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RESEARCH ARTICLE

Association of Interleukin-6 and Tumor Necrosis Factor-alpha Gene Polymorphisms with Genetic Susceptibility of Psoriatic Arthritis in Kuwaiti Arab Patients

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Abstract:

Background:

Psoriatic arthritis (PsA) is an inflammatory arthritic disease in which joint inflammation occurs with psoriasis. It results from a complex interplay between genetic, immunological and environmental factors. In PsA, the activation of T cells is considered as a crucial step in the disease process. The T-lymphocytes affect the proliferation of epidermal skin cells and result in abnormal differentiation. Altered cytokine networks have been shown to play a central role in the pathogenesis of PsA. Psoriasis is characterized by Th-1 type cytokine pattern in which there is a marked variation in the secretion of interleukin-6 (IL6), interleukin-13 (IL13) and Tumor necrosis factor-alpha (TNF-alpha). This study investigated the association of *IL6*, *IL13* and *TNF-alpha* gene polymorphisms with genetic susceptibility of PsA in Kuwaiti patients.

Methods:

The genotypes of *IL6* gene (-174G/C; rs1800795), *IL13* gene (R130Q; rs20541) and *TNF-alpha* gene (-308A/G' rs1800629) polymorphisms were detected in 113 Kuwaiti PsA patients and were compared to that in 104 healthy controls. The PsA patients were diagnosed on the basis of the presence of inflammatory arthritis with psoriasis with no rheumatoid factor in the serum. The genotypes for *IL6*, *IL13* and *TNF-alpha* gene polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods and were confirmed by DNA sequencing.

Results:

The frequency of *IL6* gene (-174G/C; rs1800795) and *TNF-alpha* gene (-308A/G' rs1800629) polymorphisms manifested a statistically significant difference between Kuwaiti PsA patients and controls. However, the frequency of *IL13* gene (R130Q; rs20541) polymorphism did not show a significant difference between Kuwaiti PsA patients and the controls.

Conclusion:

Our data show an association of two cytokine gene polymorphisms in *IL6* gene (-174G/C; rs1800795) and *TNF-alpha* gene (-308A/G' rs1800629) with PsA in Kuwaiti patients highlighting their significant contribution to genetic susceptibility of this chronic disease possibly along with other factors.

Keywords: Genotype, Cytokine gene, Polymorphism, Psoriatic arthritis, Chronic disease, Arthritic disease.

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1. INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. In 30% patients with psoriasis, PsA is eventually developed [1 - 4]. Both psoriasis and PsA show a

high heritability [5]. The relative risk of psoriasis in siblings varies between 4 and 10 in different populations [6]. A strong heritability has also been demonstrated in 'Twin-studies' in psoriasis, in which a significant increase has been observed in the concordance between monozygotic and dizygotic twins [6]. It has been postulated that PsA is a complex disease which is most likely triggered by the environmental factors in genetically susceptible individuals, and multiple genetic factors

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contribute to the disease susceptibility [7]. PsA is a heterogeneous disease, and ranges in severity from mild, nondestructive to severe, progressive, and erosive disease [8]. A high frequency of radiographic damage has also been reported in PsA (in up to 57% patients) who manifest erosive arthritis [9]. In PsA, an infiltration of the synovial tissue by lymphocytes and macrophages has been shown to occur along with new vessel formation [10]. The infiltrating cells, produced Th1 (pro-inflammatory) and Th2 (anti-inflammatory) cytokines which regulate inflammatory process in the joint.

Significantly high serum, synovial fluid, and synovial membrane levels of pro-inflammatory cytokines e. g. Interleukin-6 (IL6), Tumor necrosis factor-alpha (TNF-alpha) and anti-inflammatory cytokines such as IL1 and IL13 have been detected in the PsA patients compared to that in the controls [11 - 13]. This cytokine pattern is considered to be the cause of keratinocyte hyperproliferation, which is a salient feature of psoriasis.

A number of cytokine gene polymorphisms have been associated with altered constitutive and inducible levels of cytokines [14], and this provides a rationale for their possible role in manifesting the phenotype of PsA [15]. IL6 is a cytokine that promotes synovitis and induces bone resorption [16]. In PsA patients, it has been shown that an increase in IL6 in the synovial fluid is associated with inflammatory disease activity [17]. This increase in the production of IL6 has been attributed to different polymorphisms of the gene encoding this cytokine [18]. It has been demonstrated that the presence of 'G' allele in the *IL6* gene (-174G/C; rs1800795) polymorphism produces an increase in transcriptional activity that leads to higher blood, as well as synovial fluid, IL6 levels in rheumatoid arthritis (RA) [19, 20].

