	**3934.39±130.96**	3831.40±161.94	3934.00±1.11	**3810.35±131.21****	**4064.50±74.25**[b]	3763.50±109.60
Tibia bone SOS of non-dominant leg	**3944.50±113.88**	3833.20±126.17	3996.00±57.98	**3814.92±104.13*****	3978.50±27.58	3793.00±120.21

Values are expressed as mean ± SD. Bold numbers indicate statistically significant.
* $p<0.05$, ** $p<0.01$, and *** $p<0.001$, significantly different between athlete and non-athlete groups with same genotype.
[a] $p<0.05$, BB significantly different from bb in athletes group.
[b] $p<0.05$, BB significantly different from Bb in athletes group.
Abbreviations: BMI= body mass index; %BF = body fat percentage; FFM= fat free mass; BMR= basal metabolic rate; SOS= speed of sound

Serum vitamin D concentration and bone speed of sound

The results of serum vitamin D concentration, as well as radius and tibia bone speed of sound (SOS) at both dominant and non-dominant limbs of the participants according to *VDR* genotype are illustrated in Table I. There were no significant differences in serum vitamin D concentration between carriers of BB, Bb and bb genotypes in athletes group and non-athletes group respectively, similarly no differences were observed between athletes and non-athletes with the same genotype. Regarding bone SOS, athletes with *bb*

genotype showed significantly greater (p<0.05) SOS of the radial bone in non-dominant arms compared to athletes with BB genotype. In addition, our results showed that athletes with Bb genotype had significantly higher (p<0.05) tibial bone SOS in the dominant legs compared to athletes with BB genotype.

Isokinetic Knee and Shoulder Extension and Flexion Peak Torque, Peak Torque per Body Weight and Average Power

Table II and Table III tabulate the results of participants' isokinetic knee extension and flexion peak torque, peak torque per body weight and average power of both dominant and non-dominant legs according to *VDR* genotype respectively. Non-athletes with BB genotype showed significant greater knee extension peak torque per body weight (p<0.01) at 180o.s^{-1} in dominant legs compared to non-athletes with Bb genotype (Table II). In addition, non-athletes with BB genotype showed significantly greater isokinetic knee flexion peak torque per body weight (p<0.01) at 300o.s^{-1} in dominant leg compared to non-athletes with Bb genotype (Table III).

Table II: Isokinetic knee extension peak torque (PT), peak torque per body weight (PT/BW) and average power (AVG.P) of dominant and non-dominant legs according to *VDR* genotype of Malay female athletes and non-athletes

VDR Genotypes			Non-Athletes (n=30)			Athletes (n=30)		
			BB	***Bb***	***bb***	***BB***	***Bb***	***bb***
Number of participants			n=18	n=10	n=2	n=26	n=2	n=2
60^0s^{-1}	D	PT (Nm.)	**92.09±23.79**	**89.14±21.88**	94.50±31.68	**127.18±28.68*** **	**165.85±23.83** **	153.05±47.16
		PT/BW (%)	**201.19±42.02**	**179.74±41.05**	239.20±57.56	**246.68±58.46** **	**327.25±40.80** **	274.70±82.87
		AVG.P (W)	**53.71±12.01**	**48.77±13.54**	57.05±23.26	**79.28±22.16*** **	**98.45±4.17** **	90.85±27.65
	ND	PT (Nm.)	**90.06±24.45**	**87.47±19.10**	93.65±28.50	**116.76±29.20** **	**142.15±25.24** **	129.20±40.87
		PT/BW (%)	**196.07±43.76**	**175.63±33.22**	237.45±49.57	**227.17±47.99***	**280.40±44.55** **	233.25±73.75
		AVG.P (W)	**55.16±13.49**	**51.19±12.15**	59.40±20.22	**73.93±22.97** **	**93.30±14.57** **	78.65±25.39
180^0s^{-1}	D	PT (Nm.)	**64.11±13.08**	**53.14±7.82**	51.80±20.36	**85.05±18.41*** **	**99.75±23.26*** **	88.65±22.13
		PT/BW (%)	**138.48±22.16**	**107.81±20.73**[a]	130.75±39.24	**170.38±196.65*** **	**196.65±42.21** **	160.05±39.95
		AVG.P (W)	**95.59±23.42**	**81.07±14.66**	78.20±37.19	**136.43±31.99*** **	**150.85±11.24*** **	143.15±39.39
	ND	PT (Nm.)	**62.68±15.10**	**53.79±9.66**	58.45±23.26	**83.39±22.05** **	**88.50±15.98** **	77.05±32.88
		PT/BW (%)	**135.46±27.91**	**109.45±25.90**	147.45±45.04	**162.41±36.22***	**174.55±28.21** **	139.10±59.40
		AVG.P (W)	**93.38±28.01**	**79.41±19.47**	87.35±45.61	**126.54±34.20** **	**143.45±29.63** **	122.75±58.76
300^0s^{-1}	D	PT (Nm.)	**50.33±11.45**	**46.04±4.43**	46.35±8.41	**70.27±20.25*** **	**87.05±0.78*** **	73.90±17.11
		PT/BW (%)	**109.51±25.62**	**92.88±12.17**	118.20±9.90	**14.44±33.92** **	**172.00±1.70*** **	133.45±30.90
		AVG.P (W)	**98.41±23.02**	**86.52±15.85**	81.70±21.50	**136.38±34.42*** **	**138.55±4.88** **	153.20±22.34
	ND	PT (Nm.)	**53.44±13.23**	49.05±9.43	51.75±1.06	**67.82±16.88** **	65.00±15.98	63.05±25.53
		PT/BW (%)	**115.80±27.26**	99.23±22.46	113.30±15.84	**135.84±23.81***	128.10±29.13	113.80±46.10
		AVG.P (W)	**91.49±32.15**	**80.75±22.74**	89.10±29.98	**130.30±34.89** **	**135.40±16.12**	121.60±56.71

