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ORIGINAL ARTICLE

Interleukin (IL)-23 Receptor, IL-17A and IL-17F Gene Polymorphisms in Brazilian Patients with Rheumatoid Arthritis

Isaura Isabelle Fonseca Gomes da Silva[1] · Hildson Dornelas Angelo[2] · Eliezer Rushansky[3] · Maria Helena Mariano[3] · Maria de Mascena Diniz Maia[4] · Paulo Roberto Eleuterio de Souza[5]

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Abstract Rheumatoid arthritis (RA) is a progressive, autoimmune disease for which the previous studies have shown that some functional polymorphisms can influence its etiology. Knowing this, the aim of this study was to investigate the association of +2199 A/C *IL-23R* (rs10889677), −197 G/A *IL-17A* (rs2275913), and +7488 A/G *IL-17F* (rs763780) gene polymorphisms with RA susceptibility and clinical features in a Brazilian population. A total of 127 RA patients and 134 healthy controls were recruited for the analyses of polymorphic variants. Genotyping was performed using RFLP-PCR. Logistic regression was used to analyze the genotype distribution of the polymorphisms. Individuals carrying the homozygous CC genotype for the *IL-23R* polymorphism seem to be at lower risk for RA development (OR 0.22; $p = 0.004$), as well as those carrying the variant C allele (OR 0.56; $p = 0.002$). For the −197 G/A *IL-17A* polymorphism, the wild-type genotype (GG) was significantly associated with a 3.18-fold (OR 3.18; $p = 0.033$) increased risk for RA. In relation to the +7488 A/G *IL-17F* polymorphism, no significant difference was found between RA cases and control subjects ($p > 0.05$). Moreover, when investigating the relationship between polymorphisms and clinical features, no evidence of an association was found. Our findings suggest that the variants +2199 A/C *IL-23R* and −197 G/A *IL-17A* could contribute to RA development in the studied population. However, larger studies are needed to fully understand this genetic predisposition.

Keywords Rheumatoid arthritis · Cytokines · Th17 profile · Polymorphisms

✉ Paulo Roberto Eleuterio de Souza
prsouza30@gmail.com

[1] Pós-Graduate Program in Applied Cellular and Molecular Biology, University of Pernambuco, Recife, PE, Brazil

[2] Federal Institute of Pernambuco, Garanhuns, PE, Brazil

[3] Division of Clinical Rheumatology, University of Pernambuco, Recife, PE, Brazil

[4] Department of Biology, Federal Rural University of Pernambuco, Recife, PE, Brazil

[5] Departamento de Biologia, Universidade Federal Rural de Pernambuco, Rua Dom Manoel de Medeiros, s/n, Dois Irmãos, Recife, PE CEP 52171-900, Brazil

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease that is associated with progressive incapacity, systemic complications, socioeconomic impact, and early death. The cause of RA is unknown, and the prognosis is guarded. The disease affects approximately 1% of adults worldwide (Alamanos et al. 2006; McInnes and Schett 2011). Genetic and environmental factors are related to the etiology and pathogenesis of the disease (Guo and Li 2016; Hunt and Emery 2014; Okada et al. 2014). RA involves an immunological disorder of the innate and adaptive system, promoting inflammatory cell infiltration and bone and cartilage erosion (Brzustewicz and Bryl 2015).

Many cytokines and other mediators play an important role in inflammation and tissue damage (Brzustewicz and Bryl 2015; Zaky and El-Nahrery 2016). Cytokines corresponding to T-lymphocyte profile helper 17 (Th17) are important in stimulating the proliferation of cells to combat intracellular and extracellular pathogens and promoting chronic inflammation and autoimmunity (Brzustewicz and Bryl 2015; Isailovic et al. 2015; Shabgah et al. 2014).

Among these cytokines, interleukin (IL)-23 is responsible for stimulating proliferation of Th17 profile effector cells, including IL-17 (Langrish et al. 2005; Zaky and El-Nahrery 2016), and for inducing osteoclastogenesis via the receptor activator of nuclear factor-kappa B ligand (RANKL) (Sato et al. 2006).