The *IL6* (-174G/C) gene polymorphism has also been reported as a predictor of radiological damage in RA [21]. TNF-alpha is a crucial cytokine for local T cell proliferation [21]. It was demonstrated that the development of psoriatic lesions is mediated by TNF-alpha and proliferation of local T cells, and is dependent on local TNF-alpha production [22]. The efficiency of anti-TNF-alpha monoclonal antibodies in the treatment of psoriatic patients further highlighted the role of TNF-alpha [21]. Interleukin-13 (IL13) is an anti-inflammatory cytokine that is produced by CD4+ T cells (with Th2 features [23]). It plays an important regulatory role in Th2-mediated diseases [23]. In PsA patients, high levels of IL13 have been found in synovial fluid from actively inflamed joints but not in their skin [24]. The role of IL13 in pathogenesis of PsA is not clear, but it has been suggested that it downgrades the inflammatory process by suppressing the production of Th1 cytokines [25]. In previous studies, polymorphisms within the *IL13* gene region have been associated with psoriatic disease [26]. The association between cytokine gene polymorphisms and PsA has not been investigated well in Gulf Arab and/or Middle Eastern populations. Therefore, we undertook this study to investigate the role of these three cytokine gene polymorphisms in genetic susceptibility of PsA in a completely different population (Kuwaiti Arabs).

2. MATERIALS AND METHODS

This study included 113 Kuwaiti Arab patients with psoriatic arthritis (PsA) and 104 healthy controls who had the same ethnicity. The recruitment of PsA patients was carried out from the Rheumatic Disease Unit, Amiri Hospital, Kuwait over a two-year period. The diagnosis of PsA was made as per the guidelines described earlier [27]. The details about diagnosis, patient characteristics and selection of controls have been reported in our earlier report [28]. Briefly, the PsA patients, manifested inflammatory arthritis associated with psoriasis and were negative for rheumatoid factor in the serum. The controls were evaluated by a specialist who ascertained that they do not have any significant predisposition of a disease with genetic or immune system involvement. The control subjects were age and gender matched with the PsA patient group.

2.1. Determination of Genotypes

Venous blood (approximately 5 ml) was obtained from PsA patients and controls under appropriate conditions by a trained phlebotomist and anticoagulated by EDTA. Genomic DNA was isolated from the peripheral leukocytes using a standard method [29]. Previously described polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods were used to determine genotypes of three gene polymorphisms, *IL6* gene (-174G/C; rs1800795) [30], *IL13* gene polymorphism (R130Q; rs20541) [31, 32] and *TNF-alpha* gene (-308A/G' rs1800629) [33].

For all the three above mentioned gene polymorphisms, the details about PCR amplification conditions, primer sequences used, post PCR processing and analysis of the restriction enzyme digests by agarose gel electrophoresis have been reported in our previous report [34]. The genotypes were confirmed by DNA sequencing.

2.2. Statistical Analysis

The Statistical Package for the Social Sciences version 25 (SPSS, Chicago IL, USA) was used to analyze the data. Direct counting method was employed to document the genotype and allele frequencies in PsA patients and the controls. The confidence interval (CI) was set at 95% and statistical significance at $P < 0.05$ (two-tailed). Statistical significance of the differences between genotype and allele frequency in PsA patients and the controls was determined by using the Fisher's Exact test. To calculate the statistical significance in co-dominant and dominant genetic models, the genotype frequency in homozygous GG, RR and AA subjects and the allele frequency of 'G/R/A' in the three gene polymorphisms were considered as reference as described previously [30 - 34]. In dominant model, the genotype frequencies in respective heterozygous and homozygous subjects were pooled and then analyzed. The Hardy Weinberg equilibrium was used to test the genotype distribution by using MSTAT software.

