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Association of primary knee osteoarthritis with *DVWA* SNP in a group of Egyptian population: a case–control study

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Abstract

Background: Osteoarthritis (OA) is a highly prevalent medical condition which represents a high impact on public health. In addition, the underlying etiology still has been unelucidated. Osteoarthritis is a multifactorial disease with a high genetic predisposition. Identification of genes associated with higher OA predisposition can assist in elucidating the underlying molecular mechanisms as well as detecting possible areas for gene-targeted OA therapies. Among these genetic targets, double Von Willebrand factor domain A (*DVWA*) has been shown to be related to β-tubulin protein interaction which is considered a protecting factor from OA development. Studies have shown a reduction in protein binding strength with single-nucleotide polymorphism (SNP) *rs11718863* in the Von Willebrand factor domain A (*VWA* domain). Development of weakness between β-tubulin and the wild protein has been linked with increased risk of OA development. We aimed to investigate the association between primary knee OA susceptibility and severity with *DVWA rs11718863* SNP among a subset of Egyptian population.

Results: There was no statistically significant difference in the incidence of AA, AT and TT genotypes frequencies between patient group and control group ($P = 0.502$). There was no statistically significant difference between different genotypes of *DVWA rs11718863* SNP as regards the radiological assessment of different knee joint compartments using Kellgren Lawrence scale ($P = 0.960$ for medial tibiofemoral compartment), ($P = 0.260$ for lateral tibiofemoral compartment) and ($P = 0.597$ for patellofemoral compartment).

Conclusions: *DVWA rs11718863* SNP was not demonstrated to influence OA susceptibility and severity among the studied Egyptian population subset. Larger sample size with inclusion of more genetic variants of *DVWA* SNP would be necessary to support the presence or absence of any relationship between *DVWA* SNP and OA.

Keywords: Osteoarthritis, Primary knee osteoarthritis, *DVWA*, SNP, Egyptian

Background

Osteoarthritis (OA) is a process of joint functional loss due to cartilage degradation and synovial membrane inflammation [1]. Up till now, most of the existing treatments have targeted pain management without addressing the OA etiology [2]. The emerging genetic studies are showing promising outcomes for developing gene therapy, which could be effective in asymptomatic or early OA stage and would be useful for predicting susceptibility to OA, so that preventive measures can be started earlier before disease progression [3].

Over the last 5 years, various studies have assessed the relationship between OA and different single-nucleotide polymorphisms (SNP) among the Egyptian population

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such as leptin receptor gene, matrilin-3, tumor necrosis factor α and growth differentiation factor 5 [4–7].

Double Von Willebrand factor domain A (*DVWA*) has been shown to be related to β-tubulin protein interaction, which is considered as a protecting factor against OA development. Studies have shown a reduction in protein binding strength with SNP rs11718863 in VWA domain. Development of weakness between β-tubulin and the wild protein has been linked with an increased risk of OA development [8].

Additionally, researches have suggested an association of *DVWA* with knee OA in the Asian population but failed to show relation with the European one [9].

We aimed to investigate the association between primary knee OA susceptibility and severity with *DVWA* rs11718863 SNP among a subset of the Egyptian population.

Methods

Fifty Egyptian patients previously diagnosed as primary knee OA were recruited from the Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation. The patients fulfilled the American College of Rheumatology criteria for primary knee OA (it included knee pain, osteophytes, and the presence of one of the following: age more than 50 years, morning stiffness less than 30 min duration, or crepitus with active motion of the knee like during squatting.) [10]. Twenty-five age- and sex-matched healthy volunteers constituted the control group. Patients suffering from secondary OA, severe autoimmune diseases, severe hepatic or renal dysfunction or malignant tumors were excluded [4].

The researcher explained the study to all participants and provided them a written consent in accordance with Helsinki declaration. The study had been accepted by the local Ethics Committee of the faculty.