IL-23 is a member of the IL-12 family, is produced by dendritic cells, monocytes, and macrophages, and has two subunits, p40 and p19. The binding of IL-23 to its heterodimeric receptor can lead to the proliferation and maintenance of Th17 effector cells (Zaky and El-Nahrery 2016). The receptor appears on the surface of lymphocytes, dendritic cells, macrophages, and monocytes. The p40 subunit of IL-23 is shared with IL-12, while the p19 subunit has a specific and high affinity for IL-23R (Lupardus and Garcia 2008). IL-23R plays a role in the onset and maintenance of signal transduction of IL-23/IL-17 (Paradowska-Gorycka et al. 2010a); alterations in the signaling pathway may deregulate the inflammatory process (Floss et al. 2015).

IL-17 is part of the IL-17 cytokine family which comprises six members: IL-17A to 17F. Although other cell types produce IL-17, it is mainly produced by Th17 subset cells, as the hallmark of the Th17 profile is the production of IL-17A and IL-17F (Shabgah et al. 2014). IL-17A and IL-17F induce the production of inflammatory mediators, such as cytokines, chemokines, antimicrobial peptides, and RANKL, which can lead to an increase in the inflammatory process (Brzustewicz and Bryl 2015; Shen et al. 2015). In addition, IL-17A and IL-17F can stimulate fibroblasts, osteoblasts, synoviocytes, macrophages, and endothelial cells, thereby promoting inflammation (Benedetti and Miossec 2014). It has been seen that IL-17 may influence inflammation in different diseases, such as RA and spondyloarthritis (Rossini et al. 2016). Moreover, the literature data suggest that high levels of IL-17 are found in the synovial fluid of patients with RA, which may induce joint degradation (Kirkham et al. 2006; Shahrara et al. 2008).

It has been postulated that genetic polymorphisms affect cytokine levels; therefore, polymorphisms of genes of the IL-23/Th17 pathway may affect their structure and expression, modulating inflammation, and may contribute to the etiology and pathogenesis of RA. In recent reports, it has been suggested that polymorphisms in the *IL23R* gene were related to inflammatory and chronic diseases, such as ulcerative colitis (Yu et al. 2012), gastric cancer (Chen et al. 2011), and RA (Farago et al. 2008; Hamdy et al. 2015) in different ethnic groups (Bogunia-Kubik et al. 2015; Farago et al. 2008; Shen et al. 2015). Among the polymorphisms of *IL-23R*, the functional single nucleotide polymorphism (SNP) +2199 A/C located in the 3′-UTR region is related to over-expression of IL-23R due to increased stability of mRNA (Chen et al. 2011). In addition, polymorphisms in the *IL-17A* and *IL-17F* genes were associated with inflammatory diseases, such as chronic periodontitis (Zacarias et al. 2015), gout (Zhou et al. 2016), psoriatic arthritis (Popa et al. 2013), and RA (Bogunia-Kubik et al. 2015; Shen et al. 2015). Genetic variation in the −197 G/A promoter region of the *IL-17A* gene can alter gene transcription, resulting in higher IL-17A secretion (Espinoza et al. 2011). Meanwhile, a His-to-Arg substitution in relation to +7488 A/G *IL-17F* polymorphism can alter the conformation or the expression level of the protein (Kawaguchi et al. 2006). Nevertheless, contradictory results can be found in different populations due to high genetic diversity. However, in Brazil, there have been few studies on genetic polymorphisms related to RA.

Thus, our study has been conducted to verify a possible association of the functional gene polymorphisms +2199 A/C *IL-23R* (rs10889677), −197 G/A *IL-17A* (rs2275913), and +7488 A/G *IL-17F* (rs763780) with susceptibility to RA and their association with clinical features. This is the first study directed at the northeastern Brazilian population.

Materials and Methods

Patients and Controls

This study comprised 127 patient volunteers diagnosed with RA according to the American College of Rheumatology/European League Against Rheumatism classification criteria (Arnett et al. 1988; Smolen et al. 2010) and registered at the Division of Clinical Rheumatology of the Hospital Oswaldo Cruz, University of Pernambuco, Brazil. Patients younger than 18 years were excluded from the study.

The control group consisted of 134 healthy volunteers between 20 and 80 years with the same mean age, gender proportion, and ethnicity as the patient group. Individuals were included in the control group if their medical history did not reveal RA, other autoimmune, or infectious diseases. If an individual presented any of these conditions, they were excluded from the control group.

