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Association between primary osteoarthritis and *ADAMTS14* single nucleotide polymorphism in Egyptian population: a case-control study

Noha Abdelhady Abdelsadek Mostafa[1*], Ibrahim Khalil Ibrahim[1], Neveen Lewis Mikhael[2] and Emmanuel Kamal Aziz Saba[1]

Abstract

Background: Primary osteoarthritis is considered one of the most common and the most studied musculoskeletal disorder. Nevertheless, the risk factors remain unclear. A disintegrin and metalloproteinase with thrombospondin motifs (*ADAMTS*) 14 (*ADAMTS14*) gene is involved in the cleavage of amino-terminal propeptides from type II procollagen, a necessary step in the formation of collagen fibers. The abnormal metabolism of collagen fibers type II leads to a decreased mechanical strength of joint cartilage which is one of the most important contributing factors to joint osteoarthritis. We aimed at investigating the association between primary osteoarthritis and *ADAMTS14* gene rs4747096 single nucleotide polymorphism in a sample of Egyptian patients and analyzing the relationship between this genetic polymorphism with the severity of osteoarthritis. Sixty-five Egyptian patients who fulfilled the American College of Rheumatology criteria for primary knee osteoarthritis were compared with thirty-one apparently healthy subjects. Genotyping was performed by TaqMan single nucleotide polymorphism genotyping assay.

Results: There was a statistically significantly higher frequency of AA genotype among osteoarthritis patients compared to the control group ($P = 0.004$). The number of affected hand joints was significantly higher among patients with *ADAMTS14* AA genotype in comparison to patients with *ADAMTS14* AG genotype ($P = 0.002$). In addition, AA genotype was associated with statistically significantly higher Kellgren-Lawrence radiological grades in the knee and hand joints (proximal interphalangeal and thumb interphalangeal joints) ($P = 0.037$, 0.003, and 0.030 respectively).

Conclusion: The study showed an association between the AA genotype of *ADAMTS14* gene rs4747096 single nucleotide polymorphism with knee and hand osteoarthritis and osteoarthritis severity in these joints. The AA genotype of *ADAMTS14* gene rs4747096 single nucleotide polymorphism could be implicated in the increased incidence of primary osteoarthritis development and elevated disease severity among the Egyptian population.

Keywords: Osteoarthritis, Egyptians, *ADAMTS14*, Single nucleotide polymorphism

Background

Primary osteoarthritis (OA) is considered one of the most common and the most studied musculoskeletal disorders. Nevertheless, the etiological risk factors are still unclear [1–3]. The molecular genetic investigations have gained an increasingly significant role in elaborating the evidence for the genetic component of OA through searching for OA susceptibility loci. Recently, many studies have been conducted to investigate the relationship between gene polymorphism and primary OA in Egypt including matrilin 3, growth differentiation factor 5, leptin receptor, and tumor necrosis factor α genes [4–7].

A disintegrin and metalloproteinase with thrombospondin motifs (*ADAMTS*) 14 (*ADAMTS14*) gene is

*Correspondence: nohaemail@gmail.com
[1] Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Alexandria University, Alexandria, Alexandria Governorate 21131, Egypt
Full list of author information is available at the end of the article

involved in the cleavage of amino-terminal propeptides from type II procollagen, a necessary step in the formation of collagen fibers. The abnormal metabolism of collagen fibers type II can lead to a decreased mechanical strength of the articular cartilage which is one of the most important triggering factors for OA [8, 9].

Our aim of this study was to investigate the association between primary OA with *ADAMTS14* gene rs4747096 single nucleotide polymorphism (SNP) in a sample of Egyptian patients and to analyze the relationship between this genetic polymorphism with the severity of OA.