Patients were subjected to clinical examination with an emphasis on the musculoskeletal examination. OA assessment was conducted using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (which included 24 questions assessing the pain, stiffness, and physical function during the last week) and the Health Assessment Questionnaire (HAQ) (it included twenty questions to assess limitations in performance of daily physical activities including rising, walking, dressing, and grooming, reaching, eating, gripping, activities, and hygiene) [11, 12]. Besides, subjects were evaluated radiologically using the Kellgren–Lawrence (KL) grading scale (Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping, Grade 2: definite osteophytes and possible JSN, Grade 3: moderate multiple osteophytes, definite JSN, some sclerosis, possible bone end deformity, and Grade 4: large osteophytes, marked JSN, severe sclerosis and definite deformity of bone ends) [13].

Three milliliters of blood sample was collected from patients and healthy volunteers in K2 EDTA vacutainer tubes. The genomic DNA was amplified and purified with the QIAGEN Mini Kit QIAamp® [14].

Genotyping of *DVWA rs11718863* SNP was performed by TaqMan® SNP genotyping assay (Applied Biosystems—Life Technologies, imported from Lithuania). The genomic DNA was detected by allelic discrimination using the 5′ nuclease assay on Stratagene machine Mx3000P Q system. The TaqMan method is based on the activity of 5′–3′ exonuclease of Thermus aquaticus (Taq) DNA polymerase which cleaves to a labeled probe when it is hybridized to a complementary target. There is a fluorophore attached to the 5′ end of the probe, while in the 3′ end, there is a quencher attached to it. When there is no complementary amplicon to the probe, the probe remains intact, and the detected fluorescence will be low. When there is a complementary amplicon to the probe, the probe binds to it. At this step, 5′–3′ exonuclease activity of Taq enzyme starts to displace the 5′ end of the probe and then the process of degradation will set up.

Data were fed to IBM SPSS software package version 23.0. Qualitative data were described in the form of either numbers or percentages, while quantitative data were mentioned in terms of mean and standard deviation. A 5% level of significance was set for the 95% confidence intervals, and *P* value was interpreted as statistically significant when equal or less than 0.05. Statistical tests of significance included the chi-square test and the independent sample t test for qualitative and quantitative data, respectively.

Results

This study included fifty patients with primary knee OA (40 females [80.0%] and 10 males [20.0%]). Their mean age was 52.92 ± 7.50 years (ranged from 41 to 67 years). The control group included twenty-five apparently healthy volunteers (19 females [76.0%] and 6 males [14.0%]). Their mean age was 50.08 ± 7.04 years (ranged from 42 to 66 years). Different demographic data and anthropometric measures of patient and control group are illustrated in Table 1.

Table 1 Comparison between patient and control groups according to demographic data and anthropometric measures

Demographic data and anthropometric measures	Patients group ($n=50$)		Control group ($n=25$)		Test of significance	*P*
	No.	%	No.	%		
Age (years)						
Mean ± SD	52.92 ± 7.50		50.08 ± 7.04		$t=2.132$	0.036*
Gender						
Male	10	20.00	6	24.00	$\chi^2=0.159$	0.692
Female	40	80.00	19	76.00		
Weight (kg)						
Mean ± SD	83.21 ± 12.21		83.54 ± 11.77		$t=0.109$	0.914
Height (cm)						
Mean ± SD	161.98 ± 6.47		164.96 ± 9.34		$t=1.614$	0.111
BMI (kg/m^2)						
Mean ± SD	31.59 ± 4.89		30.67 ± 4.24		$t=0.806$	0.422

P P value for comparison between the studied groups, *SD* standard deviation, *t* value of Student's t test, χ^2 value of chi-square test, % percentage of patients or healthy volunteers

*Statistically significant at $P \leq 0.05$

Table 2 Comparison between patient and control groups according to *DVWA* rs11718863 single nucleotide polymorphism genotype

DVWA rs11718863 SNP genotype	Patients group ($n=50$)		Control group ($n=25$)		χ^2	*P*
	No.	%	No.	%		
AA	35	70.0	19	76.0	0.683	0.502
AT	14	28.0	6	24.0		
TT	1	2.0	0	0.0		
Allele					0.426	0.508
A	84	84.0	44	88.0		
T	16	16.0	6	12.0		

