Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

Association between IL-17F rs763780 and IL-17RA rs4819554 gene polymorphisms and psoriasis in a Romanian cohort

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Abstract. Background. Psoriasis is a sistemic inflammatory disease that appears as a result of complex and multifactorial interactions between polygenic background and environmental factors. Understanding of the pathogenesis of psoriasis has evolved continuously and recent evidence supports the critical role of the IL-23/IL-17 axis. Studies have identified more than 80 loci related to the risk of psoriasis. These loci encode for key factors generated by the immune response. Several studies, conducted in different populations, studied the associations between SNPs in the IL-17 family genes and risk for developing psoriasis. Material and methods: We performed a prospective case-control study that included 81 patients diagnosed with moderate-to-severe chronic plaque psoriasis and 69 healthy volunteers. The following data were collected from both groups: age, alcohol consumption, smoking habits, BMI and levels of total cholesterol and triglycerides. All the patients were genotyped for rs763780 in IL-17F gene and rs4819554 in IL-17RA gene. Results: Genotype frequencies of IL-17RA rs4819554 variants were almost similar in the patient and control groups. GG genotype in case of psoriasis patients and A allele carriers in control group register a slightly increase frequency in each situation. In the Romanian population, no significant difference was detected in patients diagnosed with moderate to severe psoriasis vulgaris in terms of rs4819554 variants as compared to the control group. In contrast, IL-17F rs763780 TT genotype showed significant differences between psoriasis patients and controls, being associated with an increased risk of psoriasis (p=0.008). The C allele frequency (in dominant model CC+TC vs TT) was more common in controls compared to psoriasis patients (42% vs 21%). The overall frequencies of TT, TC and CC genotype were 79%, 17.3% and 3.7% in psoriasis patients vs 58%, 26.1% and 15.9% in the controls. Conclusion: We report an association between TT genotype of rs763780 in IL-17F and the risk for psoriasis, and a possible protective role of C allele for psoriasis, in a Romanian population.

Key Words: psoriasis, rs763780, IL-17F, rs4819554, IL-17RA

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Introduction

Psoriasis is a common, lifelong, immune-mediated, sistemic inflammatory disease (Batalla et al 2015; Prieto-Pérez et al 2015; Raharja et al 2021) that affects 2-4% of the world population (Batalla et al 2015) and around 2% of the Caucasians (Boehncke and Schön, 2015; Prieto-Pérez et al 2015). The most common variant is chronique plaque psoriasis (psoriasis vulgaris) which is present in about 90% of the cases (Boehncke and Schön, 2015; Bolognia et al 2018; Mahil et al 2016) and associates multiple comorbidities including: PsA (psoriatic arthritis), hypertension, diabetus mellitus, cardiovascular diseas, obesity, reduced quality of life, depression and anxiety (Bu et al 2022; Mahil et al 2016; Takeshita et al 2017; Xiang et al 2022). Psoriasis appears as a result of complex and multifactorial interactions between polygenic background and environmental factors (Dand et al 2020; M Griffi ths and W N Barker, 2007; Griffiths et al 2021; Shen et al 2022). The genetic component interfers with the overall risk for psoriasis, age of disease onset, clinical variant, severity, treatment response or the risk for PsA (Batalla et al 2015; Xiang et al 2022). GWAS (genom wide association studies) studies have shown the importance of the innate immune system, adaptative immune response and antigen presentation in the pathogenesis of psoriasis (O'Rielly et al 2018). Also, these studies have identified more than 80 loci related to the risk of psoriasis (Griffiths et al 2021; Rendon and Schäkel, 2019). Most frequently, these loci encode for key factors generated by the immune response, such as: TNF-α (tumoral necrosis factor), IL-17 (interleukin-17), IL-23 or HLA (human leucocyte antigen) class I alelles (Villalpando-Vargas et al 2021). PSORS1 is the the first mapped locus and also the most studied one, being associated with the highest susceptibility for psoriasis

(Batalla et al 2015; Rendon and Schäkel 2019; Griffiths et al 2021; Kocaaga and Kocaaga 2022). HLA-Cw6 alelle is present in around 60% of the patients and is associated with early onset psoriasis, particularly severe and unstable forms (de Alcantara et al 2021; Kamiya et al 2019; Griffiths et al 2021; Rendon and Schäkel, 2019).