Methods

We recruited sixty-five Egyptian patients with primary knee OA (23 of them had primary hand OA) from those attending the Outpatient Clinic of the authors' department. All patients fulfilled the American College of Rheumatology (ACR) criteria for primary knee OA [10]. Patients who showed associated hand OA symptoms were considered generalized OA (GOA) patients if fulfilled ACR criteria for hand OA [11, 12]. Patients were compared to thirty-one apparently healthy subjects matching in age and sex. We excluded all patients with secondary OA, severe cardiovascular disease, severe liver and kidney dysfunction, malignant tumor, and autoimmune diseases [4]. Patients only were subjected to radiological assessment but not the healthy control.

The study had been approved by the local ethics committee with ethical approval number 0201272. Written informed consent was taken from all participants before the start of the study.

All patients were subjected to thorough clinical examination with stress on musculoskeletal examination. Radiographs were analyzed by Kellgren-Lawrence (KL) grading scale [13].

Genomic deoxyribonucleic acid (DNA) was extracted from EDTA whole blood samples using QIAGEN total DNA purification Mini Kit QIAamp® imported from Germany [14].

Genotyping of *ADAMTS14* gene rs4747096 SNP was performed by TaqMan® SNP genotyping assay (Applied biosystems-Life Technologies, Thermo Fisher Scientific, Lithuania). Allelic discrimination was done using the 5′ nuclease assay on Stratagene machine Mx3000P Q system [14].

Data were fed to IBM SPSS software package version 23.0. Qualitative data was described using numbers and percentages. Quantitative data was described using mean, standard deviation, minimum, maximum, and median. *P* value was statistically significant when equal to or less than 0.05. The statistical test used for qualitative data was the chi-square test and for quantitative data were Mann-Whitney and Kruskal-Wallis tests.

Results

Among the 65 OA patients, there were 42 knee OA patients and 23 GOA patients. There were no statistically significant differences between patient groups and control group as regards demographic and anthropometric characteristics (Table 1).

The genotype distribution of *ADAMTS14* gene rs4747096 SNP in the knee OA patient group was in the form of AA (47.6%) and AG (52.4%), whereas genotype distribution of the GOA patient group was in the form of AA (43.5%) and AG (56.5%). The control group genotype figure was AA (9.7%), AG (83.9%), and GG (6.5%). There was a statistically significant difference between the 3 groups as regards the frequency of different *ADAMTS14* genotypes ($P = 0.004$) (Table 2).

There were statistically significant differences between A and G allele frequency between the 3 groups ($P = 0.024$). Both genotype and allele distribution are illustrated in Table 2.

Table 1 Demographic and anthropometric characteristics in patient groups and control group

Demographic and anthropometric characteristics	Patient groups ($n = 65$)		Control group ($n = 31$) mean ± SD (median)	Test of significance	*P*
	Knee OA ($n = 42$) mean ± SD (median)	GOA ($n = 23$) mean ± SD (median)			
Age (years)	53.26 ± 8.69 (54.0)	52.74 ± 8.32 (51.0)	50.13 ± 7.68 (49.0)	(K) 2.349	0.309
Female gender[a]	36 (85.7)	19 (82.6)	23 (74.2)	(χ^2) 1.591	0.451
Weight (kg)	83.07 ± 15.73 (81.75)	83.89 ± 8.32 (86.0)	83.40±12.91 (84.0)	(K) 0.046	0.309
Height (m)	1.52 ± 0.93 (1.62)	1.63 ± 0.05 (1.63)	1.66 ± 1.01 (1.64)	(K) 1.581	0.454
BMI (kg/m^2)	31.74 ± 5.02 (32.16)	31.59 ± 4.72 (32.37)	30.57±4.94 (29.76)	(K) 1.314	0.518

BMI Body mass index, *GOA* Generalized osteoarthritis, *m* meter, *No.*, *n* Number of patients or subjects, *OA* Osteoarthritis, *K* value of the Kruskal-Wallis test, *kg* kilogram, *P P* value for comparing between the studied groups, *SD* standard deviation, χ^2 value of the chi-square test