DVWA double Von Willebrand factor domain A, *P P* value for comparison between the studied groups, *SNP* single nucleotide polymorphism, χ^2 value of chi-square test, % percentage of patients or healthy volunteers

*Statistically significant at $P \leq 0.05$

The genotypic constitution of *DVWA rs11718863* SNP in the patient group ($n=50$) was in the form of AA 70.0% ($n=35$), AT 28.0% ($n=14$) and TT 2% ($n=1$), whereas the control group ($n=25$) revealed AA 76.0% ($n=19$) and AT 24.0% ($n=6$). There were no statistically significant differences between both groups as regards the frequency of different *DVWA* genotypes ($P=0.502$) (Table 2).

Illustrations of different *DVWA* genotypes curves of some patients in the study are shown in Figs. 1, 2, and 3.

There were no statistically significant differences between different *DVWA rs11718863* SNP genotypes and age, weight, height, BMI, medical history, and clinical knee evaluation (Tables 3, 4).

Also, there were no statistically significant differences between different *DVWA rs11718863* SNP genotypes regarding WOMAC score results, HAQ questionnaire results, and KL scale severity grades of different compartments of the knee joint (Table 5, 6).

Discussion

The *DVWA* gene is located on the human chromosome 3p24.3 and codes for short (276 amino acid) proteins. Within the gene, two areas are related to the Von Willebrand factor type A (*VWA*) domain. The expressed product of *VWA* can be found in many proteins and has been proved to have a role in the membrane transport, cellular adhesion, and protein-to-protein interactions [15].

