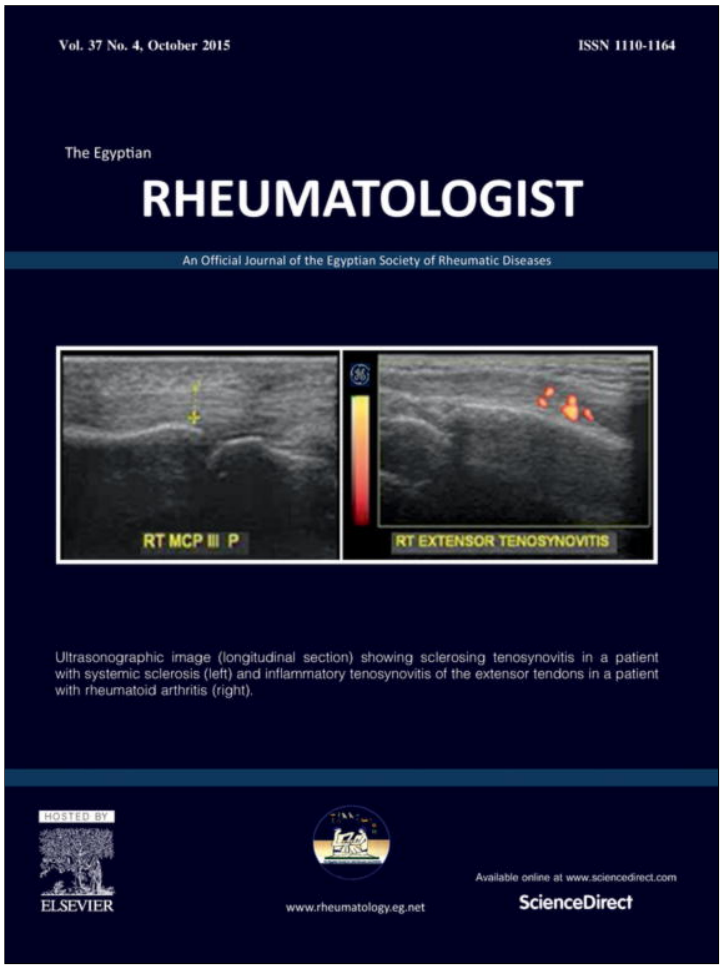

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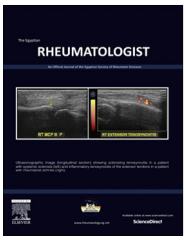

ORIGINAL ARTICLE

Association of interleukin-23 receptor (IL-23R) gene polymorphisms (rs11209026, rs2201841 and rs10889677) with Egyptian rheumatoid arthritis patients

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Abstract *Aim of the work:* To analyse interleukin 23 receptors (IL23R) single-nucleotide polymorphism (SNPs) (rs11209026, rs2201841, and rs10889677) and to detect their association with Egyptian rheumatoid arthritis (RA) patients.

Patients and methods: The study included 120 Egyptian RA patients and 120 healthy controls that were genotyped for the three SNPs by real time/polymerase chain reaction for the first SNP and restriction fragment length polymorphism/PCR (RFLP/PCR) in the last two SNPs. The disease activity score (DAS28) was assessed in the patients.

Results: The studied patients had a mean age of 42.5 ± 13.4 years, a disease duration of 5.2 ± 3.5 years and consisted of 22 males and 98 females. Joint deformities were present in 35 and 66 patients had swollen joints. The rheumatoid factor (RF) was positive in 78.3% and the DAS28 was 3.2 ± 1.2. Our data emphasize that the AA genotype of rs11209026 was significantly associated with RA patients compared to the controls ($p = 0.001$). We did not find any significant association between either rs2201841 or rs10889677 and the development of RA ($p = 1$, $p = 0.56$ respectively). The AA allele in the 3 SNPs were remarkable frequent in those with deformities and positive RF.

Conclusion: Our results suggest that IL23 receptor AA genotype variant of rs11209026 contributes to the aetiology of RA and may be considered a genetic marker and shared the susceptibility gene. We need to address the subgroup of patients who will benefit from the selective suppression of

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the IL-23 signalling which would represent new perspectives towards a personalized therapy of RA patients by further studies.

1. Introduction

Rheumatoid arthritis (RA) is a chronic progressive systemic inflammatory autoimmune disease of the joints, which can lead to long-term joint damage, resulting in chronic pain, loss of function, and disability [1]. The pathogenesis of RA is multifarious, with suspected interrelated contributions from genetic, infectious, environmental, and hormonal factors [2].