*Statistically significant at $P \leq 0.05$

[a] Data are presented as number (percentage)

Table 2 Genotype distribution of *ADAMTS14* gene rs4747096 single nucleotide polymorphism in patients' groups and control group

***ADAMTS14* gene rs4747096 SNP genotype**	**Patient groups**				**Control group ($n = 31$)**		**Test of significance (χ^2)**	***P***
	Knee OA ($n = 42$)		**GOA ($n = 23$)**					
	No.	**%**	**No.**	**%**	**No.**	**%**		
AA	20	47.6	10	43.5	3	9.7	15.410	0.004*
AG	22	52.4	13	56.5	26	83.9		
GG	0	0.0	0	0.0	2	6.5		
Allele								
A	62	73.8	33	71.7	33	53.2	7.502	0.024*
G	22	26.2	13	28.3	29	46.8		

ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs, *GOA* generalized osteoarthritis, *No.*, *n* number of patients or subjects, *OA* osteoarthritis, *P P* value for comparing between the studied groups, *SNP* single nucleotide polymorphism, χ^2 value of the chi-square test, *%* percentage of patients or control

*Statistically significant at $P \leq 0.05$

Table 3 Association between *ADAMTS14* gene rs4747096 single nucleotide polymorphism genotype and different clinical and radiological features of the hand joints in the generalized osteoarthritis patient group

Different clinical and radiological features of the hand joints	***ADAMTS14* gene rs4747096 SNP genotype**		**Test of significance[b]**	***P***
	AA ($n = 10$)	**AG ($n = 13$)**		
Number of affected hand joints				
Min.-Max.	21.00–22.00	6.00–22.00	16.500	0.002*
Median	22.00	15.00		
Number of deformed hand joints				
Min.-Max.	0.00–10.00	0.00–.00	64.000	0.976
Median	1.50	1.00		
Number of joints with Heberden node				
Min.-Max.	0.00–8.00	0.00–4.00	59.000	0.738
Median	2.50	2.00		
Number of joints with Bouchard node				
Min.-Max.	4.00–8.00	1.00–8.00	48.000	0.313
Median	8.00	6.00		
PIP KL				
Grade I[a]	0 (0.0)	4 (30.8)		
Grade II[a]	0 (0.0)	6 (46.2)	(χ^2) 13.618	0.003*
Grade III[a]	7 (70.0)	2 (15.4)		
Grade IV[a]	3 (30.0)	1 (7.7)		
Thumb IP KL				
Normal[a]	0 (0.0)	1 (7.7)		
Grade I[a]	0 (0.0)	5 (38.5)	(χ^2) 10.676	0.030*
Grade II[a]	5 (50.0)	2 (15.4)		
Grade III[a]	4 (40.0)	1 (7.7)		
Grade IV[a]	1 (10.0)	4 (30.8)		

ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs, *IP* interphalangeal joint, *KL* Kellgren-Lawrence scale, *Max.* maximal, *Min.* minimal, *n* number of patients, *P P* value for comparing between AA and AG, *PIP* proximal interphalangeal joint, *SNP* single nucleotide polymorphism, χ^2 value of the chi-square test

*Statistically significant at $P \leq 0.05$

[a] Data are presented as number and percentage

[b] Value of the Mann-Whitney test

The number of affected hand joints was significantly higher among patients with *ADAMTS14* AA genotype in comparison to patients with *ADAMTS14* AG genotype ($P = 0.002$) (Table 3), while there were no statistically significant differences between AA versus AG genotypes of *ADAMTS14* regarding the presence of knee effusion, anserine bursitis, and backer cyst ($P = 0.184$, 0.060, and 0.131 respectively) (Table 4). The frequencies of higher KL grades of the proximal interphalangeal (PIP), thumb interphalangeal (IP), and knee joints were significantly higher among patients with *ADAMTS14* AA genotype in comparison to patients with *ADAMTS14* AG genotype ($P = 0.003$, 0.030, and 0.037 respectively) (Tables 3 and 4). There were no statistically significant differences between patients with *ADAMTS14* AA genotype versus those with *ADAMTS14* AG genotype regarding BMI value ($P = 0.173$) and BMI grades ($P = 0.402$).