All the subjects inhabited the same geographic area and were recruited between July 2015 and May 2016. The study was approved by the Ethics Committee of the Health Sciences Center of Federal University of Pernambuco (protocol 1.097.918/2015) and all participants provided written, informed consent and answered a questionnaire including social and demographic features (sex, age, age at disease onset, disease duration, smoking habit, and therapy). Clinical data, such as Disease Activity Score 28 joints (DAS28), Health Assessment Questionnaire (HAQ), and

Clinical Disease Activity Index (CDAI), were also collected.

Blood Sampling

For the study, 5 mL of peripheral blood were collected from each individual using tubes with and without ethylenediaminetetraacetic acid (EDTA). Part of the collected biological samples were sent to the Clinical Analysis Laboratory (CIAC, Recife, Pernambuco) for biochemical analysis, including C-reactive protein, erythrocyte sedimentation rate, anti-citrullinated protein antibody, and rheumatoid factor. Another part of the blood samples was directed for genotyping at the Laboratory of Genetics, Biochemistry and DNA Sequencing at the Federal Rural University of Pernambuco. Clinical data of all patients are presented in Table 1.

DNA Extraction and Genotyping

Genomic DNA was extracted with the Wizard Genomic DNA Purification Kit (PROMEGA, Madison, USA), according to the manufacturer instructions. Next, +2199 A/C *IL-23R* polymorphism genotyping was performed by restriction fragment length polymorphism polymerase chain reaction (RFLP-PCR) using the following primers: 5′-AGGGGATTGCTGGGCCATAT-3′ (sense) and 5′-TGTGCCTGTATGTGTGACCA-3′ (antisense) and digested with *Mnl*I (Biolabs, New England) enzyme restriction, based on Chen et al. (2011).

The −197 G/A *IL-17A* and +7488 A/G *IL-17F* polymorphisms were detected by RFLP-PCR using primers 5′-AAC AAGTAAGAATGAAAAGAGGACATGGT-3′ (sense) and 5′-CCCCCAATGAGGTCATAGAAGAATC-3′ (antisense) for −197 G/A *IL-17A* and sense 5′-ACCAAGGCTGCTC TGTTTCT-3′ and antisense 5′-GGTAAGGAGTGGC ATTTCTA-3′ for +7488 A/G *IL-17F*. PCR products were digested with *Eco*NI (Biolabs, New England) for –197 G/A *IL17A* and *Nla*III (Biolabs, New England) for +7488 A/G *IL17F* as previously described by Zacarias et al. (2015). All products were separated by electrophoresis on a 3% agarose gel and stained with Blue Green Loading Dye (LGC Biotechnology, Cotia, Brazil).

To confirm the genotyping results, 20% of samples were sequenced by Mega BACE 1000 DNA Analysis System and sequence analyses were performed using the Bioedit sequence alignment editor 7.2.5 software (Hall 1999).

Table 1 Clinical, laboratorial, and demographic characteristics of the patients with rheumatoid arthritis

Variable	Cases ($N = 127$)
Gender: female/male; *n* (%)	124 (97.64)/3 (2.36)
Age; mean (range) years	52.86 ± 10.33
Age at RA onset; mean (range) years	41.86 ± 10.18
Disease duration, mean (range) years	11.00 ± 7.88
CRP, means (range) mg/L	5.08 ± 10.43
ESR; mean (range) mm/h	22.49 ± 12.8
Rheumatoid factor positive, *n* (%)	57 (44.88)
ACPA present[a], *n* (%)	15 (75.00)
DAS28 *n* (%)	
Remission (≤2.6)	14 (11.02)
Low (2.6 < DAS28 ≤ 3.2)	13 (10.24)
Moderate (3.2 < DAS28 ≤ 5.1)	93 (73.23)
Severe (>5.1)	7 (5.51)
HAQ; mean (range)	1.43 ± 0.66
CDAI; mean (range)	20.33 ± 10.02
Erosions present, *n* (%)	108 (85.04)
Smoke; *n* (%)	17 (13.39)
Treatment with biological DMARDs *n* (%)	61 (48.03)

ESR erythrocyte sedimentation rate, *ACPA* anti-cyclic citrullinated peptide antibodies, *CRP* C-reactive protein, *DAS28* rheumatoid arthritis disease activity score, *HAQ* Health Assessment Questionnaire, *CDAI* Clinical Disease Activity Index

