Association of IL-17A -197G/A (rs2275913) Single Nucleotide Polymorphism and Rheumatoid Arthritis in Sudanese Patients

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Research note

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Abstract

Objectives: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. The aim of this study is to determine the association of *IL-17A -197G/A* polymorphism with RA in Sudanese Patients. A descriptive cross-sectional study was conducted between March and December, 2018. Clinical and demographic data of the study participants were collected and analysed. All statistical tests were considered as statistically significant when $p < 0.05$.

Results: The study population included 266 participants, 166 (63.1%) were females [mean age 41.4 ± 15.5 years] and 97 (36.9%) were males [mean age 36.2 ± 16.0 years]. Of the 266 participants, 31% (85/266) were RA cases and 69% (181/266) were healthy controls. Prevalence of *IL-17A* genotypes among the study population was 52.6% (140/266) were AG heterozygote genotype, 38.4% (102/266) were AA homozygote genotype, and 9.0% (24/266) were GG homozygote genotype. Correlation of *IL-17A* genotypes was negatively statistically significant based on participants clinical status, and family history of RA, Pearson's correlation [$r = -0.392$, P value 0.001] and [$r = -0.226$, P value 0.001], respectively, while positively statistically significant with gender, Pearson's correlation [$r = 0.140$, P value 0.023]. Based on the duration of RA, no statistically significant correlation was observed, Pearson's correlation [$r = -0.138$, P value 0.207].

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by a chronic inflammatory response that affects various part of the human body. At late stages, RA leads to deformities of the joints and bones causing severe pain [1–5]. Certain factors were hypothesized to be involved in the induction and the development of RA; however, the most acceptable theory for the development of the disease is a multifactorial theory that involve the interaction of environmental and genetic background of patients and render them more susceptible to RA [6]. The disease severity is varied from one population to another; African populations, especially Sudanese had more severe form of the disease comparing to other countries [7].

The microenvironment is very critical for the disease progression and it usually impact treatment outcomes, in RA the affected site show an adherence of several types of inflammatory cells including polymorph nuclear cells and macrophages as well as T cells [8]. Growing body of evidence indicates the central role of T cells in the pathophysiology of RA; as the patients carrying Human Leukocytes antigen (HLA) – DRB1 are more susceptible to disease development [9–12].

Recently, a newly discovered subset of T Helper cells which is known as TH 17 was reported to play a crucial role in host defense toward several infectious agents [13, 14]. TH 17 cells form a family of cytokines which consist of *IL-17A*, *IL-17B*, *IL-17C*, *IL-17D*, *IL-17E*, and *IL-17F* [15, 16]. Recent study demonstrated the exact role of *IL-17* in RA, the level of *IL-17* expression, and the producing cells in the synovial fluid in RA patients showed increase in *IL-17* level in the patients with RA [17]. Also, a correlation

between *IL-17* levels on serum and synovial fluid with various RA activity markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) [18]. Interestingly, in the *IL-17* gene there are several polymorphisms have been detected that may influence the expression of *IL-17* [19, 20]. In this study we aimed to investigate the association between *IL-17A* -197G/A (rs2275913) polymorphism and RA among Sudanese patients.

Materials And Methods

Study Design and Study Population:

A descriptive cross-sectional hospital-based study was conducted at Zain medical center in Khartoum state, Sudan, from February 2017 to December 2018. Three ml of blood were collected into EDTA blood containers from each participant voluntary enrolled in our study after reading and signing the informed-consent, parents/guardians agreed and signed on the behalf of their children in case of an underage patient. Personal interviews with each participant/ his signatory guardian prior to the blood donation to obtain the demographics and clinical data of participants, including age, gender, locality, tribe, family history, and the duration of disease. All those who attended to the hospital for follow-up for RA were giving a similar chance to participate in the study. Also, apparently healthy co-patient individuals regardless of their age and gender were included as a control group. All participants diagnosed with autoimmune diseases other than RA were excluded from the study.

DNA extraction and *IL-17A* Genotyping:

The total genomic DNA was extracted from blood samples using QIAamp DNA Blood Mini Kit (Qiagen, Germany). Extracted DNA was checked for quality using nanophotometer (Implen, Germany) and stored at -20 °C until *IL-17A* genotyping. *IL-17A* genotyping was done using polymerase chain reaction and restriction fragment length polymorphism techniques (PCR-RFLP). The primers used for amplifying the *IL-17A* gene were adopted from Mohamed et al., [19]. PCR conditions were consisted of a pre-denaturation step of 4 minutes at 94 °C and 40 cycles each of 30 seconds denaturation at 94 °C, 30 seconds annealing at 55 °C and 30 seconds elongation at 72 °C. This was followed by a post-elongation step of 7 minutes at 72 °C. After obtaining PCR amplicons, fragmentation was done using *XagI*/endonuclease according to manufacturer's instructions (Roche, Germany). Restriction fragments were loaded on 3% agarose gel and visualized using UV-transilluminator (Sigma Aldrich, Germany).