Discussion

In the current study, there was a statistically significant higher prevalence of AA genotype rather than AG genotype among primary knee OA and GOA patients compared to the control group ($P = 0.004$). Interestingly, GG genotype was detected only in 2 subjects among the control group and was not detected in the patient groups.

Studies carried on the relation between *ADAMTS14* gene rs4747096 SNP and OA development have yielded conflicting results. This study results were in agreement with Poonpet et al. (their study was carried out on 108 knee OA cases compared to 119 healthy individuals) and Wang et al. (their study was carried out on 103 temporomandibular joint OA patients and 110 healthy people) regarding that AA genotype was significantly higher among the OA patient group [15, 16].

Meanwhile, this result was not evident with Rodriguez-Lopez et al. (their study included different sampled collections of European Caucasians, 242 hand OA patients, 307 knee OA patients, and 262 knee OA patients compared to 294 selected controls) and Ma et al. (their study enrolled 346 knee OA patients and 480 healthy controls) regarding that GG genotype was more significantly higher among the OA patient group [9, 17]. These conflicting results could be attributed to different genetic distributions between different ethnic populations.

The A allele frequency was significantly higher in the patient group ($P = 0.024$), in concordance with Poonpet et al. though not in agreement with Rodriguez-Lopez et al. and Ma et al. where the G allele was more frequent, while Wang et al. showed no significant difference between the two alleles. This could be additionally related to different ethnicities [9, 15–17].

The number of affected hand joints in patients with GOA was significantly higher among AA genotype subjects ($P = 0.002$). This result was running in agreement with Rodriguez-Lopez et al. that *ADAMTS14* gene rs4747096 SNP might be associated with hand OA [17].

Table 4 Association between *ADAMTS14* gene rs4747096 single nucleotide polymorphism genotype and different clinical and radiological features of the knee joint in all participated patients

Different clinical and radiological features of the knee joint	*ADAMTS14* gene rs4747096 SNP genotype				Test of significance (χ^2)	*P*
	AA ($n = 30$)		AG ($n = 35$)			
	No.	%	No.	%		
Knee effusion						
Absent	24	80.0	32	91.4	1.769	0.184
Present	6	20.0	3	8.6		
Anserine bursitis						
Absent	7	23.3	16	45.7	3.539	0.060
Present	23	76.7	19	54.3		
Baker cyst						
Absent	10	33.3	6	17.1	2.282	0.131
Present	20	66.7	29	82.9		
Knee KL						
Grade I	4	13.3	7	20.0		
Grade II	10	33.3	14	40.0	8.484	0.037*
Grade III	6	20.0	12	34.3		
Grade IV	10	33.3	2	5.7		

ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs, *KL* Kellgren-Lawrence scale, *No.*, *n* number of patients, *P P* value for comparing between AA and AG, *SNP* single nucleotide polymorphism, χ^2 Value of the chi-square test, % percentage of patients

*Statistically significant at $P \leq 0.05$

There was no significant difference between both genotypes in symptomatic hand OA patients regarding the number of deformed joints and number of joints with Heberden nodes and Bouchard nodes ($P = 0.976$, 0.738, and 0.313 respectively). This was similar to Rodriguez-Lopez et al. except in Santiago group in the same study showed a higher incidence of symptomatic hand OA with G allele presence. This could be attributed to different ethnicity and genetic distribution as well [17].

Regarding clinical knee evaluation, there were no statistically significant differences between AA and AG genotypes for the presence of knee effusion, anserine bursitis, and baker cyst ($P = 0.184$, 0.060, and 0.131 respectively). This was contradictory to Rodriguez-Lopez et al. in which symptomatic knee OA was higher with the G allele [17].

