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ORIGINAL ARTICLE

The Relation between Growth Differentiation Factor 5 Polymorphism and Osteoarthritis in Egyptian Population

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ABSTRACT

Background: Osteoarthritis is the most common form of arthritis worldwide. Growth Differentiation Factor 5 (GDF5) is closely related to bone morphogenic protein, and the defect in this gene might be correlated to the abnormal joint development. The aim of this study was to detect GDF5 gene polymorphism in osteoarthritis (OA) Egyptian population and its association with OA severity.

Methods: A case-control study was conducted in the Rheumatology and Rehabilitation Department, Zagazig University Hospitals. This study included 195 patients with primary OA, and 195 healthy control subjects. They were subjected to history taking, clinical examination and laboratory investigations including CBC, ESR, CRP, RF, lipid profile. Detection of GDF5 gene polymorphism was performed using PCR RFLP (restriction fragment length polymorphism) technique. Assessment of OA severity was assessed using WOMAC and Lequesne index of severity for knee and hip OA, AUSCUAN questionnaire for hand OA and K/L radiological grading of knee OA.

Results: The study showed statistically significant difference between OA patients and control groups regarding genotype frequency of GDF5 gene polymorphism. No statistically significant association between total WOMAC index, Lequesne index in OA hip and knee and AUSCUAN questionnaire for hands OA with different genotype of GDF5. However, TC genotype was higher as compared to patients with TT and CC genotypes. There was a statistically significant association between different GDF5 genotypes and K/L radiological grading of knee OA.

Conclusions: This study revealed a genetic association between GDF5, and primary OA and TC genotype may be associated with more severe and disability of primary OA.

Keywords: Osteoarthritis (OA); Growth differentiation factor (GDF5) polymorphism; PCR RFLP.

INTRODUCTION

OA is the most common chronic degenerative and disabling joint disease worldwide [1]. The major clinical manifestations of knee OA are pain and stiffness. OA leads to physical and psychosocial disability associated with deterioration of quality of life [2].OA is a complex chronic multifactorial age-associated disease which has a profound effect on the functioning of synovial joints primarily the knee, hip, and hands. The pathogenesis of the disease involves the irreversible destruction of the articular cartilage escorted by alterations in the homeostatic balance of chondrocyte cells and changes in other joint tissues [3].Metabolic, biochemical, and genetic factors are among major risk factors associated with the onset and development of OA [4]. Genetic factors contribute enormously to the etiology and pathogenesis of OA and the most important OA risk is GDF5 gene polymorphism [5]. GDF 5 was shown to play a substantial role in the process of development, maintenance, and repair of cartilage and bone [6].The aim of this study was to detect GDF5 gene polymorphism in osteoarthritis (OA) Egyptian population and its association with OA severity.

METHODS

Study Design:

This case control study included 195 patients with primary and 195 apparent healthy subjects as control group. OA patients were randomly selected from Rheumatology and Rehabilitation

Department, Zagazig University hospitals, between August 2014 and July 2017.

Inclusion Criteria:

All patients fulfilled the American College of Rheumatology (ACR) criteria for hip OA [7], hand OA [8] and knee OA [9].

Exclusion Criteria:

Exclusion criteria included patients with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, dermatomyositis, and mixed connective tissue disease.

Ethical Approvals:

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Procedures: All patients were subjected to full history taking, general and locomotor examination and routine laboratory investigations including CBC, ESR, CRP, RF and lipid profile.

Genetic analysis of GDF5 gene polymorphism:

Samples of peripheral venous blood were collected aseptically from every subject in a tube containing 0.5 ml EDTA. The collected samples were stored at -20°C until being extracted DNA was extracted from blood leucocytes by using proteinase K digestion, polymerase chain reaction (PCR) for gene amplification by applying a direct sequencing technique revealed the existence of a GDF5 gene to confirm a rapid detection method was developed where a 251-pb DNA fragment was amplified (primer forward 5' GAT TTT TTC TGA GCA CCT GCA GG 3') and (reverse 5' GTG TGT GTT TGT ATC CAG 3') its product digested with Ddel restriction endonuclease .

