Association study of single nucleotide polymorphisms of IL23R and IL17 in rheumatoid arthritis in the Algerian population

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ABSTRACT

Objective: Previous studies implicated that IL17/IL23 pathway and TH17 cells play an important role in autoimmune inflammation. Genome wide association studies have identified multiple single nucleotide polymorphisms (SNPs) in the IL23R and IL17 genes region associated with rheumatoid arthritis (RA).

Methods: In this study, we investigated the association of IL23R, IL17A and IL17F genes SNPs with RA susceptibility in the Algerian population. 343 patients with RA and 323 healthy subjects were genotyped for IL23R (rs11209026, rs1343151, rs10489629), IL17F (rs763780, rs2397084) and IL17A (rs2275913) variants by TaqMan technology.

Results: There was no evidence of a genetic association between IL23R, IL17F and IL17A SNPs and RA susceptibility in our population. However, IL23R rs1343151 variant enhanced the development of RF IgM and IgG positive (+) RA as compared with RF IgM and IgG negative (-) RA (OR 2.29, p = 0.004 and OR 0.64, p = 0.014 respectively). Also, IL23R rs10489629 was associated with all RF isotypes positive disease (IgM+: OR 2.16, p = 0,006; IgG+: OR 0.64, p = 0,004 and IgA+: OR 1.54, p = 0,013). A moderate association of IL17A rs2275913 with RF IgA- RA subgroup was shown (OR 1.95, p = 0,039). Moreover, our data showed a correlation between IL23R and IL17F variants and the parameters of disease activity such as HAQ score and disease duration.

Conclusion: The current study emphasizes the lack of association of IL23R and IL17 polymorphisms with RA susceptibility in the Algerian population. However, the data showed the relationship between IL23R and IL17A polymorphisms and the production of the different RF isotypes in RA patients.

Keywords: Polymorphism; Rheumathoid arthritis; Interleukin-17; Interleukin-23.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder with autoimmune features that affects approximately 1% of the world's population. It is characterized by chronic joint inflammation, cartilage destruction and bone erosion. Several studies have indicated that RA involves a complex interplay among genotype, environmental triggers and immune-regulatory factors[1]. The *HLA-DRB1* molecule is the first genetic factor contributing to RA susceptibility[2]. It is suggested that other non-HLA genes may play a role in RA development, among them genes that encodes for interleukins. These genes play a central role in the installation of inflammation, articular destruction and extra-articular manifestations associated with RA[3,4].

Recently, it was shown that the IL23/IL17 axis, play a key part in RA development. IL23 is required for development of Th17 cells. Additionally, IL23R is expressed on a variety of cells and can directly stimulated IL17 production from Th17 cells[5]. IL17 (A and F) is a proinflammatory cytokine, produced by the activated T cells. It induces cytokine and chemokine expression and may play a role in the aggravation of the synovial inflammation and bone destruction in RA[6].

Current evidence suggests that *IL23R* and *IL17* genes are excellent candidate genes for autoimmune inflam-

matory diseases: including inflammatory bowel disease[7,8], psoriasis[9], Ankylosing Spondilitis[10] and autoimmune thyroid disease[11]. For *IL23R* polymorphisms, a WTCCC (Wellcome Trust Case Control Consortium) study and a meta-analysis realized by Song *et al*. demonstrated that *IL23R* rs11209026, rs1343151 and rs10489629 increased RA disease susceptibility in Caucasian and Asian populations[12,13]. Conversely, several studies reported a lack of effect of *IL23R* polymorphisms on RA development[14–16]. With regard to *IL17* polymorphisms, there have been few reports, which have studied their association with susceptibility to RA and their involvement in clinical-pathological features of RA. These studies were focused on the Caucasian population[17,18]. However, literature on genetic associations of RA in the Maghreb North African population is currently limited.

The aim of our study was to examine the association of three SNPs in the *IL23R* gene, two SNPs in the *IL17F* gene and one SNP in the *IL17A* gene, with susceptibility to RA in the Algerian population, and to investigate their possible association with clinical and immunological features of disease. This could provide insightful information for their role in RA development in our population.