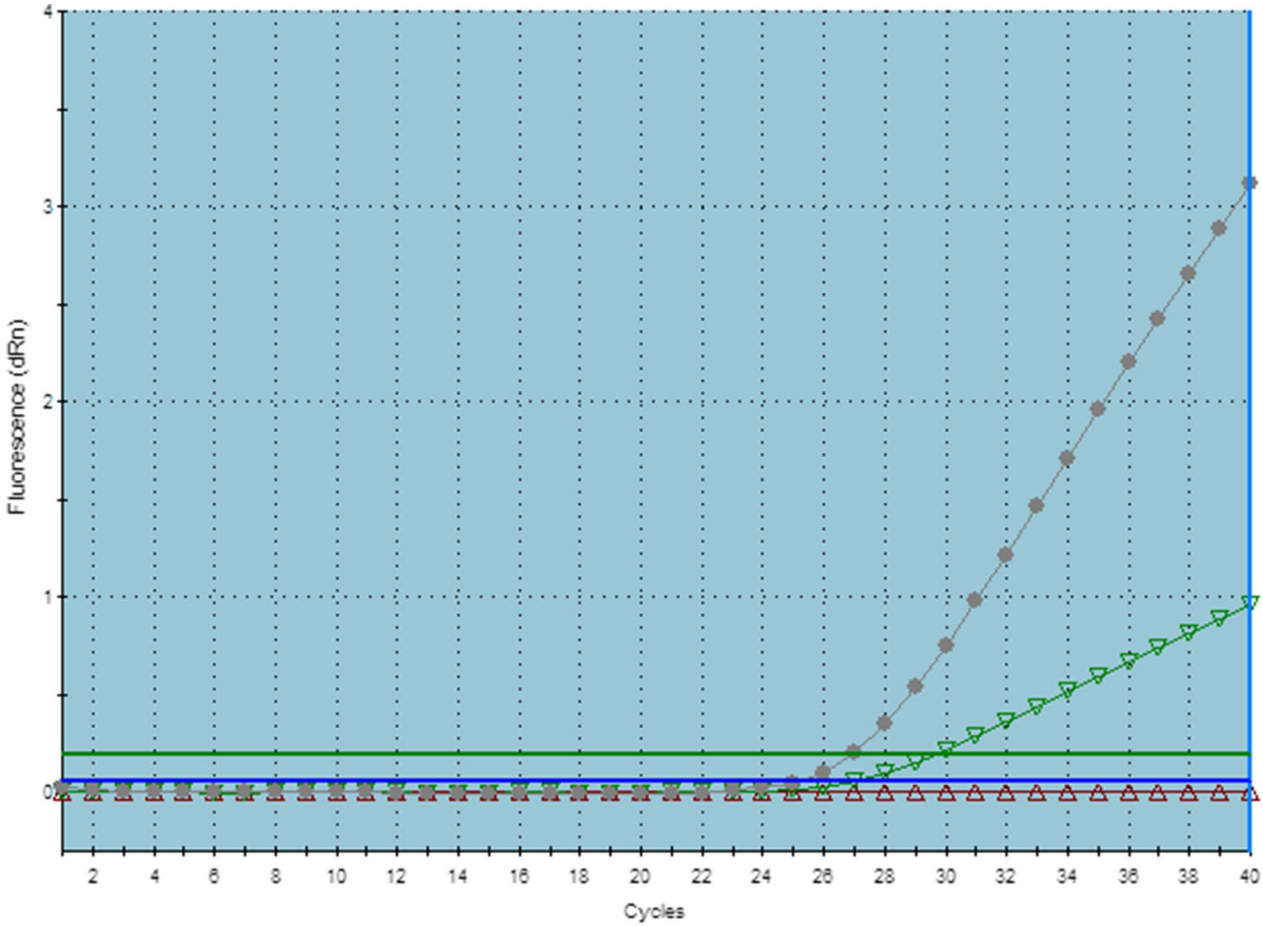

Fig. 1 Amplification plot curve showing a case with AT heterozygous genotype for *DVWA* gene SNP (*rs11718863*). It shows amplification of both A allele and T allele. A allele is represented as circles and T allele is represented as triangles

Expression of *DVWA* is present in diverse human tissues and is highly expressed in cartilage tissue, including OA patients as well as the general population [16]. Development of OA and osteochondrodysplasia has been linked with mutation within the *VWA* domain of the matrilin-3 gene [17].

In our study, there was no statistically significant difference in the frequencies of AA, AT, and TT genotypes among the patient and control groups ($P=0.502$).

Research studies conducted in the relation between *DVWA rs11718863* SNP and OA susceptibility revealed controversial conclusions as regards to the association. Our results were in agreement with Meulenbelt et al. (2009) that *DVWA rs11718863* SNP did not show any significant effect in OA susceptibility [18]. This result was contradictory to Minafra et al. (2014) and Bravata et al. (2015) where the TT genotype was much significantly higher among the OA patient group [19, 20]. This could be justified due to different genetic distribution between different ethnic populations.

There was no statistically significant difference in A and T alleles frequency between patient and control groups ($P=0.508$), although—interestingly—the A allele was the most frequent allele in our patients and in the control group. This was contradictory to Minafra et al. (2014) and Bravata et al. (2015) where the T allele was the more frequent allele in the patient and control groups [19, 20].

There was no statistically significant difference between the different genotypes of *DVWA rs11718863* SNP as regards to the age, sex, weight, height, BMI, OA disease duration, and family history of OA disease ($P=0.592$), ($P=0.123$), ($P=0.887$), ($P=0.415$), ($P=0.732$), ($P=0.539$), and ($P=0.376$), respectively. No available