In the past decades, understanding of the pathogenesis of psoriasis has evolved continuously and recent evidence supports the critical role of the IL-23/IL-17 axis. IL-23 determines the differentiation and activation of Th17 cells. Th17 cells are the most important producer of IL-17A and IL-17F which activate different cell types: keratinocytes, synoviocytes, endothelial cells, macrophages, B cells, fibroblasts or osteoclast precursors (de Alcantara et al 2021; Batalla et al 2015; Schön, 2019; Villalpando-Vargas et al 2021). In the next phase, inflammatory cells initiate and maintain inflammation responsible for the clinical manifestations in psoriasis and PsA (Villalpando-Vargas et al 2021).

The most well described proinflammatory cytokines from IL-17 family are IL-17A and IL-17F, which bind to the same receptor complex, composed of IL-17RA and IL-17RC (Batalla et al 2015). Genes that encode these interleukins are located on chromosome 6, while genes that encode IL-17RA are located on chromosome 22 (Batalla et al 2018, 2015; Prieto-Pérez et al 2015). Both members of the IL-17 family modulate the inflammatory response and exert pathogenic roles in immunoinflammatory pathologies such as psoriasis, PsA, ankylosing spondylitis or rheumatoid arthritis (Pușcaș et al 2019; Wielińska et al 2021). The number of IL-17 producing cells is increased in psoriatic lesions compared to normal skin; furthermore, their circulating levels are increased in psoriatic patients (Soderstrom et al 2017; Wilson et al 2007). As a result, higher levels of IL-17 can be detected in the affected skin and in the plasma of psoriatic patients compared to healthy subjects (Soderstrom et al 2017; Wilson et al 2007). IL-17F rs763780 polymorphism is a missense mutation that causes a histidine-to-arginine substitution at amino acid 161 (Choi et al 2019) and affects transcriptional regulation and gene expression of IL-17F (Xiang et al 2022). IL-17RA rs4819554 polymorphism is located in the promoter region of IL-17RA and interferes with gene transcription (Batalla et al 2018, 2015). This SNP has been studied in the context of neoplasic and inflammatory diseases, being most frequently associated with the risk of developing the disease (Batalla et al 2015; Sabry et al 2020).

Several studies, conducted in different populations, studied the associations between SNPs in the IL-17 family genes and risk for developing psoriasis (Batalla et al 2015; Bialecka et al 2017; Choi et al 2019; Kaur et al 2018; Pușcaș et al 2019; Sabry et al 2020; Villalpando-Vargas et al 2021; Xiang et al 2022). Besides this, associations with inflammatory (Arisawa et al 2008; Wielińska et al 2021) , neoplastic (Zhou et al 2013), infectious (Peng et al 2013) or autoimmune (Cai et al 2022; Lew et al 2012) diseases are also reported.

A growing body of evidence substantiates the relationship between certain alleles with demographic, clinical or therapeutic features of psoriasis but further studies should be conducted in different and larger populations to clarify the importance of these polymorphisms (Pușcaș et al 2019).

The selection of SNPs was based on previous studies that described a positive association with psoriasis (Batalla et al 2015; Bialecka et al 2017; Choi et al 2019; Kaur et al 2018; Prieto-Pérez et al 2015; Pușcaș et al 2019; Sabry et al 2020; Xiang et al 2022).

The aim of our study is to investigate the impact of rs763780 in IL-17F and rs4819554 in IL-17RA on psoriasis risk. The selection of this two studied SNPs was made after a review of the existing reports.