MATERIALS AND METHODS

CASE AND CONTROL COHORTS

A total of 343 RA patients, meeting the American College of Rheumatology (ACR) criteria of 1987 for RA, were recruited from the Rheumatology departments of the specialized centre of Ben Aknoun and Beni Messous teaching hospitals in Algiers. Clinical data were collected from patient's medical history, including: sex, age, disease duration, disease activity score for 28 joints (DAS28) and functional disability calculated using the health assessment questionnaire (HAQ). The control cohort consisted of 323 matched healthy individuals (sex ratio M/F: 1/5; mean age 36.6 ±11.6 years) with no familial history of autoimmune diseases. The study was approved by the regional ethics committee. Consent of participation in this study was obtained from all patients and controls. The main clinical and immunological characteristics of the study population are summarized in Table I.

IMMUNOLOGICAL ANALYSIS

All RF isotypes (IgM, IgG and IgA) and ACPA3 (IgG) were investigated using ELISA technique "Quanta LiteTM, Inova Diagnostics, CA, USA", with a cutoff

TABLE I. CHARACTERISTICS OF PATIENTS WITH RA

Characteristics	RA patients N=343	Controls N=323	p values
Age (years)	48.4 ± 13	36.6 ±11.6	NS
Sex ratio (Male/Female)	1/6	1/5	NS
Disease duration (years)	12.55 ± 8.36	/	/
Early RA (≤ 2 years)	20/257 (7.78%)	/	/
Late RA (> 2 years)	237/257 (92.21%)	/	/
DAS28-CRP	4.49 ± 1.41	/	/
HAQ	1.33 ± 0.83	/	/
CRP (mg/l)	5.25 ± 13.14	/	/
ESR (mm/h)	43.76 ± 28.67	17.4 ± 16	$< 10^{-3}$
ACPA positive	248/312 (79.48%)	/	/
ACPA (IU/ml)	223.4 ± 344	/	/
RF positive (nephelemetry)	202/301 (67.10%)	/	/
RF (nephelemetry) (IU/ml)	232.2 ± 509.7	/	/
RF-IgA positive	148/269 (55.01%)	/	/
RF-IgG positive	91/269 (33.82%)	/	/
RF-IgM positive	133/167 (79.64%)	/	/

DAS28 = disease activity score; HAQ = health assessment questionnaire; CRP = C-reactive protein; ESR = erythrocyte sedimentation ration; ACPA = anti-cyclic citrullinated peptides; RF = rheumatoid factor; RA = rheumatoid arthritis. Values are the mean ± SD (standard deviation) except for early and late RA, RF and ACPA presence which are N (%); NS: not significant.

value of 20 IU/ml for each RF isotype and 25 IU/ml for ACPA3 according to manufacturer protocol.

GENOTYPING ANALYSIS

Genomic DNA was extracted from the whole blood of RA patients and the control group, using the standard salting out extraction method. The samples were genotyped, for the *IL23R* rs11209026, rs1343151 and rs10489629 variants (Assay ID: C___1272298_10, C___8367043_10 and C__30279129_20 respectively), *IL17F* rs763780 and rs2397084 variants (Assay ID: C___2488913_10 and C___2234166_10 respectively) and *IL17A* rs2275913 variant (Assay ID: C__15879983_10), by allelic discrimination by the TaqMan technology (Applied Biosystems, Foster City, CA, USA).

STATISTICAL ANALYSIS

Comparison of genotypes distribution and alleles frequencies between RA patients and controls was evaluated by the Chi-square ($\chi 2$) test, using an odds ratio (ORs) and 95% confidence intervals (95% CIs). Correlation of the associated SNP with autoantibody status among RA cases was performed with $\chi 2$ test. The comparison between the clinical and laboratory parameters of the different genotypes was performed using Wilcoxon test and $\chi 2$ test, with Yate's correction when necessary. The frequency differences of haplotypes in patients with RA and controls were compared using the $\chi 2$ test with Yate's correction by PHASE 2.1 software. Case and control genotypes frequencies did not deviate from the Hardy-Weinberg equilibrium. All statistical analyses were performed with the SPSS, version 16.0 (SPSS, Chicago, IL). All *P* values lower than 0.05 were considered as statistically significant. Correction for multiple testing was realized using the Bonferroni adjustment. The significance of the p value was assessed at 0.01.

RESULTS

Demographic, clinical and serological characteristics of all subjects are summarized in Table I. There was a preponderance of female with 86%. The sex ratio was 1 male for 6 females, and the majority of our patients have an active disease (mean DAS28 = 4.5). A significant difference of ESR (erythrocyte sedimentation ration) was observed between patients and controls ($p < 10^{-3}$). The observed serological characteristics seem to be similar to those observed in other RA cohorts from North Africa[19, 20].