3. RESULTS

The baseline characteristics of the Kuwaiti PsA patients are presented in Table 1. The mean age at diagnosis was 39.4 (SD ± 9.0) years while the median disease duration (range) in the PsA patients' group was found to be 62 months (SD 6-240

months; Table 1). Majority of the PsA patients had the 'late-onset' disease (>40 y). The associated clinical manifestations in the Kuwaiti PsA patients have also been listed in Table 1. The frequencies of *IL6* gene (-174G/C; rs1800795) polymorphism genotypes and alleles are presented in Table 2. The genotype and allele frequency of the CC genotype and 'C' allele (1.73) were considerably higher in the PsA patients compared to that in the controls (OR 2.22, P = 0.02 in the co-dominant model of genetic analysis, Table 2). The frequency of

IL13 gene (R130Q; rs20541) polymorphism genotypes and alleles is presented in Table 3. No significant difference was detected in the genotype frequency of *IL13* gene polymorphism between PsA patients and controls in both the co-dominant and dominant models of genetic analysis (Table 3). However, in contrast to the genotype frequency, a significant difference was detected in the allele frequency of 'Q' allele between PsA patients and controls (P = 0.02), although its frequency was higher in the controls (Table 3).

Table 1. The baseline characteristics of Kuwaiti PsA patients (N* = 113).

Mean age at diagnosis (+SD) years	39.4 (+>9.0)
Median disease duration (range) months	62 (6-240)
Clinical Manifestations**	N (%)
Asymmetric polyarthritis	79 (76.4)
Symmetric polyarthritis	15 (14.1)
Oligo-arthritis	10 (9.8)
Spondylitis	21 (19.8)
Dactylitis	48 (47.1)
Enthesitis	21 (19.9)

Note: *N, number, **Some PsA patients had more than one clinical manifestation.

Table 2. Frequency of *IL6* gene (-174G/C; rs1800795) polymorphism genotypes and alleles in Kuwaiti PsA patients and controls.

Genotype/Alleles	Patients N=113 (%)	Controls N= 104 (%)	OR (95% CI)*	P-value**
Co-dominant	-	-	-	-
GG	4 (3.5)	6 (5.8)	1.00 (Reference) ^a	-
GC	35 (31.0)	48 (46.0)	1.1 (0.29 – 4.17)	1.0
CC	74 (64.5)	50 (48.1)	2.22 (0.59 – 8.27)	0.02
Dominant	-	-	-	-
GG	4 (3.5)	6 (5.8)	1.00 (Reference) ^a	-
GC/CC	109 (96.5)	98 (94.2)	1.67 (0.46 – 6.09)	0.53
Alleles	N= 226 (%)	N= 208 (%)	-	-
G	43 (19.0)	60 (29.9)	1.00 (Reference) ^a	-
C	183 (81.0)	148 (71.2)	1.73 (1.10 – 2.70)	0.02

Note: *OR (95% CI), odds ratio at 95% confidence interval; **P-values were considered significant when <0.05 (shown in bold). ^aGenotype frequency in homozygous subjects with GG genotype and allele frequency of 'G' were considered as reference for calculation of statistical significance using Fisher's Exact test.

Table 3. Frequency of *IL13* gene polymorphism (R130Q; rs20541) genotypes and alleles in Kuwaiti PsA patients and controls.

Genotype/Alleles	Patients N=113 (%)	Controls N= 104 (%)	OR (95% CI)*	P-value**
Co-dominant	-	-	-	-
RR	6 (5.3)	3 (2.9)	1.00 (Reference) ^a	-
QR	34 (30.1)	19 (18.3)	1.89 (0.20 – 3.99)	1.0
QQ	73 (64.6)	82 (78.9)	0.44 (0.11 – 1.85)	0.32
Dominant	-	-	-	-
RR	6 (5.3)	3 (2.9)	1.00 (Reference) ^a	-
QR/RR	107 (94.7)	101 (97.1)	0.53 (0.13 – 2.18)	0.50
Alleles	N= 226 (%)	N= 208 (%)	-	-
R	46 (20.4)	25 (12.0)	1.00 (Reference) ^a	-
Q	180 (79.7)	183 (88.0)	0.53 (0.32 – 0.91)	0.02

Note: *OR (95% CI), odds ratio at 95% confidence interval; **P-values were considered significant when <0.05 (shown in bold). ^aGenotype frequency in homozygous RR subjects and allele frequency of 'R' were considered as reference for calculation of statistical significance using Fisher's Exact test.