Material and methods

Patients and controls

Our prospective case-control study included a number of 150 patients divided into two groups: 81 patients diagnosed with moderate-to-severe chronic plaque psoriasis and 69 healthy volunteers. Ethics approval was obtained by way of the Ethical Committee of University of Medicine and Pharmacy "Iuliu Hatieganu ", Cluj-Napoca, Romania. The patients with chronic plaque psoriasis were recruited through the Dermatology Clinic of the County Emergency Hospital Cluj-Napoca. The control group was recruited from the same hospital, among patients who performed routine screenings. All patients and healthy subjects gave their written informed consent to participate in the study. The inclusion criteria for the psoriatic patients were as follows: presence of moderate-to-severe plaque psoriasis (defined according to the European Consensus by Mrowietz) (Mrowietz et al 2011), clinically and histopathologically confirmed diagnosis, age≥18 years old. The exclusion criteria were: patients with other forms of psoriasis, presence of other severe skin diseases, history of malignancy. In the control group there is no history of psoriasis (at least two generations), other dermatological diseases or other non-dermatological diseases. The following data were collected from both groups: alcohol consumption, smoking habits, BMI (body mass index) and levels of total cholesterol and triglycerides.

SNPs genotyping

Samples of blood taken from psoriasis patients and controls were stored at -20°C until they were sent to the genetic laboratory in the Medical Genetics Department of University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. Genomic DNA was extracted using Wizard Genomic Purification Kit (Promega, Madison, USA) from 400 µl venous blood samples. Nano drop 2000/2000c spectrophotometer (ThermoScientific, USA) was used to evaluate the concentration and purity of DNA. TaqMan 5′ nuclease allelic discrimination technology on the 96-well ABI 7900HT Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and SDS software (version 2.3) were used to genotype IL-17RA G197A (rs4819554) and IL-17F A7488G (rs763780) polymorphisms. For the PCR reaction a total volume of 20 µl reaction mixture containing DNAase-free water, 10 µL TaqMan Universal PCR Master Mix (Applied Biosystems), 20 ng DNA, 1 µL of TaqMan Applied Biosystem SNP Genotyping Assay 20× mix (assay ID C__337392_30 for rs4819554 and C__2666446_20 for rs763780) was used. For thermal cycling conditions the following steps were followed: initial AmpliTaq Gold enzyme activation at 95°C for 10 min, 35 denaturation cycles at 95°C for 15 s, and annealing/extension

Table 1. Demographic data, clinical data, genotype and allele frequencies distribution

		Psoriasis		Controls		p
		n	%	n	%	
rs763780	TT	64	79%	40	58%	0.008
	TC	14	17.30%	18	26.10%	
	CC	3	3.70%	11	15.90%	
rs4819554	AA	15	18.50%	16	23.20%	0.6
	GA	27	33.30%	24	34.80%	
	GG	39	48.10%	29	42%	
Male		55	67.90%	20	29%	<0.001
Female		26	32.10%	49	71%	
Age (mean±s.d.)		50 ± 13.9		44.1 ± 12.7		0.008
Alcohol	Yes	18	22.20%	4	5.80%	0.009
	No	63	77.80%	65	94.20%	
Smoking	Yes	26	32.10%	7	10.10%	0.002
	No	55	67.90%	62	89.90%	
BMI		28.8 ± 5.6		22.4 ± 2.1		<0.001
Cholesterol (mg/dl)		200.2 ± 44.1		143.6 ± 31.66		<0.001
Triglycerides (mg/dl)		143.6 ± 64.1		105.6 ± 28.1		<0.001

for 1 min at 60°C. Also, 6-carboxy-X-rhodamine (ROX) was used as a passive reference dye.

Statistical analysis

The statistical analysis was performed using MedCalc® Statistical Software version 20.2.18 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org). The data were assessed for normality using the Shapiro–Wilk test. Means and standard deviations were used to describe continuous variables, while frequencies and percentages were used to describe qualitative data. To assess the association between variables, the chi-square test or Student t test were used, whenever appropriate. A p-value of <0.05 was considered statistically significant.