Genotypes and alleles frequencies in RA and control groups are shown in Table II. No statistically significant differences were found between RA patients and controls when we compared genotypic and allelic frequencies of the *IL23R* (rs11209026, rs1343151 and rs10489629), *IL17F* (rs2397084, rs763780) and *IL17A* (rs2275913) SNPs under study ($p > 0.05$).

In our study, we also investigated whether the polymorphisms under study were associated with autoantibody profile (Tables II, III). No differential association could be observed for either *IL23R* rs11209026 or the *IL17F* (rs2397084, rs763780) polymorphisms. However, a significant increase in frequency of the minor allele A of *IL23R* rs1343151 was observed in patients with RF IgG+ and RF IgM+ RA as compared with patients with RF IgG - and RF IgM - RA (52.8% *vs* 41.6%, $p = 0.014$ and 48% *vs* 29,4%, $p = 0.004$, respectively). Furthermore, the minor allele C frequency of *IL23R* rs10489629 was increased in all patients with RF IgM, IgG and IgA positive subgroups as compared with patients with RF IgM, IgG and IgA negative subgroups (54% *vs* 35.3%, $p = 0{,}006$; 59.3% *vs* 46%, $p = 0{,}004$ and 55.4% *vs* 44.6%, $p = 0{,}013$, respectively). Also, our analysis showed that the frequency of the minor allele A of *IL17A* rs2275913 was increased in patients with RF IgA- RA as compared with RF IgA+ RA (22% *vs* 12.7%, $p = 0{,}039$) (Tables II, III).

Moreover, we compared the average HAQ score in patients who took the variant allele and the wild homozygous patients (Table IV), and the results demonstrated that the *IL23R* rs1343151 and rs10489629 were negatively associated with functional disability (GG: $\bar{X}$=1.54; AG+AA: $\bar{X}$=1.24; $p = 0.043$ and TT: $\bar{X}$=1.63; CT+CC: =1.83; $p = 0.011$, respectively) (Table IV). Likewise, these two SNPs (*IL23R* rs1343151 and rs10489629) were negatively correlated to C-reactive protein (CRP) titers in our patients (GG:$\bar{X}$=7.49; AG+AA: $\bar{X}$=4,29; $p = 0.045$ and TT: $\bar{X}$=6.55; CT+CC: $\bar{X}$=3.91; $p = 0.032$ respectively). Further, the polymorphism of IL17F rs763780 was associated with high ESR value (TT: $\bar{X}$= 42.86; CT+CC:$\bar{X}$=54.74; $p = 0.016$). In addition to this, our results showed that *IL23R* rs10489629 and *IL17F* rs2397084 SNPs were negatively correlated with disease duration in patients with RA (TT: $\bar{X}$=15.13; CT+CC:$\bar{X}$=11.91; $p = 0.008$ and TT: $\bar{X}$=13.21; CT+CC: $\bar{X}$=8.37; $p = 0.003$, respectively). For the *IL17A* rs2275913 polymorphism, no genotype-phenotype association was detect with all disease acti-

TABLE II. RESULTS OF ASSOCIATION AND STRATIFICATION ANALYSIS OF IL23R POLYMORPHISMS

	rs112090026				rs1343151				rs10489629			
	Allele				Allele				Allele			
	G	A	OR (95% CI)	P	G	A	OR (95% CI)	P	T	C	OR (95% CI)	P
RA (%)	93.6	6.3	/	NS	54.2	45.8	/	NS	50	50	/	NS
Control (%)	93.4	6.6			56	44			51.8	48.2		
RF status												
RF IgM+ (%)	94	6	/	NS	51	48.9	2.29 (1.25-4.30)	0.004	45.9	54	2.16 (1.20-3.93)	0.006
RF IgM - (%)	97	3			70.6	29.4			64.7	35.3		
RF IgG+ (%)	94	6	/	NS	47.3	52.8	0.64 (0.43-0.92)	0.014*	40.6	59.3	0.64 (0.44 -0.90)	0.004
RF IgG - (%)	93	7			58.4	41.6			54	46		
RF IgA+ (%)	93.2	6.7	/	NS	52	48	/	NS	44.6	55.4	1.54 (1.08-2.20)	0.013*
RF IgA - (%)	93.4	6.6			57.9	42.1			55.4	44.6		