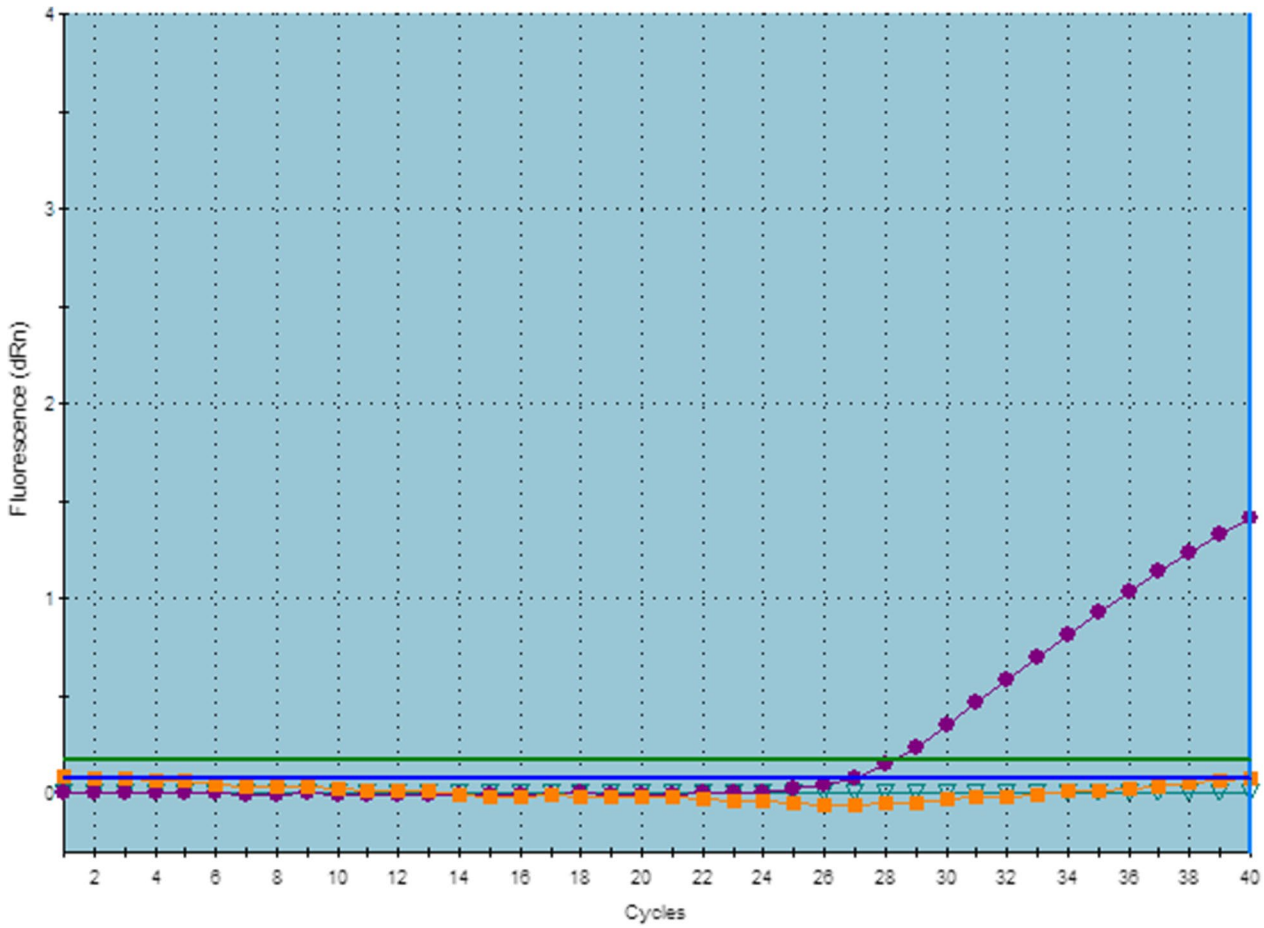

Fig. 2 Amplification plot curve showing a case with AA homozygous genotype for *DVWA* gene SNP (*rs11718863*). It shows amplification of A allele with no amplification of T allele. A allele is represented as circles and T allele is represented as triangles

detailed studies regarding the difference in demographic, anthropometric, and medical history between different genotypes of *DVWA rs11718863* SNP have been revealed. However, Miyamoto et al. (2008) showed no statistically significant difference in demographic and anthropometric measures between different genotypes of *DVWA rs7639618* SNP, which is another polymorphism of *DVWA* associated with OA susceptibility [8].

Regarding the clinical knee evaluation, there was no statistically significant difference between AA, AT, and TT genotypes regarding the presence of knee effusion, anserine bursitis, and baker cyst ($P=0.087$), ($P=0.416$), and ($P=0.665$), respectively. These results had been in accordance with our findings that *DVWA* rs11718863 SNP did not increase OA development or severity, but there were no supporting or contradictory current studies to our results so far.

