Resistin Gene Promoter -420C>G (rs1862513) and +299 G>A (rs3745367) Polymorphisms in Psoriasis

Nazli Dizen-Namdar[1], Raziye Akcilar[2], Fulya Yukcu[3], Selve Arslan-Utku[1], Zeynep Bayat-Sarioglu[4]

[1]Kutahya Health Sciences University, Faculty of Medicine, Department of Dermatology, Kutahya, Turkey; [2]Kutahya Health Sciences University, Faculty of Medicine, Department of Physiology, Kutahya, Turkey; [3]Kutahya Health Sciences University, Faculty of Medicine, Department of Biophysics, Kutahya, Turkey; [4]Kutahya Dumlupinar University, Faculty of Arts and Sciences, Department of Biochemistry, Kutahya, Turkey

Corresponding author:
Nazli Dizen-Namdar, MD
Kutahya Health Sciences University
Faculty of Medicine,
Department of Dermatology
Kutahya, Turkey
nazli.dizen@gmail.com

Received: February 21, 2023
Accepted: December 6, 2023

ABSTRACT

Background: The pro-inflammatory adipokine resistin is known to be related to obesity, insulin resistance, and inflammation. Resistin's significance in the etiology of inflammatory illnesses, such as psoriasis, is explored herein. We examined the link between resistin gene polymorphisms (-420 C>G and +299 G>A) and psoriasis in the Turkish population.

Methods: In this study, we examined 107 patients with psoriasis and 103 healthy controls. Resistin -420 C>G (rs1862513) and +299 G>A (rs3745367) gene polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: In patients with psoriasis, the frequency of the resistin -420 CG genotype was meaningfully lower than in the controls. In comparison with the controls, the resistin +299 GA genotype and A allele frequencies were significantly higher. The Resistin -420 CG genotype significantly reduced the risk of psoriasis incidence, while the resistin +299 GA genotype and A allele were found to be associated with a higher risk of psoriasis.

Conclusions: In the Turkish community, resistin gene polymorphisms at -420 C>G and +299 G>A may exert an important influence on psoriasis etiology and susceptibility.

KEY WORDS: psoriasis, resistin gene polymorphism, rs1862513, rs3745367

INTRODUCTION

Psoriasis, a systemic inflammatory disease, is observed in approximately 2-3% of the global population (1,2). Based on the clinical features of psoriasis, it is subdivided into different types such as psoriasis vulgaris, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. The most prevalent among these is psoriasis vulgaris, also known as plaque psoriasis, which comprises about 90% of cases. This type usually presents with sharply circumscribed erythematous plaques covered with whitish silvery scales (3,4). Although the etiopathogenesis of psoriasis is still largely unknown, it is thought to be a multifactorial illness affected by hereditary and environmental factors (4). In recent epidemiological studies, it has been shown that psoriasis is related to various comorbidities, such as psoriatic arthritis, metabolic and cardiovascular diseases, obesity, and diabetes (2,4). Especially in recent studies, the connection between

psoriasis and obesity has started to become clearer (4,5).

Adipose tissue, which classically has a fat-storage function, is now accepted to be an active endocrine organ that regulates various metabolic functions with bioactive proteins called adipokines (5). Although it is known that adipokines are mainly produced by adipocytes, many adipokines are also produced by non-adipocytes. These include cells that infiltrate the adipose tissue, especially macrophages, macrophages/monocytes outside the adipose tissue, and also epithelial and endothelial cells as well as hepatocytes (6,7). Adipokines have been reported to play an important part in lipid and glucose metabolism, cardiovascular function, and also in inflammatory response control (8). While obesity causes increased synthesis of pro-inflammatory adipokines, it also causes decreased production of anti-inflammatory adipokines (9).