Values are expressed as mean ± SD. Bold numbers indicate statistically significant.
* p<0.05, ** p<0.01, and *** p<0.001, significantly different between athlete and non-athlete groups with same genotype.
[a] p<0.05, BB significantly different from Bb in non-athlete group.
Abbreviations: D=dominant limb; ND=non-dominant limb; PT= peak torque; PT/BW: peak torque per body weight; AVG.P =average power

Table III: Isokinetic knee flexion peak torque (PT), peak torque per body weight (PT/BW) and average power (AVG.P) of dominant and non-dominant legs according to VDR genotype of Malay female athletes and non-athletes

VDR Genotypes			Non-Athletes (n=30)			Athletes (n=30)		
			BB	**Bb**	**bb**	**BB**	**Bb**	**bb**
Number of participants			n=18	n=10	n=2	n=26	n=2	n=2
60^0s^{-1}	D	PT (Nm.)	**37.08±7.54**	**34.48±8.49**	32.20±13.15	**54.02±13.84*** **	**71.75±8.98*** **	49.35±7.28
		PT/BW (%)	**84.28±35.62**	**69.38±14.06**	81.25±25.67	**108.64±22.80** **	**141.60±14.99*** **	89.10±13.15
		AVG.P (W)	**25.86±14.61**	**21.41±6.23**	22.10±8.63	**37.01±11.57** **	**51.70±7.35*** **	33.15±8.55
	ND	PT (Nm.)	**37.66±9.61**	**36.22±9.19**	30.55±16.76	**53.53±12.43*** **	**64.65±12.37** **	50.15±13.79
		PT/BW (%)	**81.23±38.32**	**72.25±16.41**	76.50±35.36	**107.90±21.79** **	**127.50±22.06** **	90.45±24.82
		AVG.P (W)	**26.31±15.86**	**22.59±6.41**	19.10±10.32	**36.70±10.83***	**46.65±8.70** **	30.75±14.63

CONTINUE

Table III: Isokinetic knee flexion peak torque (PT), peak torque per body weight (PT/BW) and average power (AVG.P) of dominant and non-dominant legs according to VDR genotype of Malay female athletes and non-athletes (CONT.)