The assessment questionnaire used for knee OA assessment (WOMAC score and HAQ questionnaire) did not reveal significant association with *DVWA rs11718863* SNP genotypes ($P=0.689$) and ($P=0.225$), respectively. Also, the radiological knee KL assessment scale did not show any statistically significant difference between different *DVWA rs11718863* SNP genotypes and medial tibiofemoral, lateral tibiofemoral, and patellofemoral compartments KL scores ($P=0.960$), ($P=0.260$), and ($P=0.597$), respectively.

These results were in agreement with Meulenbelt et al. (2014), while, on the other side, they were contradictory to Minafra et al. (2014) and Bravata et al.

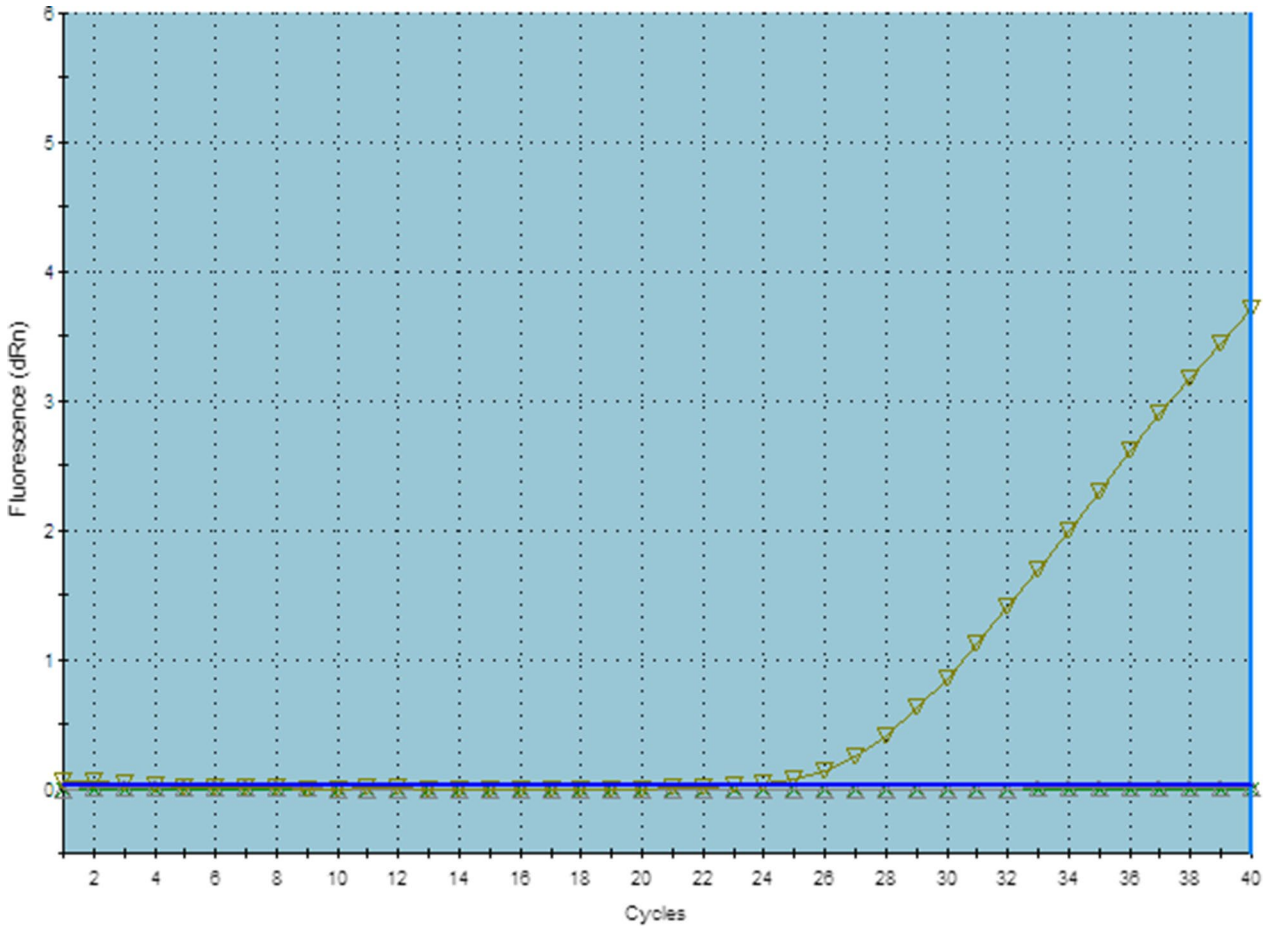

Fig. 3 Amplification plot curve showing a case with TT homozygous genotype for *DVWA* gene SNP (*rs11718863*). It shows amplification of T allele with no amplification of A allele. T allele is represented as triangles

(2015) who showed statistically significant association between *DVWA rs11718863* SNP and knee OA, both clinically and radiographically [19, 20].

Recently, *DVWA* has been incorporated to be associated with OA susceptibility. The function of *DVWA* is through interaction with β-tubulin. Tubulin proteins play an important role in secretion of protein and transportation. They also regulate differentiation of chondrocytes [8, 21].

The bindings' strength of tubulin seems to be influenced by *DVWA* SNPs alleles. Different SNPs of *DVWA* gene have been recently detected and have been still in study regarding the association with OA (*rs11718863*, *rs9864422*, and *rs7639618*, for instance). The association of *DVWA* with OA can be affected by combined effect of two SNPs together rather than a SNP [8].

Conclusions

DVWA rs11718863 SNP was not statistically proved to influence OA susceptibility and severity among Egyptian population. To our knowledge, the study was the first to analyze the association of *DVWA* rs11718863 SNP with OA among the Egyptian population. Larger sample size with inclusion of more genetic variants of *DVWA* would be necessary to be investigated in order to support the presence or absence of relationship between *DVWA* and OA.