Table 4. Frequency of *TNF-alpha* gene (-308A/G; rs1800629) polymorphism genotypes and alleles in Kuwaiti PsA patients and controls.

Genotype/Alleles	Patients N=113 (%)	Controls N= 104 (%)	OR (95% CI)*	P-value**
Co-dominant	-	-	-	-
AA	1 (0.9)	9 (8.7)	1.00 (Reference) [‡]	-
AG	22 (19.5)	48 (46.2)	4.13 (0.49 – 34.62)	0.23
GG	90 (79.7)	47 (45.2)	17.23 (2.11 – 14.23)	<0.001
Dominant	-	-	-	-
AA	1 (0.9)	9 (8.7)	1.00 (Reference) [‡]	-
AG/AA	112 (20.35)	95 (15.9)	10.61 (1.32 – 85.32)	<0.01
Alleles	N= 226 (%)	N= 208 (%)	-	-
A	24 (10.2)	66 (38.8)	1.00 (Reference) [‡]	-
G	202 (10.18)	142 (68.3)	3.91 (2.34 – 6.54)	<0.0001

Note: *OR (95% CI), odds ratio at 95% confidence interval; **P-values were considered significant when <0.05 (shown in bold). [‡]Genotype frequency in homozygous AA subjects and allele frequency of 'A' were considered as reference for calculation of statistical significance using Fisher's Exact test.

The genotype and allele frequencies of *TNF-alpha* gene (-308A/G; rs1800629) polymorphism are presented in Table 4. A statistically significant difference was detected in the frequency of GG genotype between PsA patients and controls in both the co-dominant and dominant model with high OR (Table 4 values are given in bold where significant).

The frequency of 'G' allele of the *TNF-alpha* gene (-308A/G; rs1800629) polymorphism was also significantly higher in the PsA patients compared to that in the controls (OR 3.91, P<0.0001; Table 4).

4. DISCUSSION

Our results demonstrate a statistically significant association between the CC genotype and 'C' allele of the *IL6* gene (-174G/C; rs1800795) polymorphism and PsA (Table 2). This is in sharp contrast to an earlier report on the association of this polymorphism with rheumatoid arthritis (RA) in which the GG genotype was associated with the disease onset [35]. A study in juvenile idiopathic arthritis (JIA) showed positive association with GG genotype of the *IL6* gene (-174G/A) polymorphism [19]. Relatively few studies have reported the association of *IL6* gene (-174G/C; rs1800795) polymorphism with PsA [36]. In one of these studies, the GG genotype was found to be associated with a peripheral form of PsA [18]. In contrast to this, a second study did not find any association between this polymorphism and the disease susceptibility or with associated clinical characteristics [15]. It has also been reported that *IL6* gene (-174G/C) polymorphism has a significant role in the clinical outcome during the treatment of PsA patients with methotrexate (MTX) [36]. In this study from Poland, it was reported that the PsA patients who carried 'G' allele of the *IL6* gene (-174G/C) polymorphism, responded less effectively to MTX therapy than those with the 'CC' genotype [36]. *IL6* has been shown to be involved in the pathology of RA and psoriasis, both these disorders share common pathophysiology with PsA [36]. The murine models of arthritis have been used to explore the pathological role of *IL6* [36]. It has been demonstrated that blocking *IL6* signaling by gene knockout or injection of anti-*IL6* or anti-*IL6R* antibodies resulted in suppression of the disease [37 - 39]. Also, in

humans, a humanized anti-*IL6* receptor monoclonal antibody (Tocilizumab) has been used successfully in the treatment of RA patients [36]. The circulating levels of *IL6* are elevated in both RA and psoriasis as well as in numerous other autoimmune and chronic inflammatory diseases thus highlighting its role in deregulating the signaling pathways which contribute to autoimmune pathology. Our findings in Kuwaiti patients with PsA showed a high frequency of CC genotype in PsA patients and manifested a positive association with disease susceptibility (Table 2). These findings when considered in the light of those reported from Poland [36] indicate that Kuwaiti PsA patients are likely to benefit much better with MTX therapy thus highlighting the role of this polymorphism as a prognostic marker to monitor MTX therapy in addition to being a PsA susceptibility locus.

