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Association of DVWA rs11718863 Gene Polymorphism with Knee Osteoarthritis in Iraqi Patients

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Abstract

Background Osteoarthritis (OA) is a complex degenerative articular disease that has an ambiguous pathogeny because variant risk factors participate in the process of cartilage deterioration. Genetic factors may have a role in the onset and progression of OA.

Objective To investigate potential association between severity of knee OA (KOA) and Double von Willebrand factor A domains DVWA rs11718863 gene polymorphism.

Methods One hundred and twenty Iraqi patients diagnosed with KOA, aged (45 years and above) and sixty healthy people (control) at the same age range, with no family history of OA were evaluated at Al-Imamein Al-Kadhimein Medical City (Rheumatology Department). The degree of severity of KOA was assessed by clinical and radiographic assessment. DVWA rs11718863 genotyping was performed using DNA sequencing (Sanger's method).

Results Two different genotypes wild homozygote (TT) genotype and heterozygote (AT) appeared by genotyping of DVWArs:11718863. Highly significant difference ($p<0.001$) was found in distribution of the two genotypes in the three study groupsl the genotype (TT) was more frequent in control group (95.0%). Also, high significant difference ($p<0.001$) was noted in the two alleles (A, T) frequencies between control group and KOA patients group giving odd ratio 6.437 with 95% confidence intervals of (1.93-21.42).

Conclusion Iraqi subjects carrying AT genotype of DVWA rs11718863 gene are mostly susceptible for developing of KOA and the allele A of Tyr169Asn polymorphism are more frequent in those patients indicating that allele A may be a risk factor of onset of this disease. Age and body mass index are considered risk factors of onset and progression of KOA.

Keywords Double von Willebrand factor A domains (DVWA), single nucleotide polymorphism (SNP), body mass index, Knee osteoarthritis, KOA

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List of abbreviations: DVWA = Double von Willebrand factor A domains, GWAS = Genome-wide association studies, KOA = Knee osteoarthritis, OA = Osteoarthritis, PCR = Polymerase chain reaction, SNP = Single nucleotide polymorphism, VWA = von Willebrand A

Introduction

Knee osteoarthritis (KOA) occurs as the cartilage in the knee wears away finally causing bone on bone contact between joint surfaces. Most common symptoms would comprise joint stiffness, joint swelling, and pain. KOA can be diagnosed by radiographs showing boney cysts, narrowing joint space, and sclerosis of the bone. This means that KOA comprises the deterioration of joints, including articular cartilage and subchondral bone. But also, ligaments, the capsule and the synovial

membrane disintegrate causing eventually pain and loss of function [1]. Various risk factors such as genetics, aging, obesity and joint deformation may be related with KOA onset and progression [2,3].

The genetic background of OA likely embraces numerous genes that encode proteins with considerable functions in the underlying disease process, suggesting that genetic factors are intensive stimulus of OA emergence [4]. Nineteen common variants associated with OA have been established by Genome-wide association studies (GWAS) reaching or approaching genome-wide significance [5,6].

According molecular genetic examinations have acquired more considerable role in the knowledge of OA etiology and have provided clue for a genetic component to OA [7-9].

Although OA is described as a heterogeneous disease, genetic factors have been found to be strongly affecting factor of this disease. Over the several last years, an increasing number of researches concentrated on the association between gene variants and OA, especially the double von Willebrand factor A domains (DVWA) gene [10-12]. The DVWA gene, that encodes for a protein with two von Willebrand A (VWA) domains, was found to have the rs11718863 single nucleotide polymorphism (SNP), showing a regular association with KOA in Asian OA cohorts (Japanese and Chinese) [10, 11]. Also, DVWA gene is known as collagen type VI alpha 4 pseudogenes 1 (COL6A4P1), particularly expressed in cartilage, encodes for a protein that have DVWA, which has a role in cellular adhesion and protein-to-protein interactions [13].