Regarding the radiologic findings, knee KL severity scale grade was significantly worse with the AA genotype ($P = 0.037$), suggesting that the AA genotype could be associated with increased structural damage of knee OA. Rodriguez-Lopez et al. and Ma et al.—in contradiction—showed no significant difference between different genotypes and KL scale grades of knee OA radiology [9, 17].

Regarding hand OA radiology, the KL scale grade of the PIP joint and IP joint of the thumb was similarly significantly worse with the AA genotype ($P = 0.003$ and 0.030 respectively). These suggested that hand OA severity could be increased with AA genotype and these were in agreement with Rodriguez-Lopez et al. that *ADAMTS14* gene rs4747096 SNP could be related to GOA and hand OA [17].

Originally, *ADAMTS14* gene rs4747096 SNP entitles a change of glutamic acid (GAA) to glycine (GGA) in the carboxyl terminal domain of *ADAMTS14* protein. The allele G exists in *ADAMTS14* orthologues in non-human primates such as chimpanzee, while the A allele is more frequent in humans than the G allele as the A allele is represented in a larger frequency among European, African, and Asian populations [9, 18]. Rodriguez-Lopez et al. and Ma et al. hypothesized that substitution of glutamic acid to glycine in *ADAMTS14* gene rs4747096 SNP may result in an abnormal function in the protein processing of collagen precursor and abnormal collagen type II maturation with finally cartilage degradation and OA development [9, 17].

The results of both A and G alleles which had been shown in our study—and in previous studies (like Poonpet et al. and Wang et al.)—suggested that the role of amino acid substitution caused by rs4747096 SNP in *ADAMTS14* is not the main contributing factor to OA [15, 16]. However, *ADAMTS14* gene rs4747096 polymorphic locus seems to be associated with OA development. In our study, it showed a strong relation between AA genotype with knee and hand OA susceptibility and severity.

The small sample size, absence of comparison with hip and vertebral joints, and limited percentage of participated male patients could be some limiting factors in the present study.

Further studies with larger samples and including more additional joints should be conducted in the future to assess the relation between *ADAMTS14* gene rs4747096 SNP with OA susceptibility and severity in the Egyptian population. This could be a basis for future early prevention of OA development and progression and it could be a future target for OA treatment.

Conclusions

Our study showed an association between the AA genotype of *ADAMTS14* gene rs4747096 SNP with knee and hand OA and OA severity in these joints. The AA genotype of *ADAMTS14* gene rs4747096 SNP could be implicated in the increased incidence of primary OA development and elevated disease severity among the Egyptian population. To our best knowledge, this was the first study conducted among the Egyptian population to assess the relation between *ADAMTS14* gene rs4747096 SNP and primary OA.

Abbreviations

ACR: American College of Rheumatology; *ADAMTS*: A disintegrin and metalloproteinase with thrombospondin motifs; *ADAMTS14*: A disintegrin and metalloproteinase with thrombospondin motifs 14; DNA: Deoxyribonucleic acid; GOA: Generalized osteoarthritis; KL: Kellgren-Lawrence; IP: Interphalangeal; OA: Osteoarthritis; PIP: Proximal interphalangeal; SNP: Single nucleotide polymorphism.

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Authors' contributions

All authors have contributed to the conception and the design of the study, acquisition of data, data analysis and interpretation, and article drafting and revision. The 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 the Helsinki Declaration. The study had been accepted by the 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.

Author details
[1]Physical Medicine, Rheumatology and Rehabilitation Department, Faculty of Medicine, Alexandria University, Alexandria, Alexandria Governorate 21131, Egypt. [2]Clinical and Chemical Pathology Department, Faculty of Medicine, Alexandria University, Alexandria, Alexandria Governorate 21131, Egypt.

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