Statistical analysis:

Data were analyzed using the Statistical Package for the Social Sciences (SPSS v20). Fisher's exact test was used to test the differences in genotypes frequency. Pearson's χ^2 test was used for the correlation of *IL-17A* genotypes with the study variables. A P value < 0.05 was considered statistically significant.

Results

Characteristics of the study population

The study population included 266 participants, of them 166 (63.1%) were females [mean age 41.4 ± 15.5 years] and 97 (36.9%) were males [mean age 36.2 ± 16.0 years]. The study participants overall, aged between 1 and 85 years with average of 40 years. The participants were classified into 85 (31.2%) cases and 181 (68.8%) were controls. Based on age grouping, the age groups of 21–40 years followed by 41–60 years were the most frequent age groups; with 106 (39.8%) and 101 (38.0%) participants, respectively. Whereas, the frequency of the remaining age groups was 35 (13.2%) for 1–20 years, 23 (8.6%) for 61–80 years, and 1 (0.4%) for the age group of more than 80 years.

Among the studied population, those were from Arab ethnicity were the most frequent; 109 (41.0%). Also, those with a previous history of RA were 27 (10.2%), whereas those with no family history constituted 239 (89.8%). Based on duration of RA among the case group, the most frequent age group was 41–60 years; 53 (62.3%). And the duration of RA among the case group included 42 (49.4%) were having RA for less than 5 years, 29 (34.1%) for 5–10 years, and 7 (8.2%) for each of 11–15 years and 15–20 years (Table 1).

Table 1

Age Groups					Total	P value
20-Jan years	21–40 years	41– 60 years	61– 80 years	More than 80 years		
Gender						
Male	14 (40.0%)	50 (47.2%)	25 (24.8%)	8 (34.8%)	0 (0.0%)	97 (36.5%)
Female	21 (60.05)	56 (52.8%)	76 (75.2%)	15 (65.2%)	1 (100%)	169 (63.5%)
Total	35 (13.2%)	106 (39.8%)	101 (38.0%)	23 (8.6%)	1 (0.4%)	266 (100%)
Ethnic						
Arab	10 (28.6%)	39 (36.8%)	51 (50.5%)	9 (39.1%)	0 (0.0%)	109 (41.0%)
Beja	4 (11.4%)	21 (19.8%)	23 (22.8%)	2 (8.7%)	0 (0.0%)	50 (18.8%)
Fur	18 (51.4%)	26 (24.5%)	15 (14.9%)	9 (39.1%)	1 (100%)	69 (25.9%)
Nuba	2 (5.7%)	9 (8.5%)	9 (8.9%)	0 (0.0%)	0 (0.0%)	20 (7.5%)
Nubian	1 (2.9%)	11 (10.4%)	3 (3.0%)	3 (13.0%)	0 (0.0%)	18 (6.8%)
Total	35 (13.2%)	106 (39.8%)	101 (38.0%)	23 (8.6%)	1 (0.4%)	266 (100%)
Participant status						
Case	1 (2.9%)	18 (17.0%)	53 (52.3%)	13 (56.5%)	0 (0.0%)	85 (32.0%)
Control	34 (97.1%)	88 (83.0%)	48 (47.5%)	10 (43.5%)	1 (100%)	181 (68.0%)
Total	35 (13.2%)	106 (39.8%)	101 (38.0%)	23 (8.6%)	1 (0.4%)	266 (100%)
Family history of RA						
Yes	0 (0.0%)	5 (4.7%)	18 (17.8%)	4 (17.4%)	0 (0.0%)	27 (10.2%)
No	35 (100%)	101 (95.3%)	83 (82.2%)	19 (82.6%)	1 (100%)	239 (89.8%)

Age Groups					Total	P value
Total	35 (13.2%)	106 (39.8%)	101 (38.0%)	23 (8.6%)	1 (0.4%)	266 (100%)
Duration of RA						
less than 5 years	1 (100%)	10 (55.6%)	27 (50.9%)	4 (30.8%)	0 (0.0%)	42 (49.4%)
5–10 years	0 (0.0%)	6 (33.3%)	16 (30.2%)	7 (53.8%)	0 (0.0%)	29 (34.1%)
11–15 years	0 (0.0%)	1 (5.6%)	6 (11.3%)	0 (0.0%)	0 (0.0%)	7 (8.2%)
15–20 years	0 (0.0%)	1 (5.6%)	4 (7.5%)	2 (15.4%)	0 (0.0%)	7 (8.2%)
Total	1 (1.2%)	18 (21.2%)	53 (62.3%)	13 (15.3%)	0 (0.0%)	85 (100%)