DVWA gene, on human chromosome 3p24.3, encodes short proteins (276 amino acid) with two regions corresponding to the VWA domain, which was presented in a variety of proteins [14] and it participates in cell adhesion, protein-protein interactions, and membrane transport [15,16]. OA emerges from VWA domain mutations of the matrilin 3 gene (MATN3) [17]. DVWA interacts with β-tubulin and this interaction may be considered a protective factor in OA pathogenesis. It is thought the strength of binding becomes weaker by alleles of two non-synonymous SNPs (rs11718863 and rs7639618) in VWA domain and that weaker binding between β-tubulin and the wild protein may increase the risk of developing OA [15].

Through a previous GWAS in Japanese, it was reported that a compelling association between two missense SNPs and OA risk in Japanese and Chinese KOA cohorts [15]. Then, UK cases study showed mild significant association between DVWA gene variants and OA development, but not in Netherlands, Spain and Greece [18]. Subsequently, separate European or Asian studies failed to replicate the association in Korean and UK samples [19, 20].

In a large GWA interaction study, DVWA genetic variants were tested by Miyamoto et colleagues. In particular, the DVWA rs11718863 SNP is reported to be strongly associated with OA knee injury and is able to affect β-tubulin binding in Asian populations [15].

This study aimed to figure out if the DVWA rs11718863 SNP will increase Iraqi individual`s susceptibility to developing KOA disease.

Methods

This case-control study included 120 Iraqi patients affected by primary KOA with no family history of OA in addition to 60 healthy people (control) aged (45 years and above). Blood samples were obtained at Al-Imamein Al-Kadhimein Medical City (Rheumatology Department), Baghdad, Iraq during the period from March 2017 to May 2017 after submitting all the subjects (patients and control) to clinical (Western Ontario and McMaster Universities Arthritis Index WOMAC) scale [21] and radiographic (Kellgren and Lawrence) grading scale [22] examination and according to these two examinations, subjects were divided into the following 3 groups:

60 (35 females + 25 males) subjects with mild plus moderate KOA.

60 (35 females + 25 males) subjects with severe KOA.

60 (35 females + 25 males) healthy people as control.

All subjects with one of the following conditions were excluded from the study; any other pathological condition that may explain the symptoms (e.g., other rheumatic disease, previous knee joint replacement, intra-articular fracture, septic arthritis, ligament or meniscus damage), pregnant women and co-morbidity that prevents physical examination.

Renal functions test, complete blood picture and erythrocyte sedimentation rate (ESR) test were done for all subjects to make sure they don't have any renal dysfunction that could affect the level of serum sfrp3 protein and to exclude those having rheumatoid arthritis, diabetes. Physiological factors such as body mass index (BMI) and age were evaluated in this study.

Two ml of blood were obtained from each subject by vein puncture and put into Ethylene diamine tetra acetic acid (EDTA) tubes to store in – 70˚C (deep freeze) in order to be used later for genetic analysis. DNA extraction was done using Genomic DNA G-spin DNA extraction kit supplied by Intron Biotechnology, Cat. No. 17045. For analyzing the variation of DVWA gene, polymerase chain reaction (PCR) amplification had been done for all cases and control samples using specific primers pair. A fragment 924 bp of DVWA was amplified using a forward and reverse primers that supplied by IDT (Integrated DNA Technologies company, Canada) (Table 1).

Table 1. The specific primer DVWA of gene [13]

Primer	Sequence	Tm (°C)	GC (%)	Product size
Forward	5'- AGGCTGCCTGCCATTATTCTT- 3'	57.1	47.6	924
Reverse	5'- CCCATGCTGTTTCCTTTGAACA- 3'	56.1	45.5	base pair

PCR products (25 µl) (Figure 1) was prepared and sent for sequencing, to Macrogen, Korea. DNA sequence analysis have been done using BLAST program from National Center Biotechnology Information (NCBI) [23]. Patients DNA sequence had compared and alignment with DVWA gene sequence of both standard and control. Analysis of SNP also were done using the tools that provided by these sites. PCR product samples (120) were sent for sequence analysis represent patient and 60 sample represent healthy control; the samples were sequenced using DNA sequencer 3730XL, Applied Biosystem machine in national instrumentation center for environmental management NICM/USA company online at (http://nicem.snu.ac.kr/main/en_skin=index.html). The result of the sequence analysis was analyzed by blast in the NCBI online at (http://www.ncbi.nlm.nih.gov) and BioEdit program to detect gene mutation and polymorphism in DVWA gene.