VDR Genotypes			Non-Athletes (n=30)			Athletes (n=30)		
			BB	**Bb**	**bb**	**BB**	**Bb**	**bb**
Number of participants			n=18	n=10	n=2	n=26	n=2	n=2
180^0s^{-1}	D	PT (Nm.)	**35.29±9.22**	**30.18±8.16**	31.80±11.17	**49.15±10.28*** **	**64.45±12.37*** **	48.65±1.06
		PT/BW (%)	**76.92±21.17**	**60.03±13.30**	80.40±20.65	**99.67±18.93** **	**127.10±22.06*** **	87.85±1.91
		AVG.P (W)	**43.93±15.13**	**35.15±9.90**	38.15±16.19	**71.89±19.76*** **	**100.80±22.63*** **	6.40±1.56
	ND	PT (Nm.)	**33.55±10.66**	**30.50±7.52**	32.35±16.62	**52.04±12.96*** **	**51.10±18.38***	44.50±3.82
		PT/BW (%)	**73.24±23.99**	**61.15±14.09**	81.15±34.58	**100.72±27.50** **	**100.60±34.37***	80.35±6.86
		AVG.P (W)	**40.35±16.22**	**36.84±9.70**	31.50±23.90	**67.38±19.27*** **	**75.55±15.20** **	69.25±10.11
300^0s^{-1}	D	PT (Nm.)	**46.73±10.17**	**37.04±10.73**	**41.15±3.61**	**59.48±13.94*** **	**68.85±9.69** **	**65.10±0.99***
		PT/BW (%)	**102.50±26.00**	**73.35±16.02**[a]	**105.45±1.20**	**121.80±31.48***	**136.25±21.71** **	**117.55±1.77***
		AVG.P (W)	**43.74±18.61**	**31.81±13.13**	43.40±21.92	**73.45±23.61*** **	**97.70±26.30*** **	73.10±20.65
	ND	PT (Nm.)	**45.84±13.56**	37.04±11.31	37.55±7.85	**63.49±18.92** **	55.25±9.26	60.00±9.051
		PT/BW (%)	**100.70±33.09**	74.41±22.55	45.65±60.03	**127.97±33.66***	109.00±16.26	108.35±16.33
		AVG.P (W)	**39.71±19.87**	**33.40±10.59**	34.60±34.79	**72.55±23.12*** **	**72.80±14.43** **	74.75±16.05

Values are expressed as mean ± SD. Bold numbers indicate statistically significant.
* $p<0.05$, ** $p<0.01$, and *** $p<0.001$, significantly different between athlete and non-athlete groups with same genotype.
[a] $p<0.05$, BB significantly different from Bb in non-athlete group.
Abbreviations: D=dominant limb; ND=non-dominant limb; PT= peak torque; PT/BW: peak torque per body weight; AVG.P =average power

Table IV and Table V show the results of participants' isokinetic shoulder extension and flexion peak torque, peak torque per body weight and average power of dominant and non-dominant arms according to *VDR* genotype respectively. Non-athletes with BB and Bb genotypes had significantly higher ($p<0.05$) shoulder flexion peak torque at $60o.s^{-1}$ in non-dominant arm compared to non-athletes with bb genotype (Table V).

Table IV: Isokinetic shoulder extension peak torque (PT), peak torque per body weight (PT/BW) and average power (AVG.P) of dominant and non-dominant arms according to *VDR* genotype of Malay female athletes and non-athletes