Results

Table 1 summarizes the demographic data, clinical data, genotype and allele frequencies distribution in both groups. All patients and controls were Caucasians and were 18- 83 years old. The psoriasis patients group had a mean age of 50 ± 13.9 years, and the mean age at the onset of the disease was 33.7 ± 15.9 years. The control group had a mean age of 44.1±12.7 years.

Genotype frequencies of IL-17RA rs4819554 variants were almost similar in the patient and control groups. GG genotype in case of psoriasis patients and A allele carriers in control group register a slightly increase frequency in each situation. In the Romanian population, no significant difference was detected in patients diagnosed with moderate to severe psoriasis vulgaris in terms of rs4819554 variants as compared to the control group. In contrast, IL-17F rs763780 TT genotype showed significant differences between psoriasis patients and controls, being associated with an increased risk of psoriasis (p=0.008). The C allele frequency (in dominant model CC+TC vs TT) was more common in controls compared to psoriasis patients (42% vs 21%). The overall frequencies of TT, TC and CC genotype were 79%, 17.3% and 3.7% in psoriasis patients vs 58%, 26.1% and 15.9% in the controls.

We noticed that consumption of alcohol and cigarettes is more frequent in psoriatic patients (22.2%) compared with control group (5.8%) (p=0.009 and p=0.002 respectively). Hypercholesterolemia was found in 49.3% (40) and hypertriglyceridemia in 40.7% (33) of the patients with psoriasis, while in the control group the percentage was 6.5% (4) for both biological markers. Psoriasis group had a significant higher cholesterol and triglycerides levels compared with controls (p=0.0001 for both situations). Also, BMI was significantly higher in case of those with psoriasis compared with healthy subjects (the mean was 28.8 vs 22.4, p=0.0001). Obesity was present in 37% (30) of those with psoriasis, but none of the healthy subjects were obese.

Discussion

Members of the IL-17 family and their receptors are involved in a wide spectrum of autoimmune and autoinflammatory diseases and play a pivotal role in the pathogenesis of psoriasis. Several studies that evaluated the association between IL-17F, IL-17RA polymorphisms and inflammatory diseases are available in the literature, but discrepancies are observed between the reported results. To our knowledge, this is the first study that evaluates the impact of rs763780 in IL-17F and rs4819554 in IL-17RA in patients diagnosed with psoriasis vulgaris in Romanian population.

In our present study the results revealed that TT genotype of rs763780 in IL-17F is associated with susceptibility for developing psoriasis. On the other hand, carriers of C allele are more common in the control group which may suggest a protective role of this allele in psoriasis, in a Romanian population. Interestingly, our results seem to be similar to those of an Indian study, published by Kaur et al in 2018 (Kaur et al 2018)

The most studied IL-17F polymorphism is rs763780 (with T>C substitution), but the data concerning it are controversial. Two studies conducted in a Korean population reported an association between rs763780 in IL-17F, CC genotype, and increased risk for psoriasis (Choi et al 2019; Kim et al 2017). The same assumption was confirmed in a meta-analysis published last year, which suggests that CC genotype carriers have a two-fold increase for the risk of psoriasis in Asians (Xiang et al 2022). Fouad et al reporter that the same SNP, in those who were carriers for C allele, is associated with increased risk for disease and influence the levels of IL-17F in Egyptian patients (Fouad NA et al 2020). A meta-analysis by Villalpando-Vargas et al concluded that T allele for psoriasis and TT genotype for psoriasis and PsA are reduction factors for susceptibility to psoriasis (Villalpando-Vargas et al 2021). Contrary, an Indian study reported that C allele has a protective role against psoriasis, while TT and TC genotypes were associated with the risk for disease (Kaur et al 2018). It seems that CC genotype is more frequently detected in Asian countries (Xiang et al 2022). The incidence of CC genotype is 11.5% in Indian psoriasis patients vs 24% in Indian controls (Kaur et al 2018; Xiang et al 2022) and is absent in Korean controls or European population (Xiang et al 2022). Regarding TT genotype of rs763780 in IL-17F, is present in 89-94% of the Caucasian patients, while the reported frequency in Asians is 39-78%, supporting the role of ethnicity (Xiang et al 2022). Studies conducted in Japanese, Spanish, Turkish and Polish patients did not support this association between rs763780 in IL-17F and psoriasis doesn't exist (Batalla et al 2015; Bialecka et al 2017; Ozkol et al 2021; Prieto-Pérez et al 2015; Shibata S et al 2009).