Resistin is a proinflammatory adipokine related to inflammation, immunity, obesity, and insulin resistance. In humans, it is produced mainly by macrophages and monocytes found in adipose tissue and by peripheral blood monocytes (5,10). Resistin stimulates the expression of proinflammatory cytokines via the nuclear factor-kappa beta signaling pathway, including interleukin-1, interleukin-6, and interleukin-12, as well as tumor necrosis factor-alpha (11). Recent studies have focused on resistin in the pathophysiology of inflammatory illnesses, including psoriasis (12,13). A few studies have found that serum resistin levels were higher in patients with psoriasis than in controls and were also related to the severity of the disease (14,15). The RETN gene encodes resistin, a cysteine-rich peptide (11). Studies have shown that single nucleotide polymorphisms (SNPs) in the resistin gene are related to some diseases (16,17). The link between resistin gene polymorphisms (-420 C>G and +299 G>A) and psoriasis in the Turkish community was examined in this study. To the best of our knowledge, this is the first study which analyzed the relationship between psoriasis and resistin gene polymorphisms.

PATIENTS AND METHODS

Study population

The participants in this cross-sectional study were 107 patients with psoriasis and 103 healthy people who had no prior or family history of psoriasis. The patient and control groups were gender and age-matched. Other clinical types of psoriasis, except psoriasis vulgaris, were not included in the study. Exclusion criteria for participants were those under 18 years of age, those with a serious systemic or another skin disease, and those who were breastfeeding or pregnant. The Psoriasis Area and Severity Index (PASI) score was calculated to determine the severity of the illness in patients with psoriasis (18). They were separated into two groups according to the onset of psoriasis disease before and after the age of 40. This study was initiated after Ethics Committee approval was obtained for clinical trials at Kütahya Health Sciences University.

Genetic analysis

The phenol-chloroform method was performed to isolate genomic DNA from each patient's peripheral blood samples. To assess resistin gene polymorphisms, we used the PCR–RFLP technique and the method as reported by Younis et al. (16). The sequences of primers and PCR conditions for each SNP are shown in Table 1. The PCR products were digested overnight with 5U of BbsI (for resistin -420 C>G) and

Table 1. Summary of conditions for the resistin -420C>G and +299 G>A genetic analyses

	-420C>G (rs1862513)	+299 G>A (rs3745367)
Primer sequence (5'-3')	**F:** 5'- TGT CAT TCT CAC CCA GAG ACA-3' **R:** 5'- TGG GCT CAG CTA ACC AAA TC -3'	**F:** 5'-CAG CGC TCA CCA AAT CTC ATC C-3' **R:** 5'-TCC AGG ACC CTG TCT TGA GTT GG-3'
PCR reaction conditions	95°C for 7 min 35 cycles of 95°C for 30 s, 64°C for 1 min, 72°C for 1 min 15 s, 72°C for 10 min.	95°C for 5 min 35 cycles of 95°C for 30 s, 59°C for 1 min, 72°C for 2 min 72°C for 10 min.
PCR product size	533 bp	173 bp
Restriction enzyme, incubation conditions	BbsI 37 °C overnight	AluI 37 °C overnight
Fragment length (bp)	CC: 207 bp - 327 bp GC: 207 bp - 327 bp - 533 bp GG: 533 bp	GG: 173 bp GA: 76 bp - 97 bp - 173 bp AA: 76 bp - 97 bp

Table 2. Clinical characteristics of subjects with psoriasis

	Psoriasis (n = 107)	Control (n = 103)
Gender (M/F)	53(49.5%) / 54(50.5%)	46(44.7%) / 57(55.3%)
Age (years)	36.7±1.53	37.5±1.72
PASI	5.22±0.33	
Onset age		
< 40	68 (63.6%)	
> 40	39 (36.4%)	
Family history	6 (33.6%)	

Values are presented as mean ± standard error and number for age, and psoriasis area and severity index (PASI). Data were analyzed by analysis of variance and the χ2 test.

Alu I (for resistin +299 G>A) restriction endonuclease. 2% agarose gel stained with ethidium bromide was used to separate the digestive products.