Table 3 Relation between *DVWA rs11718863* single nucleotide polymorphism and demographic data and anthropometric measures in patient group

Demographic data, anthropometric measures, and medical history	*DVWA rs11718863* SNP genotype				Test of significance	*P*
	AA (*n* = 35)		AT + TT (*n* = 15)			
	No.	%	No.	%		
Age (years)						
Mean ± SD	53.54 ± 7.76		54.80 ± 7.05		$t = 0.538$	0.592
Gender						
Male	5	14.3	5	66.7	$\chi^2 = 2.381$	0.123
Female	30	85.7	10	33.3		
Weight (kg)						
Mean ± SD	83.38 ± 11.88		82.83 ± 13.36		$t = 0.143$	0.887
Height (cm)						
Mean ± SD	161.49 ± 6.55		163.13 ± 6.36		$t = 0.822$	0.415
BMI (kg/m^2)						
Mean ± SD	31.75 ± 4.77		31.23 ± 5.31		$t = 0.344$	0.732
Family history						
Negative	16	45.7	4	26.7	$\chi^2 = 1.958$	0.376
First degree	14	40.0	7	33.3		
Second degree	5	14.3	4	26.7		
Disease duration according to the most severe side						
Mean ± SD	3.81 ± 2.92		4.96 ± 6.85		$t = 0.627$	0.539

DVWA double Von Willebrand factor domain, *P P* value for comparison between AA and AT + TT, *SD* standard deviation, *SNP* single nucleotide polymorphism, *t* value of Student's t test, χ^2 value of chi-square test, % percentage of patients

*Statistically significant at $P \leq 0.05$

Table 4 Relation between *DVWA rs11718863* single nucleotide polymorphism and clinical evaluation of the knee joint in patient group

Clinical evaluation of the knee joint according to the most severe affected joint	*DVWA rs11718863* SNP genotype				χ^2	*P*	OR	CI
	AA (*n* = 35)		AT + TT (*n* = 15)					
	No.	%	No.	%				
Effusion								
Absent	6	17.1	0	0.0	2.92	0.087	0.629	0.533–0.815
Present	29	82.9	15	100.0				
Anserine bursitis								
Absent	16	45.7	5	33.3	0.661	0.416	0.594	0.168–2.099
Present	19	54.3	10	66.7				
Baker cyst								
Absent	9	25.7	3	27.8	0.188	0.665	0.722	0.165–3.156
Present	26	74.3	12	80.0				