Advances in genotyping technology and the use of single-nucleotide polymorphism (SNP) assays have facilitated the application of whole genome association approaches to link genetic variants with disease susceptibility [3]. Gene polymorphism of various cytokines have been importantly considered in RA; The tumour necrosis factor-α (TNF-α) –308G/A promoter polymorphism as well as interleukin-6 (IL-6) –174G/C polymorphisms were significantly detected in RA patients and would predict the disease activity and functional status [4,5].

IL-23 was found during a genome scan for the IL-6/IL-12 cytokine family. IL-23 is a heterodimer, sharing a p40 subunit with IL-12 but having a distinct p19 subunit. IL-23 plays a role in type 1-polarized T cell immune responses [6]. A role of IL-23 has been implemented in the pathogenesis of many rheumatic diseases; being overexpressed in psoriatic arthritis and related to disease severity [7], and considered a critical biomarker for the development of arthritis in inflammatory bowel disease [8].

IL-23 binds to IL-12Rβ1. The receptor for this cytokine is heterodimeric and uses a novel second subunit, IL-23R, which is a member of the hematopoietin receptor family [9]. Soon researches were directed towards interleukin-23 receptor (IL23R) gene polymorphism, which maps to chromosome 1. The encoded protein forms a receptor for IL-23, together with the β1 subunit of IL-12 (IL12Rβ1) [10]. IL-23 and its gene polymorphism played a significant role in neuro-Behçet's and uveitis in Egyptian Behçet's disease patients with a significant relation to disease activity, making both potential markers [11]. IL-23R is a type I cytokine transmembrane protein, it consists of 629 amino acids. The extracellular domain contains a signal sequence, an *N* terminal Ig-like domain, and two cytokine receptor domains [9]. Eleven exons encode for the standard form of IL-23R. Through alternative splicing, they can generate at least six spliced isoforms (IL- 23R1 to 6) [12].

Expression of IL-23 receptors occurs on activated or memory T cells, on natural killer cells, and to a less extent on macrophages and dendritic cells. The corresponding legend cytokine, IL-23, is a key component of the immunoregulatory pathway and plays an important role in the development, differentiation, and effector functions of immune cells [13].

In chronic inflammation, the antigen-stimulated macrophages and dendritic cells produce IL-23. Binding of IL-23 to its receptor leads to the activation of Janus Kinases (Jak2 and Tyk2), which can phosphorylate IL-23R at discrete locations and thus form docking sites for signal transducers and activators of transcription (STATs). The STATs are then phosphorylated by the Jaks, and are thus capable of dimerising and translocating to the nucleus where they influence the transcription of key pro-inflammatory genes [14]. IL-23 promotes the development of Th17 cells producing IL-17, which enhances T cells and induces the production of several inflammatory mediators. IL-23 also stimulates dendritic cells and macrophages in an autocrine/paracrine manner to generate other pro-inflammatory cytokines, like IL-1, IL-6, and TNF-α [15,16]. The pro-inflammatory cytokines IL-23 and IL-17 are present in RA synovial fluid in increased levels [17,18]. IL-17 stimulates osteoclast differentiation by inducing the expression of receptor activator of NF-κB legend (RANKL) [19]. In addition, IL-17 directly stimulates osteoclastogenesis from monocytes alone, via the TNF,-α or RANK–RANKL pathway [20]. IL-17 is important in joint destruction in animal models and in patients with RA [21,22].

Polymorphisms of IL23R are associated with numerous different autoimmune diseases like inflammatory bowel disease, ankylosing spondylitis, Graves' ophthalmopathy, and psoriasis [23–26]. Yet conflicting results from different researches as regards the role of allelic variants or haplo-groups of IL-23R in the development of RA were illustrated.

Therefore, we aimed in the current study to assess the possible association of the IL23R p.Arg381Gln (rs11209026) substitution, rs2201841 and rs10889677 variants with the susceptibility for developing RA.

2. Patients and methods

We conducted this study on 120 patients with rheumatoid arthritis diagnosed according to the (2010) ACR criteria for the classification of RA [27]. We selected our cases from the Rheumatology and Rehabilitation and Internal Medicine departments and their outpatient clinics of Cairo, Al Fayoum and Zagazig, University hospitals; they were collected in the period from March 2012 till April 2014. A hundred and twenty apparently healthy volunteers matched for age and sex were taken as a control group. All patients were subjected to full history taking and thorough general and musculoskeletal examination (age, sex, disease duration, age of onset, duration of morning stiffness, presence of extra-articular manifestations and their current treatment). The disease activity in RA patients was assessed by the 28 joint count Disease Activity Score (DAS 28) using the number of swollen and tender joints, erythrocyte sedimentation rate (ESR) and patient's global status and pain evaluated by the visual analogue scale (VAS) range from 0 to 100 mm [28].