Statistical analysis

The continuous data were presented as mean values ± standard error (SE); comparison of these data between two groups was performed by applying a Student's t test, and ANOVA (analysis of variance) and post hoc Tukey test was used for comparison of means of more than two groups. While for calculation of genotyping and allele frequency, Chi-square test was used to compare between percentages between groups. P value <0.05 was considered significant. The software used was statistical package for social sciences (SPSS), version 23.

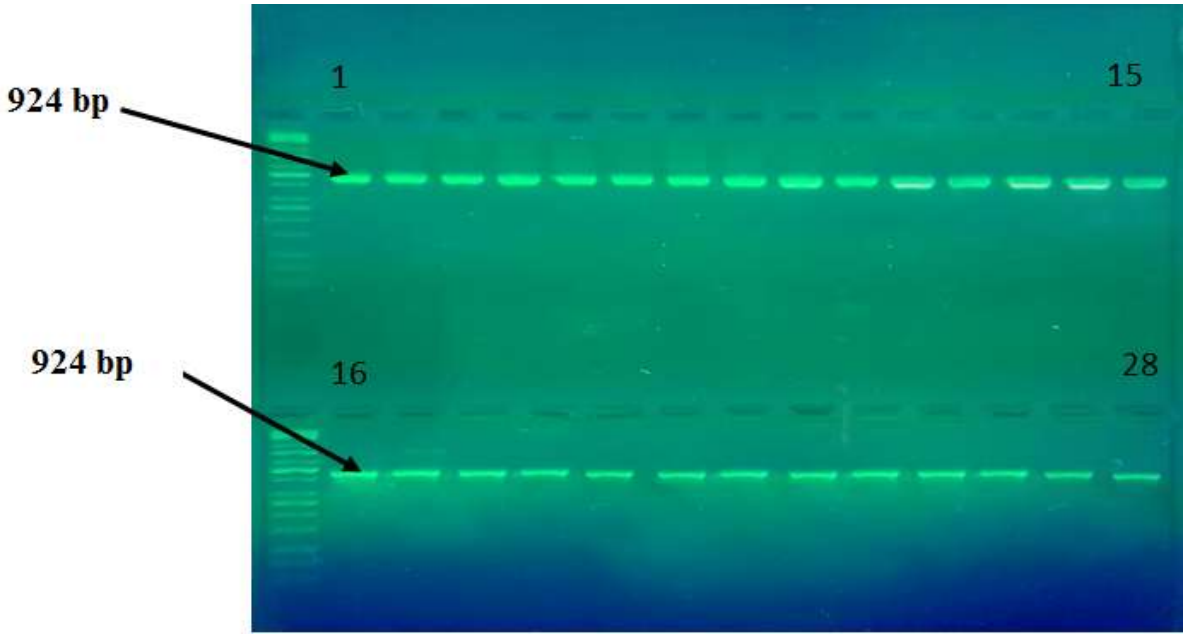

Figure 1. PCR product of DVWA gene, the band size 924 bp. The product was electrophoresed on 1.5% agarose at 7 volt/cm^2. 1x TBE buffer for 1:30 hours. N: DNA ladder (100)

Results

There was high significant difference in the mean age and BMI of patients among the three study groups (p<0.001, p<0.001) respectively (Table 2).

Table (3) shows comparison between each two groups using post hoc Tukey test. Regarding age, there was significant difference between severe KOA group compared to control and mild plus moderate KOA groups (p<0.001, p<0.001) respectively, whereas, no significance in age between control and mild plus moderate KOA (p=0.967). BMI of both groups of KOA (mild plus moderate and severe) was significantly higher than control (p=0.028, p=0.004) respectively, while no significance was found between the two KOA groups (p=0.787).