[a] Data available for 20 patients

Statistical Analyses

Categorical variables were analyzed by direct counting and expressed as number and percentage, while the quantitative variables were expressed as mean and standard deviation. Differences in genotype distribution and allele frequencies, as well as features in all subjects were evaluated using the χ^2 test with 95% confidence intervals (CIs) and the p value was considered significant below 0.05. The genotype distributions were assessed by the Hardy–Weinberg equilibrium proportion tests. The post hoc statistical power calculation was performed for all polymorphisms using the G Power 3.1 software (Faul et al. 2009). Univariate analysis was performed to determine the association of SNP genotypes and variable demographic characteristics using the BioEstat 5.0 software. Multivariate logistic regression analysis was employed to evaluate the association between the SNPs and RA. Finally, odds ratios (ORs) were calculate considering a p value less than 0.05 with adjustment for age and gender. The multivariate analysis was executed using the R version 3.2.1 software.

Results and Discussion

Considering that the Th17 profile emerges as a new source of chronic inflammation due to an immune imbalance, our study examined possible polymorphisms related to immunological disorders and consequent development of RA. Clinical and demographic data of the RA patients are

Table 2 Genotypic distribution and allele frequencies of the *IL-23R* (+2199A/C), *IL-17A* (–197 G/A), and *IL-17F* (+7488 A/G) gene polymorphisms in patients with rheumatoid arthritis and healthy control

Genotypes	Patients		Controls		*p**	OR (95% CI)	*p*
	n (%)	P_{HWE}	*n* (%)	P_{HWE}			
IL-23R (rs10889677)							
AA	15 (11.81)	0.009	7 (5.23)	0.086	0.003	1.00	
AC	76 (59.84)		63 (47.01)			0.48 (0.16–1.25)	0.148
CC	36 (28.35)		64 (47.76)			**0.22 (0.07–0.60)**	**0.004**
C allele vs A allele	148 (58.27) vs 106 (41.73)		191 (71.27) vs 77 (28.73)		0.002	**0.56 (0.39–0.81)**	**0.002**
IL-17A (rs2275913)							
AA	6 (4.72)	0.712	13 (9.70)	0.135	0.218	1.00	
GA	40 (31.50)		46 (34.33)			2.25 (0.77–7.26)	0.149
GG	81 (63.78)		75 (55.97)			**3.18 (1.13–9.95)**	**0.033**
G allele vs A allele	202 (79.53) vs 52 (20.47)		196 (73.13) vs 72 (26.87)		0.106	1.43 (0.95–2.14)	0.106
IL-17F (*rs763780*)							
AA	119 (93.70)	0.714	120 (89.55)	0.343	0.366	1.00	
AG	8 (6.30)		13 (9.70)			0.66 (0.24–1.71)	0.400
GG	0 (0.00)		1 (0.75)			<0.0001	0.986
G allele vs A allele	246 (96.85) vs 8 (3.15)		253 (94.40) vs 15 (5.60)		0.251	0.548 (0.23–1.32)	0.251

Bold means significant values

P_{HWE} *p* value from Hardy–Weinberg equilibrium test, *p** *p* value of χ^2, *OR* odds ratio, *CI* confidence interval, *p* *p* value from logistic regression analyses, adjusted for age and gender

shown in Table 1. The RA patient group had a mean age of 52.86 ± 10.33 years; 97.6% were women; 44.8% showed positive rheumatoid factor; and 78.7% had a moderate or high Disease Activity Score (DAS28). Patients received prednisone 5 mg/day one-to-four times/day. 51.97% ($n = 66$) of patients received Methotrexate as monotherapy or in combination with Leflunomide, while 45.67% ($n = 58$) of patients used anti-TNF and 2.36% ($n = 3$) used anti-CD20 as biological agents.

In the control group, the mean age was 48.79 ± 12.47 years and 95.52% were women. In Table 2, the frequencies are shown of +2199 A/C *IL-23R* (rs10889677), −197 G/A *IL-17A* (rs2275913), and +7488 A/G *IL-17F* (rs763780) gene polymorphisms in RA patients and controls. The genotype distributions were in agreement with the prediction of Hardy–Weinberg equilibrium, except for +2199 A/C *IL-23R* in the patient group. The statistical power of +2199 A/C *IL-23R*, −197 G/A *IL-17A,* and +7488 A/G *IL-17F* polymorphisms in RA group vs. control group was 82, 60, and 58.5%, respectively.