Blood samples were drawn from the cubital vein in patients and controls at the day of clinical examination after overnight fasting. Blood samples were collected on EDTA tubes and were stored at −20 °C till the time of assay which was performed for all samples at the same time. Erythrocyte sedimentation rate (ESR), complete blood count (CBC), Rheumatoid

Table 1 Characteristics of the rheumatoid arthritis patients.

Characteristics of the rheumatoid arthritis patients (N = 120)		
Age	years	42.5 ± 13.4
Gender	male/female	22/98
Disease duration	years	5.2 ± 3.5
Joints deformity	N (%)	35 (29.2)
Swollen joints	N (%)	66 (55)
TLC	$\times 10^3/\mu l$	7.5 ± 2.8
ESR	mm/1st hour	59.1 ± 37.5
RF positivity	N (%)	94 (78.3)
DAS28	range (mean ± SD)	1.5–4.7 (3.2 ± 1.2)

TLC, total leucocytic count; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; DAS28, disease activity score in 28 joints.

factor (RF), liver function tests, renal function tests and urine analysis were done. The molecular analysis was performed using DNA extracted from peripheral blood leukocytes of the patients and control. We obtained oral consent after proper orientation of the patients and volunteers about the objectives of the study. The study was approved by the local ethics committee prior to their inclusion in the study.

The rs11209026 (IL23R Arg381Gln) was genotyped using Real-time PCR method using Light Mix® Kit human IL23R Arg381GlnKit produced under license from Roche Diagnostics GmbH (TIB MOLBIOL GmbH, Berlin, Germany).

The rs2201841 and rs10889677 SNPs were genotyped separately using PCR-RFLP method from Huber et al. [25]. Instead of using fluorescently labeled forward primers, DNA was amplified using the ordinary primer pairs (from Operon Biotechnologies (GmbH/Bio campus, Germany).

Forward primer 5′-GGCCTATGATTATGCTTTTTCC TG-3′, reverse primer 5′- GAACATAACCCTATTGACAC CCTG-3′ for rs2201841 and forward primer 5′- AGGGGATT GCTGGGCCATAT-3′ and reverse primer 5′TGTGCCTGTA TGTGTGACCA-3′ for rs10889677. We added 2U to digest amplification products separately.

Statistical analysis: All patients' data were tabulated, and processed using Statistical package for sciences and society (SPSS 12.0) (SPSS Inc. Chicago, USA). Quantitative variables were expressed by mean and standard deviation (SD) and then compared using Mann–Whitney U test for comparing two independent variables and Kruskal–Wallis analysis for more than two independent variables. We expressed Qualitative variables by frequency and percentage and compared it using the chi-square test or Fischer's exact test. P value was considered significant if less than 0.05. Odd ratio (OR) and their 95% confidence interval (CI) were calculated for the interleukin 23 receptors genotype using multivariate logistic regression analysis.

3. Results

One hundred and twenty cases with RA were included in the present study. They were 98 females and 22 males, their ages ranged from 18 to 69 years with a mean of 42.5 ± 13.42 years, disease duration ranged from one year to 15 years with a mean of 5.24 ± 3.45 years. One hundred twenty age and sex matched healthy controls were also enrolled in the study. They were 95 females and 25 males, their ages ranged from 20 to 65 years with a mean 44.26 ± 12.36. Rheumatoid factor (RF) was positive in 94 (78.3%) cases and 35 (29.16%) had deformities. 66 (55%) patients had swollen joints; 18 (15%) had 1 swollen joint, 15 (12.5%) had 2, 8 (6.7%) had 3, 14 (11.7%) had 4, 6 (5%) had 5 and 5 (4.2%) had 6 swollen joints. At the time of the study, all patients were treated with NSAIDs, 51 patients (42.5%) were maintained on a combination of methotrexate (MTX) and hydroxychloroquine, 62 (51.6%) were treated with a combination of MTX and leflunomide and 7 (5.8%) patients were maintained on a combination of leflunomide and steroids. Clinical and demographic data of the RA patients are shown in Table 1.

We tested SNPs of interleukin-23 receptors rs11209026, rs2201841, and rs10889677 for association with RA. Our results revealed that the frequency of the AA genotypes of rs11209026 was significantly increased (95%) in the patients compared with the controls (61.7%) (p = 0.001), OR (0.37) with CI (0.26–0.57), while the allele and genotype frequencies of rs2201841 and rs10889677 showed no association with RA (p = 0.73, p = 0.56 – OR = 1.82, OR = 1.35 respectively). The comparison of allele and genotype frequencies between the control and RA cases has been illustrated in Table 2. The AA genotype of the rs11209026 was detected in 95.7% of RF positive patients and in 88.6% of those having deformity. The frequency of the interleukin-23 genotypes and alleles in cases with positive RF and deformity has been illustrated in Table 3.