Prevalence of IL-17A genotypes in the study population

The distribution of the different *IL-17A* genotypes among the study population was 52.6% (140/266) AG heterozygote genotype, 38.4% (102/266) AA homozygote genotype, and 9.0% (24/266) GG homozygote genotype. The heterozygote AG genotype was most frequent among those aged 41–60 years; 63 (45.0%), followed by 50 (35.7%) among 21–40 years. While the homozygote AA genotype was most frequent among 21–40 years followed by 41–60 years; 46 (45.1%) and 27 (26.5%), respectively. Whereas, the homozygote GG genotype was frequent among 11 (45.8%) of the age group 41–60 years followed by 10 (41.7%) of the age group 21–40 years. A statistically significant difference was noted for the distribution of the different *IL-17A* genotypes among the different age groups, *P* value 0.022.

Based on the different ethnic groups of the study population, the homozygote AA genotype was more frequent among Fur; 31 (30.4%), while the homozygote GG genotype was more frequent among Arab; 13 (54.2%). Whereas, heterozygote AG genotype was among Arab ethnicity; 68 (48.6%). The distribution of the different *IL-17A* genotypes among the different ethnic groups was statistically significant, *P* value 0.034.

Regarding the family history and duration of RA, the heterozygote AG genotype was found among 23 (16.4%) of those with family history of RA, as well as those with duration of RA for less than 5 years; 36/85 (55.4%). However, a statistically significant difference was noted for the distribution of the different *IL-17A* genotypes according to family history, no statistically significant difference was seen for the distribution of *IL-17A* genotypes according to duration of RA, *p* values 0.001 and 0.321, respectively (Table 2).

Table 2

	IL17Genotype			Total	P value
	AA	GG	AG		
Age Group					
1–20 years	22 (21.6%)	1 (4.2%)	12 (8.6%)	35 (13.2%)	0.022
21–40 years	46 (45.1%)	10 (41.7%)	50 (35.7%)	106 (39.8%)	
41–60 years	27 (26.5%)	11 (45.8%)	63 (45.0%)	101 (38.0%)	
61–80 years	7 (6.9%)	2 (8.3%)	14 (10.0%)	23 (8.6%)	
More than 80 years	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.4%)	
Total	102 (38.4%)	24 (9.0%)	140 (52.6%)	266 (100%)	
Ethnic					
Arab	28 (27.5%)	13 (54.2%)	68 (48.6%)	109 (41.0%)	0.034
Beja	27 (26.5%)	2 (8.3%)	21 (15.0%)	50 (18.8%)	
Fur	31 (30.4%)	4 (16.7%)	34 (24.3%)	69 (25.9%)	
Nuba	9 (8.8%)	3 (12.5%)	8 (5.7%)	20 (7.5%)	
Nubian	7 (6.9%)	2 (8.3%)	9 (6.4%)	18 (6.8%)	
Total	102 (38.4%)	24 (9.0%)	140 (52.6%)	266 (100%)	
Family History of RA					
Yes	2 (2.0%)	2 (8.3%)	23 (16.4%)	27 (10.2%)	0.001
No	100 (98.0%)	22 (91.7%)	117 (83.6%)	239 (89.8%)	
Total	102 (38.4%)	24 (9.0%)	140 (52.6%)	266 (100%)	
Duration of RA					
less than 5 years	2 (28.6%)	4 (30.8%)	36 (55.4%)	42 (49.4%)	0.321
5–10 years	3 (42.9%)	7 (53.8%)	19 (29.2%)	29 (34.1%)	
11–15 years	1 (14.3%)	2 (15.4%)	4 (6.2%)	7 (8.2%)	
15–20 years	1 (14.3%)	0 (0.0%)	6 (9.2%)	7 (8.2%)	
Total	7 (8.2%)	13 (15.3%)	65 (76.5%)	85 (100%)	

Correlation of IL-17A genotypes with gender, family history of RA, and clinical status of the study participant

The correlation of the different *IL-17A* genotypes was negatively statistically significant based on participants clinical status; case and control, and family history of RA, Pearson's correlation [$r = -0.392$, p -value 0.001] and [$r = -0.226$, p -value 0.001], respectively. While correlation of *IL-17A* genotypes was positively statistically significant with participant gender, Pearson's correlation [$r = 0.140$, p -value 0.023]. Whereas based on the duration of RA, no statistically significant correlation was observed, Pearson's correlation [$r = -0.138$, p -value 0.207] (Table 3).