PCR Thermal Cycler,Veriti 96 Well Thermal cycler and applied biosystems was used which allows both heating and cooling of the block holding the PCR tubes constantly then electrophoresis reagents .Instruments: Micro-computer Electrophoresis power supply (Consort, Belgium), UV Trans-illuminator (Red imager, Cell Biosciences, California, USA), Micro-wave oven (Whirlpool, USA) and Balance (OHAUS, New Jersey, USA). Agarose preparation:2% agarose solution was prepared by adding 2gm agarose to 98 ml of 1Xelectrophoresis buffer in 250 ml flask the agarose was then dissolved by heating in a micro-wave oven for 1.5minutes. Interpretation: The gel was examined under ultraviolet light as ethidium bromide intercalate between the bases of the DNA and fluoresces molecular size marker gave different bands ranging from 31 to 251 bp. In the absence of the mutation (allele a present) the 251 bp fragment was cleaved into three segments of 156 -, 64 - and 31- bp and in the presence of mutation (Gallele) we found two fragments of 156 - b and 95-bp.

Assessment of OA severity scores was assessed:

Using WOMAC index [10] for the hip and knee OA, Lequesne index of severity for OA hip and knee [11] and AUSCUAN questionnaire for hand OA [12]. Plain radiography was performed for both knees (weight bearing view), hips (anterio-posterior view) and hands (postero-anterior view) OA of the knees graded according to K/L method of classification [13].

Statistical Analysis:

Data collected was coded, entered, and analyzed using Microsoft Excel software. All analysis was performed with Statistical Package for Social Sciences (SPSS) version 20.0 (Armonk, NY: IBM Corp) [14].

Continuous data were presented as Mean±SD if normally distributed or Median (Range) if not normally distributed. Categorical data were presented by the frequency and percentage. Normality was checked by Shapiro-Wilk test. Variables were compared using the independent t-test and Chi-squared test of association.

Threshold for significance P-value<0.05 indicates significant, P<0.01 indicates highly significant difference and P<0.001 indicates very highly significant difference while P>0.05 indicates non-significant difference.

RESULTS

Demographic data of patients and healthy controls: The OA patients were 114 females and 81 males, their ages ranged from 35-70 years, with a mean of 54.77±8.42years. The control group included 110 females and 85 males; their ages ranged from 35-72 years with a mean of 55.21±8.48 years. There was no statistically significant difference between patients and controls as regard to age and sex. There was a highly statistically significant difference (P< 0.001**) between OA patients and control groups regarding genotypes frequency of GDF5 gene polymorphism where genotype TC was more in OA patients (60%) than controls (36.4%) indicating that the presence of genotype TC was higher by 2.7 times (Table 1).

There was a statistically significant difference (P< 0.05*) between OA patients and control groups regarding alleles frequency of GDF5 gene polymorphism, however allele T was more in controls (63.3%) than OA patients (56.2%) and allele C was more in OA patients (43.8%) than controls (36.7%) indicating that the presence of allele C was higher by 1.3 times (Table 2).

There was a statistically significant difference (P< 0.05*) between control group and OA knee and OA hip patients regarding genotypes frequency of GDF5 gene polymorphism where genotype TC

was more in OA knee (55.3%) and OA hip (60%) patients than control group (36.4%). Also, there was a highly statistically significant difference (P< 0.001**) between OA hands patients and control groups regarding genotypes frequency of GDF5 gene polymorphism, where genotype TC was more in OA hands patients (70.4%) than controls (36.4%), indicating that the presence of genotype TC was higher (Table 3).

On studying relation between different GDF 5 genotypes with WOMAC Index in hip and knee OA patients no statistically significant association (P≥0.05) between different genotypes of GDF5 gene and total Womac index however TC genotype higher as compared to patients with TT and CC genotypes (Table 4).On studying relation between different GDF5 genotypes and Lesquene index for activity among the OA knee and hip no statistically significant association (P≥0.05) between different genotypes of GDF5 gene and Lesquene index for activity among the OA knee and hip. However, genotype higher as compared to patients with TT and CC genotypes (Table 5).

On studying relation between different GDF5 genotypes and AUSCAN questionnaire among the OA hand patients no statistically significant association (P≥0.05) between different genotypes of GDF5 gene and Lesquene index for activity among the OA knee and hip. However, TC genotype higher as compared to patients with TT and CC genotypes (Table 6).

Relation between different genotype of GDF5 gene and K/L radiographic score of OA knee patients showed statistically significant association (P<0.05) between different genotypes of GDF5 gene and K/L radiographic score among the OA knee patients where grade 4 was more associated with genotype TC (Table 7).

Table (1): Genotypes frequency of GDF5 gene polymorphism among the studied groups (n=390).