VDR Genotypes			Non-Athletes (n=30)			Athletes (n=30)		
			BB	**Bb**	**bb**	**BB**	**Bb**	**bb**
Number of participants			n=18	n=10	n=2	n=26	n=2	n=2
60^0s^{-1}	D	PT (Nm.)	**31.77±5.53**	33.15±7.62	24.55±1.34	**39.78±8.86** **	36.80±1.41	36.75±14.63
		PT/BW (%)	**69.63±14.47**	65.88±10.58	63.05±2.76	**80.46±15.86***	72.75±4.17	66.35±26.38
		AVG.P (W)	**13.36±5.54**	14.33±5.01	9.70±0.42	**21.26±7.57*** **	17.10±3.11	22.50±14.71
	ND	PT (Nm.)	**28.75±7.52**	29.33±6.32	21.25±4.88	**33.84±8.03***	30.20±0.57	28.45±8.84
		PT/BW (%)	62.37±15.15	58.78±11.02	54.05±7.14	68.07±12.38	59.70±2.26	51.35±15.91
		AVG.P (W)	**11.04±13.09**	13.09±6.35	8.85±3.61	**18.83±6.94*** **	18.40±1.98	14.95±9.54
180^0s^{-1}	D	PT (Nm.)	**63.75±18.13**	66.20±15.79	57.40±16.69	**76.04±14.66***	62.20±17.54	67.20±14.14
		PT/BW (%)	139.33±43.04	132.57±33.02	149.85±57.49	154.80±32.23	123.25±36.98	121.35±25.53
		AVG.P (W)	**15.44±10.91**	15.88±8.08	8.35±3.04	**35.79±15.91*** **	26.60±12.16	33.90±37.33
	ND	PT (Nm.)	**48.21±17.63**	59.93±13.37	45.55±25.67	**70.19±17.89*** **	60.25±14.64	53.20±37.34
		PT/BW (%)	**104.76±38.78**	124.79±40.81	113.95±54.52	**137.81±40.88***	119.35±31.18	96.05±67.39
		AVG.P (W)	**9.91±8.43**	13.01±8.33	12.70±13.01	**33.05±16.11*** **	17.15±1.77	21.90±24.47
300^0s^{-1}	D	PT (Nm.)	**71.78±31.98**	75.91±29.21	57.30±0.14	**101.36±34.75** **	84.60±43.70	78.95±43.07
		PT/BW (%)	**155.17±67.05**	155.67±67.85	147.45±14.21	**203.36±34.75***	168.00±89.52	142.55±77.71
		AVG.P (W)	**12.21±8.15**	12.13±10.02	6.60±1.27	**34.91±20.75*** **	19.85±19.30	33.75±37.83
	ND	PT (Nm.)	**58.46±20.59**	64.26±22.14	75.80±29.98	**103.19±31.43*** **	53.90±6.08	81.95±57.06
		PT/BW (%)	**127.66±43.68**	133.40±54.69	191.25±57.91	**197.23±72.48***	106.60±14.00	147.95±103.02
		AVG.P (W)	**8.80±5.29**	10.31±4.58	11.25±7.71	**32.71±17.69*** **	15.00±2.69	21.75±25.53

Values are expressed as mean ± SD. Bold numbers indicate data with statistically significant.
* $p<0.05$, ** $p<0.01$, and *** $p<0.001$, significantly different between athlete and non-athlete groups with same genotype.
Abbreviations: D=dominant limb; ND=non-dominant limb; PT= peak torque; PT/BW: peak torque per body weight; AVG.P =average power

Table V: Isokinetic shoulder flexion peak torque (PT), peak torque per body weight (PT/BW) and average power (AVG.P) of dominant and non-dominant arms according to *VDR* genotype of Malay female athletes and non-athletes