CI confidence interval, *DVWA* double Von Willebrand factor domain A, *OR* odds ratio, *P P* value for comparison between AA and AT + TT, *SNP* single nucleotide polymorphism, χ^2 value of chi-square test, % percentage of patients

*Statistically significant at $P \leq 0.05$

Table 5 Relation between *DVWA rs11718863* single nucleotide polymorphism with WOMAC and HAQ scores results in patient group

WOMAC and AQ scores results	*DVWA rs11718863* SNP genotype				Test of significance	*p*
	AA ($n=35$)		AT + TT ($n=15$)			
	No.	%	No.	%		
WOMAC total						
Mean ± SD	50.20 ± 12.42		52.20 ± 8.58		$t=0.402$	0.689
WOMAC interpretation						
Mild	3	8.6	0	0.0	$\chi^2=1.893$	0.595
Moderate	9	25.7	4	26.7		
Severe	22	62.9	11	73.3		
Extreme	1	2.9	0	0.0		
HAQ score						
Mean ± SD	1.18 ± 0.55		0.98 ± 0.42		$t=1.228$	0.225
HAQ interpretation						
Mild	19	54.3	9	60.0	$\chi^2=0.918$	0.632
Moderate	14	40.0	6	40.0		
Severe	2	5.7	0	0.0		

DVWA double Von Willebrand factor domain A, *HAQ* Health Assessment Questionnaire, *P P* value for comparison between AA and AT + TT, *SD* standard deviation, *SNP* single nucleotide polymorphism, *t* value of Student's t test, χ^2 value of chi-square test, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index, *%* percentage of patients

*Statistically significant at $P \leq 0.05$

Table 6 Relation between *DVWA rs11718863* single nucleotide polymorphism with KL scale severity grades of the knee joint in patient group

KL scale severity grades according to the most severe joint	*DVWA rs11718863* SNP genotype				χ^2	*P*
	AA ($n=35$)		AT + TT ($n=15$)			
	No.	%	No.	%		
MTF KL						
Grade I	6	17.1	3	20.0	0.298	0.960
Grade II	11	31.4	5	33.3		
Grade III	12	34.3	4	26.7		
Grade IV	6	17.1	3	20.0		
LTF KL						
Normal	0	0.0	1	6.7	5.280	0.260
Grade I	13	37.1	3	20.0		
Grade II	8	22.9	3	20.0		
Grade III	13	37.1	6	40.0		
Grade IV	1	2.9	2	13.3		
PF KL						
Normal	1	2.9	0	0.0	2.773	0.597
Grade I	10	28.6	2	13.3		
Grade II	6	17.1	5	33.3		
Grade III	10	28.6	4	26.7		
Grade IV	8	22.8	4	26.7		

DVWA double Von Willebrand factor domain A, *KL* Kellgren–Lawrence scale, *LTF* lateral tibiofemoral, *MTF* medial tibiofemoral, *P P* value for comparison between AA and AT + TT, *PF* patellofemoral, *SNP* single nucleotide polymorphism, χ^2 value of chi-square test, % percentage of patients

*Statistically significant at $P \leq 0.05$

Abbreviations
DVWA: Double Von Willebrand Factor Domain A; HAQ: Health Assessment Questionnaire; JSN: Joint space narrowing; KL: Kellgren–Lawrence; OA: Osteoarthritis; SNP: Single nucleotide polymorphism; VWA: Von Willebrand factor type A; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

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Author contributions
All authors have contributed to the conception and the design of the study, acquisition of data, data analysis and interpretation, article drafting and revise. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants were subjected to written consent in accordance with Helsinki declaration. Study had been accepted by Ethics Committee of Faculty of Medicine, Alexandria University, with Serial Number 0201272.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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