Group	OA patients (n=195)	Controls (n=195)	OR (95%CI)	[a]X^2	P value
Genotypes	**No (%)**	**No (%)**			
TT	52 (26.7%)	88 (45.1%)	Ref	20.67	**<0.001****
TC	115 (59%)	71 (36.4%)	2.7 (1.7-4.3)		
CC	28 (14.3%)	36 (18.5%)	1.3 (0.7-2.4)		

[a] Chi square test (X^2), OR= Odds ratio, CI= Confidence interval.

Table (2): Alleles frequency of GDF5 gene polymorphism among the studied groups (n=780).

Group	OA patients (n=390) No (%)	Controls (n=390) No (%)	OR (95%CI)	[a]X^2	P value
Alleles					
T	219 (56.2%)	247 (63.3%)	Ref	4.179	**0.041***
C	171 (43.8%)	143 (36.7%)	1.3 (1.01-1.8)		

[a] Chi square test (X^2), OR= Odds ratio, CI= Confidence interval, GDF5 genotype has two alleles.

Table (3): Genotypes frequency of GDF5 gene polymorphism among the studied groups (n=390) with relation to each type of OA.

Diagnosis	Genotype TT No (%)	Genotype TC No (%)	Genotype CC No (%)	[a] Test	P value
OA knee (n=85)	25 (29.4%)	47 (55.3%)	13 (15.3%)	8.97	**0.011***
OA hip (n=55)	16 (29.1%)	33 (60%)	6 (10.9%)	9.85	**0.007***
OA hands (n=44)	8 (18.2%)	31 (70.4%)	5 (11.4%)	17.29	**<0.001****
Controls (n=195)	88 (45.1%)	71 (36.4%)	36 (18.5%)		

[a] Chi square test (X^2).

Table (4): Relation between different of GDF5 gene and Womac index among OA hip and knee patients (n=151).

Variables	Genotype TT (n=44) No (%)	Genotype TC (n=84) No (%)	Genotype CC(n=23) No (%)	[a]X^2	P value
Pain					
Less severe (n=79)	29 (36.7%)	41 (51.9%)	9 (11.4%)	5.28	0.072
More severe (n=72)	15 (20.8%)	43 (59.7%)	14 (19.5%)		
Stiffness					
Less severe (n=83)	27 (32.5%)	46 (55.4%)	10 (12.1%)	1.96	0.376
More severe (n=68)	17 (25%)	38 (55.9%)	13 (19.1%)		
Function					
Less severe (n=76)	22 (28.9%)	42 (55.3%)	12 (15.8%)	0.04	0.982
More severe (n=75)	22 (29.3%)	42 (56%)	11 (14.7%)		
Total					
Less severe (n=77)	24 (31.2%)	42 (54.5%)	11 (14.3%)	0.34	0.840
More severe (n=74)	20 (27%)	42 (56.8%)	12 (16.2%)		

[a] Chi square test (X^2).

Table (5): Relation between GDF5 genotypes and Lequesne index of severity among hip and knee patients (n=151).

Variables	Genotype TT (n=44) No (%)	Genotype TC (n=84) No (%)	Genotype CC(n=23) No (%)	[a]X^2	P value
Mild (n=63)	25 (39.7%)	31 (49.2%)	7 (11.1%)	14.2	0.076
Moderate (n=63)	11 (17.5%)	40 (63.5%)	12 (19%)		
Severe (n=15)	7 (46.7%)	5 (33.3%)	3 (20%)		
Very severe (n=7)	1 (27.8%)	5 (55.5%)	1 (16.7%)		
Extremely severe(n=3)	0.0 (00%)	3 (100%)	0.0 (00%)		

[a] Chi square test (X^2).

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Table (6): Relation between GDF5 genotypes and K/L radiographic score of OA knee patients (n=96).

Variables	Genotype TT (n=28) No (%)	Genotype TC (n=51) No (%)	Genotype CC(n=17) No (%)	[a]X^2	P value
Grade 0 (n=2)	2 (100%)	0.0 (00%)	0.0 (00%)	17.3	**0.027***
Grade 1(n=19)	4 (21%)	11 (58%)	4 (21%)		
Grade 2(n=28)	9 (32.1%)	13 (46.4%)	6 (21.5%)		
Grade 3(n=30)	13 (43.3%)	10 (33.3%)	7 (23.4%)		
Grade 4(n=17)	0.0 (00%)	17 (100%)	0.0 (00%)		

[a] Chi square test (X^2).

Table (7): Relation between different genotypes GDF5 gene and AUSCAN questionnaire among the OA hand patients (n=47).