The results on the genotype and allele frequency of *IL13* gene (R130Q; rs20541) polymorphism did not show a significant difference between Kuwaiti PsA patients and the controls (Table 3). This finding indicated that *IL13* gene polymorphism may not be a susceptibility locus for PsA in Kuwaiti population. This is not surprising because it has been shown that *IL13* is an anti-inflammatory cytokine whereas PsA is a disease with autoimmune and inflammatory pathology. It has also been reported that *IL13* is produced by CD⁺ T cells with Th2 characteristics and manifests its influence in Th2 mediated diseases by affecting the Th1-Th2 balance [40]. The lack of association between this polymorphism in Kuwaiti PsA patients means that it may not have a significant direct role in manifesting the skin symptoms.

This received support from the data reported in a previous study, in which high levels of *IL13* have been detected in synovial fluid but not in the psoriasis skin [24].

The most important finding in this study is that a statistically significant difference was detected in the frequency of GG genotype and 'G' allele of the *TNF-alpha* gene (-308A/G; rs1800629) polymorphism between Kuwaiti PsA patients and controls (Table 4). A study from Spain found that *TNF-308*-GG genotype was more prevalent in Spanish psoriasis patients than in the controls which implicated GG genotype as a risk factor [41]. Similar findings have been

reported from psoriasis patients from Egypt, in which the GG genotype was found to be associated with psoriasis [42]. Some other studies have reported that *TNF-308*A* allele was less common in patients with early-onset psoriasis than in the controls [43, 44]. In contrast to these reports, *TNF-308*A* was found to be more frequent in psoriasis patients from Germany [45]. However, some studies reported no association between *TNF-308*A* and psoriasis in Caucasians [46 - 47]. The lack of association between *TNF-308*A* and susceptibility to develop psoriasis has also been reported in Japan [48, 49] and Korea [50]. It has also been shown that *TNF308*A* is associated with a lower response to anti-TNF drugs [51]. Clearly, the findings on the association of *TNF-alpha* gene (-308A/G, rs1800629) polymorphism with psoriasis and/or PsA in different populations/ethnic groups are quite divergent. Our results from a completely different population (Kuwaiti Arabs) are in concordance with those reported from Spain and Egypt (positive association with the GG genotype). These results from Kuwaiti Arabs highlight that the knowledge of *TNF-alpha* gene (-308A/G, rs1800629) polymorphism genotype/allele can assist the physician to identify the 'high-risk patients' who can potentially develop psoriasis along with arthritis and therefore a more appropriate treatment strategy can be followed based on the information about this polymorphism.

CONCLUSION

Our data showed an association between *IL6* gene (-174G/C; rs1800795) polymorphism, and *TNF-alpha* gene (-308A/G, rs1800629) polymorphism and PsA in Kuwaiti patients highlighting their significant contribution in genetic susceptibility, possibly along with other factors.

AUTHORS' CONTRIBUTIONS

Conceptualization: MZH, AMA

Data curation: MZH

Formal analysis: MZH, AMA

Funding acquisition: Not applicable

Investigation: AMA, MZ, AMA, JS, AKK, EAHH, YAB

Methodology: AMA, MZ, AMA, JS, AKK, EAHH, YAB

Statistical analysis: JS, MZH

Resources: AMA, MZH, EAHH, YAB

Supervision: MZH

Writing – original draft: MZH

Writing – review and editing: AMA, MZH. All authors read and approved the manuscript.

LIST OF ABBREVIATIONS

IL	= Interleukin
TNF-alpha	= Tumor necrosis factor alpha
PsA	= Psoriatic arthritis
RA	= Rheumatoid arthritis
PCR	= Polymerase chain reaction

RFLP	= Restriction fragment length polymorphism
SD	= Standard deviation
CI	= Confidence interval
OR	= Odds ratio

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The approval was granted by the Ethics Committee of Health Sciences Centre, Kuwait University (Ref. No. VDR/EC/3243).

HUMAN AND ANIMAL RIGHTS

In this research no animals were used. The procedures followed for human research were in accordance with the ethical standards of the Committee responsible for human experiments (Institutional and national), and in line with the Helsinki Declaration of 1975 and the revised guidelines of 2013.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the subjects included in this study. The identity of the participants was kept confidential to protect their privacy.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The raw datasets used and/or analyzed during the current study are available from the corresponding author [M.Z.H] on special request.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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