*P value not significant after Bonferroni's correction (alpha=0.01)
NS= Not significant; OR = odds ratio; 95% CI = 95% confidence interval; RA = Rheumatoid arthritis; RF = rheumatoid factor

TABLE III. RESULTS OF ASSOCIATION AND STRATIFICATION ANALYSIS OF IL17F AND IL17A POLYMORPHISMS

	IL17F rs2397084				IL17F rs763780				IL17A rs2275913			
	Allele				Allele				Allele			
	T	C	OR (95% CI)	P	T	C	OR (95% CI)	P	G	A	OR (95% CI)	P
RA (%)	93.5	6.4	/	NS	93.7	6.2	/	NS	82.5	17.5	/	NS
Control (%)					94	6			79.8	20.2		
RF status	93.6	6.4	/	NS								
RF IgM+ (%)	92.7	7.3			95.1	4.9	/	NS	83.1	16.9	/	NS
RF IgM - (%)					95.6	4.4			81.8	18.2		
RF IgG+ (%)	94	6	/	NS	94	6	/	NS	88.8	11.2	/	NS
RF IgG - (%)	94.6	5.3			94	6			80.3	19.6		
RF IgA + (%)	94.6	5.4	/	NS	93.2	6.8	/	NS	87.3	12.7	1.95 (0.98-3.91)	0.039*
RF IgA - (%)	94.2	5.8			94.6	5.4			78	22		

*P value not significant after Bonferroni's correction (alpha=0.01)
NS= Not significant; OR = odds ratio; 95% CI = 95% confidence interval; RA = Rheumatoid arthritis; RF = rheumatoid factor

TABLE IV. THE ASSOCIATION BETWEEN IL23R (RS1343151, RS10489629)/IL17F (RS763780) AND FUNCTIONAL DISABILITY OF RA PATIENTS

SNP	Genotype	HAQ (0-3) Mean value ± SEM	p
IL23R	GG	1,54 ± 0,12	0,043
rs1343151	AG+AA	1,24 ± 0,08	
IL23R	TT	1,63 ± 0,13	0,011
rs10489629	CT+CC	1,23 ± 0,08	

HAQ = health assessment questionnaire, p ≤ 0.05 was considered as significant.

vity and laboratory parameters under study ($p > 0.05$) (data not shown).

To determine whether any specific haplotype would confer a higher risk or protection for RA in our population, we performed haplotype test of association. Analysis of the haplotype structure revealed 8 distinct haplotypes for *IL23R* and 4 for *IL17F*. Our haplotype analysis did not reveal any significant association with RA susceptibility or with autoantibodies status in our cohort (data not shown).

DISCUSSION

The identification of genetic risk factors is an on-going process that will aid in the understanding of RA etiology. A genome-wide association scan in RA disease highlighted the *IL23R* and *IL17* genes as a susceptibility factors. To date, there is emerging evidence showing that the IL23/IL17 axis have a central role in the autoimmune inflammation in joints, and interaction between IL-23 and IL-17 is essential for the destruction phase of RA characterized by the T cell-mediated activation of osteoclastogenesis[5]. In the present study, we examined for the first time the possible influence of previously described *IL23R* and *IL17A/F* genes polymorphisms on RA predisposition in the Algerian population. No association of these genetics variants with RA was observed (Tables II, III). Indeed, results concerning the role of *IL23R* SNPs in RA are contradictious. Similar to our data, rs112090026 was not associated with RA susceptibility in European cohorts[13,21,22]. Also, this lack of association with RA has been reported in the meta-analysis conducted by Hollis *et al*. (OR 0.99, $p = 0.94$)[16]. However, a recent study conducted on the Egyptian population has shown a significant association of rs112090026 of *IL23R* to RA susceptibility (OR 0.37, $p = 0.001$)[23]. Chen-Xu and colleagues[24], and subsequently other investigators[12,16], showed that the *IL23R* rs1343151 was strongly associated with RA susceptibility in Caucasian populations. Nevertheless and similar to our data, no association was found between RA and rs1343151 in the Australian, Norwegian[24] and Korean[25] populations (OR 1.00, $p = 0.98$; OR 1.00, $p = 0.97$ and OR 1.20, $p = 0.31$, respectively). In contrast to our data, in the WTCCC study[13], the minor allele of IL23R rs10489629 was associated with increased RA susceptibility (OR 0.74, $p < 10^{-5}$). Similar to our result, data from Spanish[21], New Zealand[16] and Korean[25] cohorts did not find any significant difference between RA patients and controls.