Table 2. Comparison of age and body mass index among the three study groups (according to severity) by ANOVA

Parameter	Control N=60 Mean±SE	Mild plus moderate KOA N=60 Mean±SE	Severe KOA N=60 Mean±SE	P value*
Age (yr)	61.47±1.54	60.98±1.42	69.52±1.17	<0.001
BMI (kg/m^2)	27.46±0.74	30.67±0.87	31.49±1.0	٠,٠٠٣

KOA = Knee osteoarthritis, BMI = Body mass index, *ANOVA

Table 3. Comparison of age and body mass index between each pair of the three study groups (according to severity) by post hoc Tukey test

Dependent Variable	1st Group	2nd Group	P value
Age (yr)	Control	Mild plus moderate	0.967
	Control	Severe	<0.001
	Mild plus moderate	Severe	<0.001
BMI (kg/m^2)	Control	Mild plus moderate	0.028
	Control	Severe	0.004
	Mild plus moderate	Severe	0.787

BMI = Body mass index

Two different genotypes were found by genotyping the DVWA rs11718863 gene; wild homozygote (TT) and heterozygote (AT). There was a highly significant difference in the distribution of them among the 3 study groups (p> 0.001); as the highest percentage of the wild type was found in control group 95.0% compared to 88.7% in mild plus moderate KOA group and to 51.7% in severe KOA group. While the highest percentage of the heterozygote type was found in severe KOA group 48.3% compared to 11.3% in mild plus moderate KOA group and to 5.0% in control group. The mutant genotype (AA) was not found in any group in this study (Table 4). The distribution of both genotypes of DVWA gene are shown in figures (2 and 3).

The frequencies of the two alleles (T and A) between control group and the KOA patients groups in general were demonstrated in the table (5). The percentage of T allele in control group was 97.5% compared to 85.8% in total KOA patients. While the percentage of allele A was 2.5% only in control group compared to 14.2% in total Knee OA patients. This difference was highly significant (p< 0.001) with a high odd ratio 6.437 and confidence interval of (1.93-21.42). shows high significant difference.

Table 4. Genotyping distribution of DVWA gene polymorphisms in the three study groups

Group	DVWA			Total	P value
	TT	AT	AA		
Control	57 (95.0%)	3 (5.0%)	0 (0.0%)	60	< 0.001*
Mild plus moderate	55 (88.7%)	5 (11.3%)	0 (0.0%)	60	
Severe	31 (51.7%)	29 (48.3%)	0 (0.0%)	60	
Total	143 (79.4%)	37 (20.6%)	0 (0.0%)	180	