In control groups of studies conducted in patients with non-dermatological diseases such as: asthma, rheumatoid arthritis, or inflammatory bowel disease, the frequency of the rs763780 C allele is higher in Asians (Chinese 15.8% and Japanese 11.1%) compared to Europeans (3.2-3.8%), supporting the contradictory results obtained in different populations [36,38]. For example, this SNP confers a protective role for ulcerative colitis in Chinese patients while in Japanese patients it seems to be an independent risk factor for the disease (Arisawa et al 2008; Chen et al 2009). In a Polish population, no association was found between this SNP and rheumatoid arthritis while in a Pakistani population and a meta-analysis conducted by Eskandari-Nasab et al reported a strong connection between those two (Amin et al 2021; Eskandari-Nasab E et al 2017; Paradowska-Gorycka et al 2010). Kawaguchi et al performed a functional study and found out that rs763780 exerts a protective role in asthma (Kawaguchi et al 2006), but a meta-analysis conducted by Ke et al reported no association between those two (Ke et al 2015). Despite all of this, IL-17F polymorphism seems to be associated with response to anti-TNF-α drugs in psoriasis, rheumatoid arthritis or ankylosing spondylitis (Bogunia-Kubik et al 2015; Prieto-Pérez et al 2015, 2013; Wielińska et al 2021). In this regard, it is reasonable to hypothesize that this IL-17F polymorphism has a significant role in many inflammatory diseases, but it can have either a risk or protective effect in different populations.

The existence of this association between IL-17 polymorphism and psoriasis in some populations, can be explained by the relationship between IL-17 and NF-ϰB (nuclear factor-ϰB), the last one being an important transcription factor for the inflammatory genes (Kaur et al 2018). In psoriasis, an increased expression of IL-17 stimulates NF-ϰB that activates inflammatory pathway and by inhibiting IL-17 (by biologics that antagonise IL-17), this mechanism is blocked and results an improvement of psoriasis (Gaffen et al 2006; Kawaguchi et al 2004; Krueger et al 2012; Starnes et al 2001).

As the other studied SNP, rs4819554 in IL-17RA is reported to be associated with either the susceptibility or protection to inflammatory, neoplastic or immunological pathologies. Several dermatological diseases are associated with this IL-17RA SNP. In a meta-analysis, by Villapando-Vargas et al this SNP of IL-17RA, AG genotype seems to be associated with a lower risk of psoriasis compared to GG genotype (Villalpando-Vargas et al 2021). Batalla et al reported an association between rs4819554 G allele and risk for psoriasis (Batalla et al 2015). In the same study, a higher frequency of AA genotype was detected in control group compared to psoriasis patients and authors concluded that in Spanish population AA genotype has a protective role for psoriasis (Batalla et al 2015). Similar results were reported by Sabry et al in Egyptian population (Sabry et al 2020). In Egyptian subjects, GG genotype was associated with risk for chronic spontaneous urticaria, while AA genotype was linked to the severity of this pathology (Nada et al 2021). Lew et al found out that in Korean subjects this SNP is not associated with risk for developing alopecia areata but influence the age of onset of the disease (Lew et al 2012). In our study there is a lack of association between this polymorphism in IL-17RA and susceptibility for psoriasis. Thus, we observed that GG genotype is present in a higher proportion in the psoriasis group, while AA or GA genotypes are slightly increased in control group, like the previously mentioned results in Spanish and Egyptian psoriasis population. In addition, this SNP is also linked to non-dermatological diseases: increased risk for end stage renal disease (Kim et al 2012), decrease risk for autoimmune type 1 diabetes in case of those who were GG genotype (Junxian Li et al 2022), increased risk for aspirin exacerbated respiratory disease (AERD) (Batalla et al 2015) or absence of papillary thyroid carcinoma (Lee et al 2015).