All association studies of *IL23R* and *IL17* polymorphisms have shown conflicting results. This inconsistencies among previous and the current report is probably due to the difference of ethnic groups. Further studies on these polymorphisms will be required in different ethnic populations to highlight the implication of IL23R and IL17 polymorphisms in RA susceptibility and severity.

IL17 is produced by the activated T cells, induces cytokines and chemokines expression and may play a role in skeletal tissue destruction and inflammatory process in RA[6]. Moreover, few studies have recently examined the association between *IL17A* and *IL17F* polymorphisms with RA development. Here, we analyzed two SNPs in the *IL17F* gene at position 7383A/G and 7488A/G, localized in exon3, and one *IL17A* SNP in a promoter region (-197A/G). The results showed no significant relationship with RA susceptibility in our cohort. This lack of association of *IL17F* polymorphisms was reported in the study conducted by Paradowska-Gorycka *et al*. on the polish population[17]. Gry *et al*. analyzed *IL17A* (-197A/G) in a Norwegian RA patients and found a modest association (OR = 1.17, $p = 0.02$)[18]. However, our data and data from New Zealand sample sets did not support this[18].

RF is the term for autoantibodies directed to the Fc chains of IgG molecules. RF-IgM can be detected in 60% to 80% of RA patients with established disease and can precede the onset of disease by several years. In addition to RF-IgM, raised levels of RF-IgG and IgA have been reported in RA patients and were associated with more severe disease outcome. Thus, RF may contribute to the activity and chronicity of RA through complement-mediated pathways[26]. Our findings

demonstrate an association between two SNPs of *IL23R* (rs1343151 and rs10489629) and positive RF disease: the minor allele of rs1343151 was associated with RF IgG and IgM positive disease, the variant rs10489629 was associated with all RF isotypes positive disease. This finding suggests that the *IL23R* variants, within the IL23/IL17 pathway, may play a role in the production of RF autoantibody in RA patients; which implicate probably a more severe disease. IL23 p19 produced by synovial fibroblasts promotes inflammatory response in RA synovial tissue by increased production of IL6 and IL8 and chemokines such as CCL20[5]. These cytokines of the TH17 axis may be implicated in the production of RF autoantibody in RA patients. Thus, the induction of IL6 may suggest that IL23/IL17 could be associated with TH2 immune response in RA[27]. Also, it has been reported that IL22, produced by TH17 cells, may regulate antibody production in collagen-induced arthritis[28]. Furthermore, our analysis showed a moderate association of *IL17A* rs2275913 with RF IgA negative RA subgroup. It was reported that IL-17 is associated with the survival and proliferation of human B cells and their differentiation into immunoglobulin-secreting cells[29]. It is probably that the variant rs2275913 negatively influences the RF production in RA patients. However, further investigations are needed to identify the potential role of the IL23/IL17 axis in the autoimmune process of RA.

Finally, in our study, we also found an association of SNPs with disease severity and other clinical characteristics in RA. The polymorphisms *IL23R* rs1343151 and rs10489629 had a negative relationship with functional disability. Further, *IL23R* rs1343151, *IL23R* rs10489629 and *IL17F* rs763780 were associated with inflammatory activity in our patients. Also, the major allele T of the *IL17F* rs2397084 SNP was associated with disease duration in our patients. However, Paradowska-Gorycka *et al*. showed that carriers of polymorphic allele C, of *IL17F* rs2397084, had a tendency to have longer disease duration compared to RA patients with two wild-type alleles, but the difference was not statistically different ($p = 0,07$)[17]. No genotype-phenotype association was found for the *IL17A* rs2275913 variant in our cohort. A similar result was developed in the study conducted by Nordang *et al.* on the Caucasian population[18].

The present study has some potential limitations, which could contribute to the false positive or negative results. The power of this work may be not high because the size of RA patients and controls cohorts is not very large. Unluckily, only 3 SNP of IL23R, 2 SNP of IL17F and 1 of IL17A were the subjects of the study. More polymorphisms of TH17 axis cytokines should be studied to clarify the role of this SNP in the development of RA.

CONCLUSION

In summary, our study investigated the association of SNPs of *IL23R*, *IL17A* and *IL17F* with RA risk in the Algerian population. Our data suggests that these variants do not play a relevant role in the susceptibility of RA; however, an association of *IL23R* and *IL17A* variants with RF status was shown. Further studies are needed to confirm our current data in others Maghreb North African populations.

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