Logistic regression analyses of the +2199 A/C *IL-23R* gene polymorphism indicated that individuals with the CC genotype showed a protective effect against the development of RA as compared with the AA genotype (OR 0.22; 95% CI 0.07–0.60; $p = 0.004$). Likewise, a significantly decreased risk of RA was found for the C variant (OR 0.56; 95% CI 0.39–0.81; $p = 0.002$), suggesting that the AA genotype confers an increased risk for RA. A few studies have reported an association of this polymorphism with RA with divergent results. Farago et al. (2008) and Szabo et al. (2013) found an increased risk for RA in patient carriers of the AA genotype in a Hungarian population. On the other hand, Hamdy et al. (2015) found no association between the genotype variant of *IL-23R* with RA in an Egyptian population. Furthermore, this polymorphism has been associated with other inflammatory diseases in a Chinese population, such as Crohn's disease (Xu et al. 2015), breast, lung and nasopharyngeal cancer (Zheng et al. 2012), and gastric cancer (Chen et al. 2011).

Our findings are corroborated by other studies which indicate that the AA genotype of *IL-23R* located in the 3′-UTR region is related to over-expression of IL-23R due to increased stability of mRNA (Chen et al. 2011). In addition, biochemical assays indicate that the A allele (wild type) of *IL-23R* promotes an interruption in the binding site for the micro-RNA miR-let-7f, which leads to increased transcription of the IL-23R in vitro and in vivo (Zheng et al. 2012). Thus, the presence of variant C might lower the level of IL-23R expression and modulate Th17 differentiation, resulting in a decreased release of other cytokines and leading to inflammation (Chen et al. 2011; Hamdy et al. 2015).

IL-17 has been detected at high levels in serum and synovial fluid of patients with RA (Shahrara et al. 2008). Studies indicate that IL-17A can act in synergy with other inflammatory cytokines, such as TNF, promoting joint inflammation and cartilage and bone erosion (Zenobia and

Table 3 Genotypic distribution of the *IL-23R* (+2199 A/C), *IL-17A* (–197 G/A), and *IL-17F* (+7488 A/G) gene polymorphisms and clinical features of the rheumatoid arthritis patients

Clinical features	*IL-23R* genotypes		OR (95% CI)	*p*	*IL-17A* genotypes		OR (95% CI)	*p*	*IL-17F* genotypes		OR (95% CI)	*p*
	AA (*n*)	AC + CC (*n*)			GG (*n*)	GA + AA (*n*)			AA (*n*)	AG + GG (*n*)		
Age at RA onset												
≤40 years	10	57	0.382 (0.62–6.00)	0.382	43	24	0.82 (0.40–1.67)	0.716	62	5	0.65 (0.14–2.85)	0.838
>40 years	5	55			38	22			57	3		
CRP												
≤5 mg/L	13	83	2.27 (0.48–10.67)	0.457	62	34	1.15 (0.49–2.65)	0.907	89	7	2.35 (0.27–19.97)	0.700
>5 mg/L	2	29			19	12			30	1		
ESR												
≤20 mm/h	10	52	2.30 (0.74–7.18)	0.231	41	21	1.22 (0.59–2.52)	0.723	57	5	1.77 (0.41–7.60)	0.669
>20 mm/h	5	60			40	25			62	3		
RF												
Positive	9	48	2.00 (0.66–6.00)	0.328	34	23	0.72 (0.34–1.49)	0.491	52	5	0.46 (0.10–2.03)	0.504
Negative	6	64			47	23			62	3		
Erosions												
Positive	11	97	0.42 (0.11–1.49)	0.325	71	37	1.72 (0.64–4.62)	0.402	100	8	NS	NS
Negative	4	15			10	9			19	0		
DAS28												
Moderate/severe	11	89	0.71 (0.20–2.24)	0.834	60	34	2.33 (0.86–6.28)	0.138	93	7	0.511 (0.06–4.34)	0.857
Remission/low	4	23			21	6			26	1		

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* rheumatoid arthritis disease activity score, *RF* rheumatoid factor, *OR* odds ratio, *CI* confidence interval, *p* *p* value of OR, *NS* not significant