VDR Genotypes			Non-Athletes (n=30)			Athletes (n=30)		
			BB	**Bb**	**bb**	**BB**	**Bb**	**Bb**
Number of participants			n=18	n=10	n=2	n=26	n=2	n=2
60^0s^{-1}	D	PT (Nm.)	**32.43±5.21**	33.28±6.75	36.90±6.93	**40.88±8.51****	44.65±6.15	39.45±6.86
		PT/BW (%)	**71.44±15.84**	68.44±20.17	94.10±8.48	**82.51±14.78***	88.35±13.79	71.25±12.37
		AVG.P (W)	**16.13±3.62**	**16.64±3.79**	15.65±1.20	**23.32±6.10*****	**25.15±7.14***	2.20±5.94
	ND	PT (Nm.)	**34.90±6.01**[a]**	**35.91±2.96**[b]**	**24.95±5.30**	**40.60±6.42****	40.10±5.94	39.90±1.56
		PT/BW (%)	75.94±13.97	72.54±9.72	64.90±19.94	82.64±13.85	79.35±13.22	72.05±2.75
		AVG.P (W)	**16.66±3.03**	**18.45±2.71**	14.15±2.05	**25.17±12.25****	**25.05±2.05****	24.45±0.50
180^0s^{-1}	D	PT (Nm.)	**40.28±8.87**	42.19±7.12	40.00±11.46	**54.17±14.40****	48.30±3.67	46.70±1.27
		PT/BW (%)	**89.08±23.76**	85.40±17.41	104.40±39.60	**109.30±23.80****	95.50±9.05	84.30±2.26
		AVG.P (W)	**25.19±7.19**	**25.29±8.40**	19.05±3.60	**40.67±11.67*****	**40.45±10.68***	50.00±17.68
	ND	PT (Nm.)	**38.02±7.60**	43.11±4.15	34.80±5.23	**54.87±16.50*****	40.83±2.73	45.20±1.27
		PT/BW (%)	**83.62±20.13**	87.39±14.72	90.25±22.27	**110.05±24.95****	80.55±.37	81.60±2.26
		AVG.P (W)	**23.46±5.77**	**27.89±5.02**	23.75±0.78	**46.84±31.89****	**40.95±4.17****	40.60±4.38
300^0s^{-1}	D	PT (Nm.)	**35.01±7.49**	**39.41±9.52**	**34.60±7.07**	**61.92±27.73*****	**58.15±7.00***	**54.75±22.84***
		PT/BW (%)	**76.63±18.25**	**79.04±18.45**	**89.95±26.94**	**122.29±39.70*****	**115.05±16.05***	**98.85±41.22***
		AVG.P (W)	**24.59±5.99**	**24.11±7.33**	20.20±0.14	**42.84±15.72*****	**41.50±12.16***	54.25±21.57
	ND	PT (Nm.)	**32.66±7.44**	**36.75±6.49**	33.70±1.98	**63.56±29.16*****	55.45±8.27	48.20±18.95
		PT/BW (%)	**71.74±18.24**	**74.22±15.73**	86.95±13.65	**127.55±45.71*****	**109.70±18.38***	87.00±18.38
		AVG.P (W)	**23.32±7.04**	**27.51±4.89**	23.50±0.28	**43.48±15.55*****	**47.45±4.17*****	41.40±7.78

Values are expressed as mean±SD. Bold numbers indicate statistically significant.
* $p<0.05$, ** $p<0.01$, and *** $p<0.001$, significantly different between athlete and non-athlete groups with same genotype.
[a] $p<0.05$, BB significantly different from bb in non-athlete group.
[b] $p<0.05$, Bb significantly different from bb in non-athlete group.
Abbreviations: D=dominant limb; ND=non-dominant limb; PT= peak torque; PT/BW: peak torque per body weight; AVG.P =average power

DISCUSSION

According to the results of this study, there was more of B allele than b allele in both Malay female athletes and non-athletes. Likewise, BB genotype was the most frequent *VDR BsmI* genotype observed in both Malay female athletes and non-athletes. The observed frequencies of BB genotype in Malay population of the current study were not consistent with other studies in Caucasians populations (27-29). The most common vitamin D receptor genotype was Bb genotype, and BB genotype was the lowest frequent genotype found in American girls of Mexican descent (21) and Swedish women (22). Previous studies indicated that among Chinese women (30) and Japanese women (31), the most frequent genotype was bb genotype, while BB genotype was the lowest frequencies in their studies.

The inconsistent findings between Malay population and other population regarding the *VDR BsmI* genotype distribution imply that genotype and phenotypic variation exists in different ethnicities and population. The Minor Allele Frequencies (MAF) of the b allele ranges from 30% to 45% in various studies across countries such as Italy, Spain, and Germany (32). East Asian populations (Chinese, Japanese, and Koreans) tend to have a lower frequency of the b allele (33). MAFs for the b allele in the Latin American populations, such as in Brazil and Mexico, range from 30% to 40% (34). In addition, the number of participants recruited in the present study was a small cohort of sixty participants compared to the previous studies which involved 706, 191, 126, and 308 participants respectively (27, 28, 31, 25). This might have caused contradictory results between the aforementioned studies and the present study. The small sample size in the current study may indeed contribute to contradictory findings. The decision not to include a larger sample size was influenced by several practical constraints, such as funding limitations and accessibility to the target population. If a larger sample size was to yield similar findings, it would reinforce the robustness of the present results and suggest that the observed effect is consistent across different population subsets. Such results would encourage further research to explore the underlying mechanisms. Regarding the distribution of genotypes, this can be attributed to genetic variation within the population, influenced by factors such as historical migration patterns and environmental conditions. Additionally, lifestyle and health-related behaviors may also play a significant role in the observed genotype frequencies. Ultimately, these findings highlight the complex interplay between genetics and environmental factors in shaping health outcomes.