Table 3

	IL17 Genotypes			M ± STD	Pearson's r	P value	95% Confidence Interval	
	AA	GG	AG				Lower Bound	Upper Bound
Participant status								
Case	7 (6.9%)	13 (54.2%)	65 (46.4%)	1.68 ± 0.467	-0.392	0.001	1.62	1.74
Control	95 (93.1%)	11 (45.8%)	75 (53.6%)					
Gender								
Male	47 (46.1%)	6 (25.0%)	44 (31.4%)	1.64 ± 0.482	0.14	0.023	1.58	1.69
Female	55 (53.9%)	18 (75.0%)	96 (68.6%)					
Family History								
Yes	2 (2.0%)	2 (8.3%)	23 (16.4%)	1.9 ± 0.303	-0.226	0.001	1.86	1.94
No	100 (98.0%)	22 (91.7%)	117 (83.6%)					
Duration of RA								
less than 5 years	2 (28.6%)	4 (30.8%)	36 (55.4%)	2.75 ± 0.925	-0.138	0.207	2.55	2.95
5–10 years	3 (42.9%)	7 (53.8%)	19 (29.2%)					
11– 15 years	1 (14.3%)	2 (15.4%)	4 (6.2%)					
15– 20 years	1 (14.3%)	0 (0.0%)	6 (9.2%)					

Discussion

Investigation of *IL-17A* polymorphisms among Sudanese population to determine the frequency distribution of the different *IL-17A* genotypes among healthy individuals [19]. in this study we investigated the frequency distribution of *IL-17A* genotypes among Sudanese patients diagnosed with RA and to determine the genetic susceptibility to RA in comparison to healthy individuals. The results of *IL-17A* genotypes distribution showed that the three genotypes were more prevalent in females compared to males, and among Sudanese Arab ethnic group. This result was similar to previous report, in which *IL-*

17A polymorphism was significant among Sudanese Arab ethnic group [19]. As well as, the significant distribution of *IL-17A* genotypes among those with family history of RA, this could be attributed to the role of *IL-17A* SNPs inheritance to the descendants [6, 19]. This was also supported by the negatively significant correlation of *IL-17A* with the family history of RA.

In this study, *IL-17A* genotypes showed a significant association to be linked with RA. This result is agreeing with a previously published systematic review including Fourteen studies and comprising more than three thousand patients with RA and more than two thousand healthy individuals to evaluate the relationship between serum level of IL-17 cytokine among RA patients and the possible SNPs that might be associated with the disease severity [21]. Their results showed a positive correlation between IL-17 level and RA compared to the control populations and they found some polymorphisms including *IL-17A* (rs2275913) was linked to increase the susceptibility toward developing the disease [21]. However, in a previous report investigated *IL-17A* (rs2275913) and the susceptibility to RA, the results showed that there were no statistically significant associations between *IL-17A* genotypes and the possibility of developing RA among Polish population [4]. And also, in a study conducted in a Tunisian population, *IL-17A* polymorphisms did not show any significant association with RA prevalence [22].

Conclusion

This study is the first study in Sudan established the association between *IL-17A* (rs2275913) polymorphisms and susceptibility to RA. These findings appeal for further research in various settings in Sudan to investigate the exact role of IL-17 in immunopathology and disease severity among Sudanese RA patients.

Limitations

- Analysis of further SNPs that found in the *IL-17A* gene could also be linked to RA.
- Functional analysis should be done to establish the effect of this SNP on the level of IL-17 and correlated the cytokine level with each genotyping and linked it to the outcome of the disease.

Abbreviations

DNA

Deoxyribonucleic acid; HLA:Human Leukocytes antigen; RA:Rheumatoid arthritis; *IL 17A*:Interleukin 17A

IFN-γ

Interferon gamma

IL-2

Interleukin 2

PCR

Polymerase chain reaction

SNP
single nucleotide polymorphism
RF
rheumatoid factor
ESR
Erythrocyte sedimentation rate
CRP
C reactive protein

Declarations

Ethics approval and consent to participate

The study ethical approval was obtained from the Ministry of Health Ethical Committee on February 2018 (No. 1.2.2018). A written, informed consent was obtained from all the study participants.

Consent to publish

Not Applicable.

Availability of Data and Materials

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

Competing interests

No competing interests to disclose.

Funding

Not Applicable.

Authors' contributions

RMO, AAM, AME, and EES designed and led the study. RMO, MN, AEA, RAO, NSM, MMA, AAM, AME and EES analyzed and interpreted the data. RMO, MN, AEA, RAO, NSM, MMA, AAM, AME and EES prepared the manuscript. All authors read and approved the final manuscript.

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