Hajishengallis 2015). In the present study, for the −197 G/A *IL-17A* polymorphism, logistic regression analyses revealed that the GG genotype was significantly associated with an increased risk of RA. Subjects carrying the GG genotype presented a chance of developing RA about three times greater than controls (OR 3.18; 95% CI 1.13–9.95; $p = 0.033$). However, the G allele (wild type) did not reach the level of statistical significance (OR 1.43; 95% CI 0.95–2.14; $p = 0.106$). Similar results were reported by Nordang et al. (2009) in a Norwegian population which showed an increased risk of RA susceptibility. Evaluating the AA genotype in an RA Chinese population, Shen et al. (2015) observed a decreased risk of RA. On the other hand, Bogunia-Kubik et al. (2015) and Pawlik et al. (2016) found no association between this polymorphism and RA in Polish patients. Although functional analysis of the −197 G/A *IL-17A* polymorphism indicated that the A variant was associated with higher IL-17A secretion compared to the G variant in Japanese patients following bone-marrow transplantation (Espinoza et al. 2011), contradictory results can be explain as different populations having high genetic diversity (Nordang et al. 2009). Moreover, the −197 G/A *IL-17A* polymorphism has been associated with other inflammatory diseases in different populations, such as ulcerative colitis (Hayashi et al. 2013; Yu et al. 2012), Henoch–Schonlein purpura (Xu et al. 2016), and chronic periodontitis (Zacarias et al. 2015).

For the +7488 A/G *IL-17F* polymorphism, no significant difference between RA patients and healthy controls for both the AG (OR 0.66; 95% CI 0.24–1.71; $p = 0.400$) and GG (OR < 0.0001; $p = 0.986$) genotypes was observed using AA genotype as a reference. The same was observed for the G allele (OR 0.548; 95% CI 0.23–1.32; $p = 0.251$) using A allele as a reference. Similar to our study, the previous studies have also not found an association of RA susceptibility in Polish (Paradowska-Gorycka et al. 2010b; Pawlik et al. 2016) and Algerian populations (Louahchi et al. 2016). However, literature data show contradictory results, since another study with Polish patients showed an increased risk of RA (Bogunia-Kubik et al. 2015). The +7488 A/G *IL-17F* polymorphism is responsible for a His-to-Arg substitution at amino acid 161 (H161R), which can change the conformation or the level of molecular expression and influence the inflammatory process (Kawaguchi et al. 2006). Moreover, Kawaguchi et al. (2006) indicated that patients carrying the GG genotype can show decreased IL-17F expression, suffering a blockage in the induction of IL-8 expression and consequently reduced inflammation as compared to individuals with the AA and AG genotypes. The lack of any association found in our study can be explained by the low frequency of the G variant as seen in different ethnic groups, such as Algerian (Louahchi et al. 2016), Polish (Pawlik et al. 2016), and Chinese (Zhou et al. 2016).

When we analyzed the relationship among polymorphisms and clinical features of RA patients, no statistical differences were observed (Table 3). These results indicate a lack association between the polymorphisms evaluated and the features analyzed in this Brazilian population. Similar outcomes were described by Pawlik et al. (2016) who also found no association among the −197 G/A *IL-17A* and +7488 A/G *IL-17F* polymorphisms and age of disease onset, rheumatoid factor, and erosion presence in RA patients. On the other hand, Bogunia-Kubik et al. (2015) suggested a weak association between the −197 G/A *IL-17A* polymorphism and the RA disease activity score (DAS28) in a Polish population. In addition, another study in the same population suggested an association among the +7488 A/G *IL-17F* polymorphism and parameters of disease activity (Paradowska-Gorycka et al. 2010b). Moreover, the inconsistency among our study and literature data is probably due to the genetic heterogeneity among study populations.

There were potential limitations to our study. First, the limited sample size may restrict our ability to recognize genotype–phenotype associations. Although our study had limited statistical power for the −197 G/A *IL-17A* and +7488 A/G *IL-17F* polymorphisms, the +2199 A/C *IL-23R* polymorphism reached a higher statistical power. However, larger sample size studies, including more ethnic groups, should be considered to confirm the current conclusions. Second, our study did not evaluate expression or serum concentration of cytokines, but these analyses need to be clearly addressed in the future.

In summary, our findings suggest that the +2199 A/C *IL-23R* and −197 G/A *IL-17A* polymorphisms could potentially play a role in RA etiology, but not with clinical features.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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