The current study also discovered that athletes had a

higher frequency of the BB genotype compared to non-athletes. These findings imply that more Malay female athletes are with BB genotype than non-athletes. Given that no research has been done to examine the *VDR BsmI* genotypes frequency in Malay female athlete and non-athlete population, our data might provide fresh insights into the field of sports medicine, genetics and sports science.

The body's vitamin D receptors mediate the activity of Vitamin D which is essential for bone metabolism. Hence, *VDR* gene is one of the genes which has been broadly researched in relation to bone health (45). Most studies used bone mineral density to reflect the bone health status in humans (20, 21, 31, 36, 37). In the present study, bone speed of sound (SOS) was used to indicate the bone density of the participants (3). One notable findings of the current study was that athletes with bb genotype showed a significantly greater radial bone SOS in non-dominant arms compared to athletes with BB genotype. This implies that bb genotype may be associated with higher bone SOS, i.e. better bone health status of the arms in athletes. In addition, athletes with Bb genotype showed significantly greater tibial bone SOS in the dominant legs in comparison to athletes with BB genotype. This result reflects that Bb genotype may be associated with higher bone SOS, i.e. better bone health status of the legs in athletes.

It was reported that Bb genotype was related with greater bone density in the lumbar spine of Japanese females (31). Nevertheless, Riggs et al. (36) reported that high bone mineral density was associated with bb genotype in femoral neck compared to BB genotype in younger women. Study carried out on Pennsylvanian population showed that women with BB genotype possess a notably lower bone mineral density at spinal, trochanter and hip region compared to those with bb genotype (37). In addition, a study which involved white and black premenopausal women demonstrated that mean bone mineral density was reduced in women with BB genotype than women with bb or Bb genotypes (20). It is documented that there was significantly greater lumbar bone mineral density in Italian women with bb genotype than BB genotype (38). Morrison et al (29) stated that females with BB genotype reached an early fracture threshold at the lumbar spine compared to females with bb genotype, and their finding implies that the bb genotype was linked to improved bone health status in Caucasian females. The previous study by Sainz et al. (21) which involved young females with 6.70 to 11.70 years of age range is in strong support to the study of Morrison et al. (29). They also discovered that the bone density of the femur and vertebrae was higher in girls with bb compared to girls with BB genotypes (21).

In line with the conclusions of the earlier research mentioned in the previous paragraph, the present study also found that bb and Bb genotype have tendency to be associated with better bone health status. Nevertheless, our present study findings are not consistent with the other finding which reported that *VDR* genotypes were not associated with bone mineral density in a French and Norway population (36, 37). The inconsistency between the present study finding and the above findings could be due to genetic differences in ethnicity, site of bone measurement and bone mineral density measurement by using DEXA in their studies instead of using bone sonometer in the present study.

Muscle tissues from both humans and animals has been found to contain *VDR* (38, 39). The biologically active form of vitamin D attaches to the vitamin D receptor, and its metabolites affect the metabolism of muscle cells via various pathways (40). 1, 25-dehydroxy vitamin D interacts with the nuclear receptor at the genomic level, altering the mRNA gene transcription and triggering formation of new protein (41). The genomic pathway influences muscle calcium transport (42-44) which is important for muscle contraction and phospholipids metabolism (43, 45). These reactions subsequently affect skeletal muscle movement in the body. In the present study, isokinetic muscular strength and power were measured at three velocities of $60o.s^{-1}$, $180os^{-1}$ and $300os^{-1}$ using an isokinetic dynamometer to determine the relationship of *VDR* polymorphism with muscular power and strength of the participants.

Our current data demonstrated that non-athletes with the BB genotype exhibited significantly greater flexion and extension peak torque per body weight at dominant legs in comparison to non-athletes with Bb genotype. This implies that greater muscle strength of the legs in non-athletes may be linked to the BB genotype. Bahat et al. (23) also revealed that knee extensor strength was higher in Istanbul elderly men with BB genotype. Individuals with BB and Bb exhibited higher concentric knee flexor strength than bb genotype in young Asian women (30). In addition, Swedish premenopausal women with BB had greater isokinetic knee flexion strength than bb (22). Literature data from the above studies and the present study showed that BB genotype has tendency to be associated with higher leg muscular strength.