Our results also showed a higher rate of alcohol and tobacco consumption in moderate-to-severe psoriasis patients compared to controls. It is well known that these habits are risk factors for psoriasis. Armostrong et al performed a systematic review and meta-analysis and concluded that smoking is more common among psoriasis patients and that the incidence of psoriasis is higher among smokers (Armstrong et al 2014). A Mendelian randomization study reported a causal association between psoriasis and smoking, but the relationship with alcohol consumption did not reach statistical significance (Wei J et al 2022). Contrary, a review conducted by Szentkereszty-Kovács et al confirmed that alcohol is strongly related to psoriasis due to its multiple effects at genetic and cellular level, influence on treatment outcomes, onset and severity of the disease or prognosis (Szentkereszty-Kovács et al 2021).

In the current study, higher cholesterol (200.2 ± 44.1mg/dl) and triglycerides (143.6 ± 64.1mg/dl) levels were measured in psoriasis patients compared to controls (143.6 ± 31.66 mg/dl, 105.6±28.1mg/dl respectively). In concordance with our results Sabry et al reported higher cholesterol levels in Egyptian patients (Sabry et al 2020). Another study by Xiao et al found

that triglycerides level is positively correlated with psoriasis (Xiao et al 2022). It is important to mention that lipid profile abnormalities are the most frequent metabolic changes reported in psoriasis and are closely related to a higher incidence of atherosclerosis in psoriasis patients (Sabry et al 2020). Also, the BMI was significantly higher in our moderate-to- severe psoriasis group, which again is in concordance with other reports in the literature. Several studies concluded that obesity is more frequent in psoriasis patients compared to those without psoriasis and that the most affected are those with severe forms of disease (Armstrong et al 2012; Jensen and Skov, 2017; Kumar et al 2013).

We are well aware that our study has some limitations, for example: limited number of cases and controls or the fact that we used data collected from subjects having the same ethnicity.

To our knowledge, this is the first study that reports an association between rs763780 in IL-17F gene in a Romanian population. Our results suggest that the IL-17F locus plays a pivotal role in the pathogenesis of psoriasis and may be a promising biomarker for those at risk. This polymorphism has different effects depending on the targeted organ, which could explain the variability in risk or protective effects of various diseases in different races (Choi et al 2019; Xiang et al 2022). We encourage further studies on larger cohorts, in different populations to confirm our results and to elucidate the real impact of this polymorphism in gene expression, clinical and translational approaches.

Conclusions

In conclusion, we report an association between TT genotype of rs763780 in IL-17F and the risk for psoriasis, and a possible protective role of C allele for psoriasis, in a Romanian population. We did not identify a significant difference in rs4819554 in IL-17RA gene polymorphism in psoriasis group and healthy controls. The rs763780 in IL-17F gene seems to be a promising candidate biomarker for those at risk.

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Citation	Pușcaș AD, Morar II, Vesa SC, Cătană A, Ilieș RF, Candrea E, Pușcaș C, Orasan RI. Association between IL-17F rs763780 and IL-17RA rs4819554 gene polymorphisms and psoriasis in a Romanian cohort. HVM Bioflux 2023;15(1):7-13.
Editor	Antonia Macarie
Received	8 May 2023
Accepted	24 May 2023
Published Online	25 May 2023
Funding	None reported
Conflicts/ Competing Interests	Ștefan C. Vesa is the editor-in-chief of HVM Bioflux.