Variables	Genotype TT (n=9) No (%)	Genotype TC (n=32) No (%)	Genotype CC(n=6) No (%)	[a]X^2	P value
Pain					
Less severe (n=39)	7 (18%)	27 (69.2%)	5 (12.8%)	0.22	0.897
More severe (n=8)	2 (25%)	5 (62.5%)	1 (12.5%)		
Stiffness					
Less severe (n=46)	9 (19.6%)	31 (67.4%)	6 (13%)	0.48	0.787
More severe (n=1)	0.0 (00%)	1 (100%)	0.0 (00%)		
Function					
Less severe (n=34)	7 (20.6%)	22 (64.7%)	5 (14.7%)	0.70	0.704
More severe (n=13)	2 (15.4%)	10 (76.9%)	1 (7.7%)		

[a] Chi square test (X^2).

DISCUSSION

This study aimed to detect the relation between GDF5 polymorphism and osteoarthritis in Egyptian population and to assess the association of GDF5 gene polymorphism with OA severity. The present study found that GDF5 gene polymorphism was associated with OA where TC allele gene can increase the risk of OA and indicated GDF5 as a susceptibility gene for OA.

These results agree with Hassanien et al. [15] on Egyptian population who reported weak but significant association between GDF5 gene polymorphism and knee OA. Also, in accordance with studies carried by Tuluce et al. [16] and Sabah-ozcan et al. [17] on Turkish population and Tawonsawatruk et al. [18] on Thai population and Mishara et al. [19] on the North Indian population, who found that GDF5 polymorphism was associated with knee OA. Miyamoto et al [20] also reported that the gene encoding GDF5 is associated with OA in Asian population and showed significant association with hip OA in Japanese population. However, our results were in contrast with Mohasseb et al. [21], who conducted a study in Egypt populations and found no statistically significant association on comparing frequency distribution of GDF5 between patients and healthy controls. Studies carried by Huang et al. [22] and Tsezou et al. [23] in the Greek population and Cao et al. [24] on Korean population did not confirm the association of GDF5 gene polymorphism and knee OA and GDF5 gene does not influence knee OA susceptibility.Regarding genotype and allele frequencies of GDF5 there was statistically significant difference between OA patients and control groups regarding genotype and alleles frequency where TC genotype higher in OA patients and allele C was higher by 1.3 times. This agrees with Hassanien et al. [15] study on Egyptian population, who found TC genotype at the allele level C increase risk of OA. On the other hand, Francisco et al. [25] on Northern Mexico and Tawonsawatruk et al. [18] on Thai population found TT genotype increased risk of OA knee where T allele was a risk factor. Moreover, the discrepancy between the results of the present study and previous studies performed worldwide may be attributed to the following reasons: sample size, mixed study patients with different OA with KOA patients larger sample size and different study populations as different populations have different genetic background. In this study, we used WOMAC index and Lequesne index to assess the genetic influence of GDF5 on the severity and disability in primary hip and knee OA and we also used AUSCAN questionnaire among the OA hand patients. Regarding WOMAC index we found no statistically significant association between different genotypes of GDF5 gene and total Womac index however TC genotype higher as compared to patients with TT and CC genotypes.

In contrast to the study by Mohasseb et al. [21] showed statistically significant difference between different genotype of GDF5 (TT, TC, CC) and total WOMAC index. Similarly, Lequesne index no statistically significant association between different genotypes of GDF5 gene, however patients carrying TC genotype were higher when compared to patients of TT and CC genotype. This indicates that GDF5 TC genotype may be associated with more severe and disability primary knee and hip OA than TT and CC genotype.

Also, AUSCAN questionnaire among the OA hand patients. The study showed the patients carrying TC genotype were higher when compared to patients of TT and CC genotype in pain, stiffness, and function with no statistically significant association between different genotypes of GDF5 gene. Up to our knowledge no previous studies used Lequesne index and AUSCAN questionnaire for assessment of patients with OA hips, knees, and hands. Regarding the radiological assessment of knee OA severity, the current study showed statistically significant association between different GDF5 genotypes and K/L radiological grading of knee OA among the studied patients, where grade 4 was more associated with genotype TC. This indicates that GDF5 gene TC genotype associated with severe knee OA. These results were in accordance with the studied carried by Mohasseb et al. [21], Minafra et al. [26] and Valdes et al. [27], which reported a statistically significant association between different GDF5 genotypes and K/L radiological grading of knee OA.

CONCLUSIONS

In conclusion the current study revealed a genetic association between GDF5 and primary OA knee, hip and hands and TC genotype may be associated with more severe and disability of primary OA.

Conflicts of Interest/ Financial Disclosures: Nothing to declare.

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