Results from several previous studies were contradictory with results from the present investigation between the relationship of *VDR BsmI* genotypes and muscular performance. For instance, Geusens et al. (25) found that elderly Belgium women who had bb allele had higher isometric strength in the quadriceps compared to those with the BB genotype. Gavin and Williams (46) reported *VDR BsmI* genotype was not associated with the strength of knee extensor and flexor in young British Caucasian females. Similarly, significant associations between *VDR* genotype, and isometric strength of the knee extensor and flexor were not observed in adult Belgium females. These observations suggest that ethnicity affects how the *VDR* genotype influences leg muscle strength.

The current study also showed that in non-athletes group, participants with Bb and BB genotype had significantly greater peak torque in non-dominant arm when compared to non-athletes with bb genotype. This finding implies that Bb and BB genotypes may be associated with higher peak torque, i.e. muscular strength of the arm when compared to non-athletes with bb genotype. Barr et al. (47) reported that the association between *VDR* polymorphism and risk of falls in elderly, i.e. a positive relationship between *BsmI* polymorphism and muscular power. Inconsistent with the above-mentioned study, the present investigation shows a positive association between *BsmI* polymorphism with muscular strength but not with power in young Malay females. The participants' age, genetic make-up and environmental factors may have played a role in the divergent findings between this study and earlier research.

In the current study, no significant differences were observed in serum vitamin D concentration between different *VDR BsmI* genotypes in the athletes and non-athletes groups. These findings indicate that there was no correlation between vitamin D levels and *VDR BsmI* genotype in Malay female athletes and non-athletes. Consistent with our results, the absence of significant relationships between *VDR BsmI* genotypes and vitamin D concentration in Russian middle-age women was also reported by Karonova et al (48).

The *VDR* gene polymorphisms, particularly BsmI, *FokI, TaqI,* and *ApaI,* have garnered increasing attention in Southeast Asia due to their potential influence on health outcomes, including bone health, immune response, and susceptibility to various diseases. The unique genetic makeup and environmental conditions in this region provide a critical backdrop for understanding these polymorphisms. Southeast Asia is home to a diverse population with various ethnic backgrounds, which may contribute to the variability in the frequency of *VDR* gene polymorphisms. Recent studies have shown that certain populations in Southeast Asia exhibit distinct allele frequencies compared to populations from other regions, which could affect the public health implications of vitamin D deficiency (49). The tropical climate of Southeast Asia, characterized by high UV radiation exposure, may interact with genetic factors, impacting vitamin D metabolism and health outcomes. While higher UV exposure is generally associated with increased vitamin D levels, the prevalence of certain *VDR* polymorphisms may modulate this relationship (50).

Despite the growing body of research, there remains a gap in comprehensive studies examining the implications of *VDR* polymorphisms in various Southeast Asian populations. Future research should focus on larger, ethnically diverse samples to elucidate the interactions between genetic factors, environmental influences, and health outcomes. By understanding the distribution and implications of *VDR* gene polymorphisms in Southeast Asia is crucial for addressing vitamin D-related health issues in the region. The interplay of genetics, environment, and culture necessitates further exploration to develop tailored public health strategies.

Limitations in the present study were including state level athletes but not higher competition level of national level athletes, and only one gender, i.e. female participants were recruited. Therefore, future studies with other age categories, higher competition level such as national level, and involving both genders, i.e. female and male participants are recommended. The strength of the present study is that comparison of measured parameters had been carried out between athletes and non-athletes, which was not commonly conducted in other related studies on genetic and physical performance. Since *VDR* gene polymorphism has many variants, more single nucleotide polymorphisms in *VDR* region can be recommended to be studied for determining the associations between other genotypes of *VDR* gene with sport performance.

CONCLUSION

In conclusion, based on the set up of this study, *VDR BsmI* BB genotype is the most common genotype of *BsmI* found in Malay teenage female athletes and non-athletes. Findings of the current study reflect that *VDR BsmI* bb and Bb genotype may be associated with better bone health status in Malay teenage female athletes. In addition, *VDR BsmI* BB and Bb genotypes appear to be linked to greater muscular strength in non-athletic Malay teenage females. It is hoped that these findings can provide new scientific information on the role of genetics in Malay female population in the field of sports science and sports medicine.

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