* Chi square test

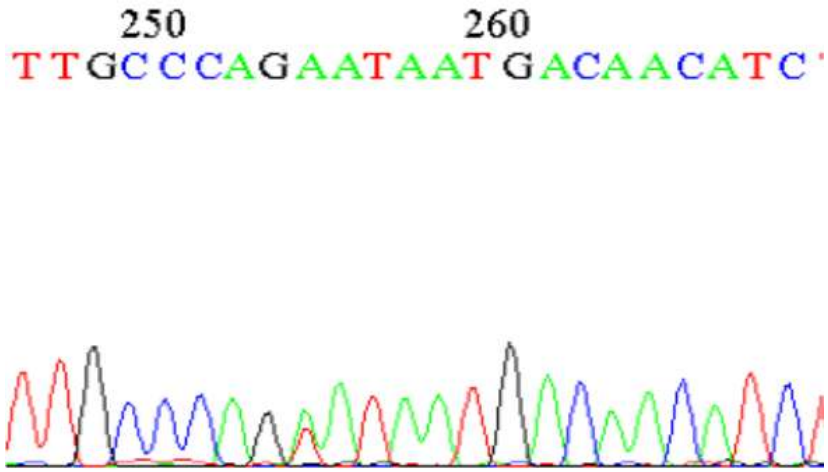

Figure 2. Photographic of Macrogen appeared AT genotyping

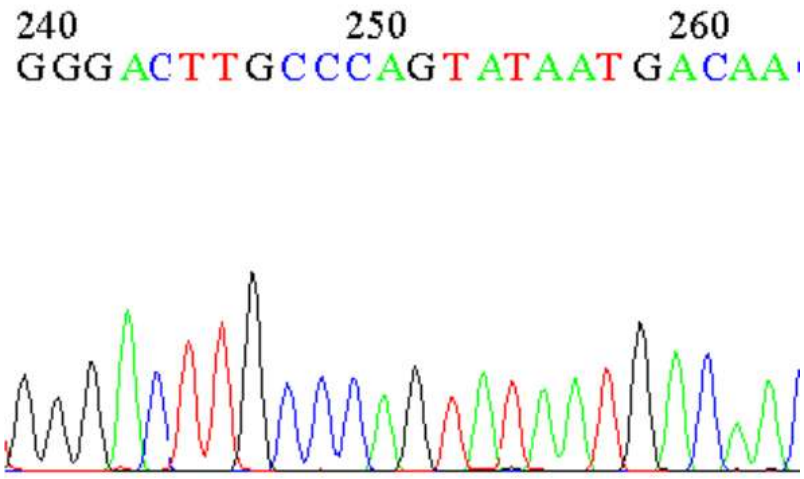

Figure 3. Photographic of Macrogen appeared TT genotyping

Table 5. Allele frequencies and percentage, odd ratio (OR) and confidence interval (CI) of DWVA gene in control and knee OA patients' groups

Group	T	A	Total	P value	Odd ratio	95% CI
Control	117 (97.5%)	3 (2.5%)	120	<0.001*	6.437	1.93-21.42
KOA	206 (85.8%)	34 (14.2%)	240			
Total	323	37	٣٦٠			

KOA: Knee osteoarthritis, * Fisher exact test

When comparison done between control group and mild plus moderate KOA groups, there was no significant difference in the two alleles (T & A) percentage (p=0.772), the odd ratio was 1.696 with confidence interval (0.4-7.26) as illustrated in table (6).

Table 6. Allele frequencies and percentage, odd ratio (OR) and confidence interval (CI) of DWVA gene in control and mild knee OA patients' groups

Group	T	A	Total	P value	Odd ratio	95% CI
Control	117 (97.5%)	3 (2.5%)	120	0.722	1.696	0.4-7.26
Mild plus moderate KOA	115 (95.8%)	5 (4.2%)	١٢٠			
Total	232	8	٢٤٠			

KOA: Knee osteoarthritis, * Fisher exact test

High significant difference (p<0.001) was noted in the two alleles percentage (T and A) between mild plus moderate KOA and severe KOA groups. For the allele T; high percentage 95.8% was found in mild plus moderate KOA group compared to 75.8% in severe KOA group, whereas the high percentage 24.2% of allele A was found in severe KOA group compared to only 4.2% in mild KOA group. This variation in frequencies gave high odd ratio 7.33 with confidence interval (2.728-19.69) (Table 7).

Table 7. Allele frequencies and percentage, odd ratio (OR) and confidence interval (CI) of DWVA gene in control and mild knee OA patients' groups

Group	T	A	Total	P value	Odd ratio	95% CI
Mild KOA	115 (95.8%)	5 (4.2%)	١٢٠	<0.001*	7.33	2.728-19.69
Severe KOA	91 (75.8%)	29 (24.2%)	١٢٠			
Total	206	34	٢٤٠			

KOA: Knee osteoarthritis, * Fisher exact test

Discussion

Considering OA as a degenerative disease, it always occurs in elderly populations indicating that aging is a major risk factor for primary OA, the most common form in humans [24]. Current results showed age of severe KOA patients was significantly higher than age of patients with mild plus moderate KOA patients and with controls. Regarding controls, it was hard to obtain complete healthy subjects at the same age group of severe KOA patients in our country with all its circumstances at time of the study. In concern to mild plus moderate KOA, it agreed with other study that found increasing age accompanied by increasing OA change [24]. Driban et al. [25] mentioned that during aging, senescence is caused by a continuous decrease in telomere due to repeated cell division or environmental stress factors, such as oxidative damage, chronic inflammation or ultraviolet radiation. Other studies showed that the role of reactive oxygen species (ROS) in many of the

age-related changes found in articular cartilage that alter cartilage homeostasis and contribute to the development of osteoarthritis. An increase in chondrocyte ROS levels occurs with aging [26-28]. Others factors suggested may reduce the "wear and tear risk" for developing OA [29,30].

BMI is one of the risk factors in developing of KOA; in current study, a significant association is found between the higher BMI and the severity of KOA as it is revealed in the results that show significant association.

Two previous meta-analyses studies found that increasing BMI associated with increased incidence of both knee and hip OA. They mentioned that for each 5-unit increase in BMI, the risk of KOA increased by 35%, and the risk of hip OA increased by 11% [31,32].