4. Discussion

Rheumatoid arthritis (RA) represents the most common form of chronic inflammatory joint disease. The range of presentations of RA is broad; the clinical course can range from mild, self-limiting arthritis to progressive multisystem inflammation. The first and most common manifestations are pain, stiffness and swelling of peripheral joints. Though not directly life

Table 2 Comparison of the allele and genotype frequencies between the rheumatoid arthritis patients and controls.

SNP	Genotype allele	Cases (N = 120)	Controls (N = 120)	p	OR	CI (95%)
rs11209026	AA	114 (95)	74 (61.7)	0.001	0.37	0.26–0.57
	AG	6 (5)	46 (38.3)			
rs2201841	AA	104 (86.7)	104 (86.7)	1	1	0.23–4.43
	AG and GG	16 (13.3)	16 (13.3)			
rs10889677	AA	82 (68.3)	89 (74.2)	0.56	1.35	0.43–3.83
	CC and AC	38 (31.7)	33 (27.5)			

SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table 3 The frequency of the interleukin-23 receptor genotypes and alleles in rheumatoid arthritis patients with positive rheumatoid factor and deformity.

IL-23 receptor genotypes in rheumatoid arthritis patients (N = 120)					
SNP	Genotype allele	Positive RF (N = 94)		Deformity (N = 35)	
		N	(%)	N	(%)
rs11209026	AA	90	(95.7)	31	(88.6)
	AG	4	(4.3)	4	(11.4)
rs2201841	AA	78	(83)	23	(65.7)
	AG and GG	16	(17)	12	(34.3)
rs10889677	AA	55	(58.5)	25	(71.4)
	CC and AC	39	(41.5)	10	(28.6)

SNP, single-nucleotide polymorphism; RF, rheumatoid factor.

threatening, RA severely affects the quality of life of a patient and has major economic consequences for society [2].

The strategies that guided us to select the studied gene were based on choosing a susceptibility gene already identified in other related diseases considering its relevant functions that might be crucial in the pathogenesis of RA. In this study, we selected the IL23 receptor (IL23R) as a candidate gene principally based on the fact that the interaction of IL23R with its legend IL23 results in an increase of signal transducers and activators of transcription signalling which can consequently promote the production of IL17. IL17 is a potent pro-inflammatory cytokine already identified in various chronic inflammatory diseases [14]. Up-regulated production of IL23R that is associated with certain SNP alleles in its gene could confer risk for the disease [29].

The present study was performed to investigate the association of three IL-23R gene SNPs in Egyptian RA patients. The results showed that the AA genotype of the rs11209026 SNP was significantly associated with an increased susceptibility to RA compared to the control (p = 0.001). However, there was no significant difference with regard to the genotypes of rs7517847 and rs17375018 between patients and controls.

The significant association demonstrated here is consistent with earlier reports showing the relationship between the same genotypic variant and other autoimmune diseases including Behçet's disease, psoriatic arthritis, inflammatory bowel disease, and ankylosing spondylitis [23,24,30,31]. However, others [10,32–34] have reported contradictory findings to our result.

The biological impact of the investigated polymorphisms on the expression and functionality of IL23R is currently unknown but it is obvious that these SNPs can represent an important link in the development of autoimmune and inflammatory diseases [13]. Several mechanisms are suggested by which polymorphisms can change the function of the receptor. The rs11209026 SNP is located in the cytoplasmic domain and encodes the fifth amino acid internal to the transmembrane domain [35]. The arginine allele has a side chain with positive charge while the rare glutamine has an uncharged polar one and thus the substitution can have considerable effect on the protein structure [13].

To investigate the relation of the other IL23R variants with RA, we genotyped rs2201841 and rs10889677 SNPs in our RA patients and controls. No significant difference was found. It has been reported that the rs10889677 located in the 3′-UTR can cause overexpression of the IL23R, driving differentiation of T-cells towards a Th17 subpopulation with an increased release of other proinflammatory cytokines. The rs2201841 is an intronic variant in significant linkage disequilibrium with rs10889677, and therefore is unlikely to confer an independent risk [13]. The study on a Spanish Caucasian population supports our findings [32]. On the other hand, a case–control study on Hungarian Caucasian RA-patients and healthy controls showed that both rs10889677 GG and rs2201841 GG are risk alleles in RA [36].

Like other candidate gene studies, there are several limitations in our study. As the power to detect disease susceptibility genes is influenced by the number of the patient's samples, the size of patient samples in our study seemed to be relatively small. The results observed in this study need to be confirmed using a large sample size involving RA patients from different areas in upper and lower Egypt.

In conclusion, our results suggest that IL23 receptor AA genotype variant of rs11209026 would contribute to RA aetiology; consequently, it might be a genetic marker for RA. Further studies are needed to address the subgroup of patients who will benefit from the selective suppression of the IL-23 signalling which would represent new perspectives towards a personalized therapy of RA patients.

Conflict of interest

None.

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