Concerning the mutational analysis; the current study revealed that there is a significant statistical association between DVWA rs11718863 genetic alterations and the susceptibility and progression of KOA in Iraqi patients as there was high percentage of A allele in KOA patient while T allele was higher in control group. The same significant difference was also shown between two groups of KOA patients where T allele was higher in severe group in comparison to mild plus moderate KOA group.

Current results agree with other studies, which showed that DVWA gene specifically expressed in normal and OA cartilage tissues, encodes a protein showing VWA domain, having a role in cell adhesion and protein-protein interactions [13,14].

Minafra et al. (2014) found the DVWA rs11718863 SNP is reported to be strongly associated with the risk of KOA (odds ratio = 1.43, P <0.001) and able to influence β-tubulin binding in Asian populations [13]. Nevertheless, Valdes and colleagues (2009) showed an association between this genetic alteration and KOA in the UK Nottingham total knee replacement OA group (P <0.046) [33].

Miyamoto et al. suggested that both rs11718863 DVWA and rs7639618 polymorphisms may be involved in the etiopathogenesis of OA in Japanese and Chinese people, in particular, DVWA rs11718863 SNP is reported to be strongly associated with KOA. The OA susceptibility rs11718863 polymorphism is found in the exonic region of the DWVA type and causes a change of missense by following the amino acidic Tyr169Asn. In addition, Tof169-Cys260 double-protein isoform modification, may have a weak binding effect of β-tubulin and appears to be overexpressed to OA, and suggests that this interaction may be a basis for protecting OA members [15].

Meulenbelt and colleagues also described a moderately important association in the UK sample (P = 0.046), which is not validated in other European countries. However, the high frequency of allele risk in European samples highlighted the unique penetration of OA susceptibility genes and the need to evaluate the distribution of alleles 'geographic [18].

The DWVA protein, which is involved in cell adhesion and protein-binding proteins, binds to β-tubulin microtubules and plays an important role in regulating chondrocyte separation, protecting articulate joints from the onset of OA. In particular, rs11718863 SNP attracts a diminished link between DVWA and β-tubulin and causes the development of OA [10,16].

Other study conducted on Finnish women found that the variants in many candidate genes including DVWA gene were associated with OA across multiple sites [34].

Furthermore, another study on 66 Sicilian individuals affected by primary KOA revealed a significant statistical association between severity of KOA disease and DVWA rs11718863 genetic alterations. This gene was associated with a more severe radiographic grade, displaying its predictive role as OA marker progression [13].

Bravata et al. (2015) proposed a hypothesis that DVWA gene rs11718863 and rs7639618 polymorphisms cause missense mutation with a consequent amino acidic substitution (Tyr169Asn and Cys260Tyr, respectively). The Tyr169-Cys260 isoform decreases the strength interaction between the DVWA protein and the β-tubulin, which affects regulation of chondrocyte differentiation, subsequently resulting in OA especially in Asians [20].

Hämäläinen et al. (2014) found in subgroup analysis, that DVWA gene rs7639618 and rs11718863 polymorphisms were closely associated with the risk of OA in Asians, but not in Caucasians [35].

In contrast, other studies did not find any significant association between the DVWA polymorphisms (rs7639618, rs9864422 and rs11718863) and susceptibility to Developmental dysplasia of the hip DDH in the Chinese Han population [36,37].

DVWA rs11718863 and rs7639618 polymorphisms have both been found in the exonic region (third) and cause genetic mutations by amino acidic substitution (Tyr169Asn and Cys260Tyr, respectively). These SNPs are involved in reducing the energy interaction between DVWA protein and β-tubulin, this protein-binding binding is important in regulating chondrocyte differentiation that protects the joints from the onset of OA [16,18].

In conclusion, Iraqi people carrying AT genotype of DVWA rs11718863 gene are mostly susceptible for developing of KOA and the allele A of Tyr169Asn polymorphism are more frequent in those patients indicating that allele A may be a risk factor of onset and progression of this disease.

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Author contribution

Dr. Hasan: Design of the study, data collection, DNA sequencing, results interpretation. Dr. Alwasiti: Design of study, supervision of all steps of the study. Dr. Ahmed: Statistical analysis and final revision of the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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