Statistical analysis

The distribution of alleles, genotypes, and the compliance of analyzed SNPs with Hardy-Weinberg equilibrium was investigated using SPSS 20 software (SPSS Inc., Chicago, IL, USA). The correlation between resistin +299 G>A and -420 C>G and clinical features in patients with psoriasis as calculated performing the independent samples t-test and ANOVA analysis. The odds ratios (OR) and 95% confidence interval (95% CI) ranges were calculated using logistic regression. In the study, a *P* value <0.05 was defined as statistically significant.

RESULTS

The clinical characteristics of the patients with psoriasis are shown in Table 2. In the control and psoriasis groups, the frequency of resistin -420 C>G (rs1862513) polymorphism genotypes showed a meaningful deviation from Hardy-Weinberg equilibrium (*P*=0.000). In both groups, the genotype frequency for resistin +299 G>A (rs3745367) was in line with the Hardy-Weinberg rule (*P*>0.05) (data not shown).

The genotypic and allele frequencies in the resistin -420 C>G and +299 G>A gene polymorphisms are shown in Table 3. The frequencies of resistin -420 GG and CC genotypes were significantly higher in patients with psoriasis compared with the control group (18.7% vs. 1.9% and 13.1% vs. 6.8%, respectively), whereas the frequency of the CG genotype was significantly higher in controls (91.3% vs. 68.2%). In particular, the CG genotype significantly decreased the risk of incidence of psoriasis (OR: 0.07; 95% CI: 0.01-0.34; *P*=0.000). Compared with controls, the frequency of the resistin -420 C allele was increased in patients with psoriasis (52.8% vs. 47.6%), while the frequency of the resistin -420 G allele was decreased (47.2% vs. 52.4%). However, this difference was not statistically significant (*P*=0.284) (Table 3).

Table 3. Distribution of resistin -420C>G and +299 G>A genotypes and alleles frequencies in patients with psoriasis and controls

Resistin Polymorphic site		Control		Psoriasis		OR	95 %C	*P*
		n=103	%	n=107	%			
-420C>G (rs1862513)	**CC**	2	1.9	20	18.7	1	-	-
	CG	94	91.3	73	68.2	0.07	0.01 - 0.34	**0.000**
	GG	7	6.8	14	13.1	0.20	0.03 – 1.11	0.05
		χ2=19.2 **df=2 p=0.000**						
	C allele	98	47.6	113	52.8	1	-	-
	G allele	108	52.4	101	47.2	0.81	0.55 - 1.19	0.284
		χ2=1.14 **df=1 p=0.284**						
+299 G>A (rs3745367)	**GG**	93	90.3	82	76.6	1		
	GA	10	9.7	25	23.4	2.85	1.28 - 6.22	**0.008**
	AA	-	-	-	-			
		χ2=7.04 **df=1 p=0.008**						
	G allele	196	95.1	189	88.3	1		
	A allele	10	4.9	25	11.7	2.59	1.21 - 5.54	**0.01**
		χ2=6.40 **df=1 p=0.01**						

Table 4. The relation between resistin -420C>G and +299 G>A polymorphism genotypes and the characteristics of the patients with psoriasis

SNP	Gender		Onset age				
–420C>G (rs1862513)	**Male**	**Female**	**Age (years)**	**PASI**	**< 40**	**> 40**	**Family history**
CC	9 (45%)	11 (55%)	36.7±3.32	4.66±0.73	13 (65%)	7 (35%)	8 (40%)
GC	35 (47.9%)	38 (52.1%)	36.4±1.95	5.33±0.42	46 (63%)	27 (%37)	24 (32.9%)
GG	9 (45%)	11 (55%)	37.9±3.70	5.41±0.69	9 (64.3%)	5 (%35.7)	4 (28.6%)
P	0.483		0.952	0.721	0.985		0.762
+299 G>A (rs3745367)							
GG	40 (48.8%)	42 (51.2%)	37.2±1.80	4.99±0.30	51 (62.2%)	31 (37.8%)	28 (34.1%)
GA	13 (52%)	12 (48%)	34.9±2.89	5.96±1.01	17 (68%)	8 (32%)	8 (32%)
AA	-	-	-	-	-	-	-
P	0.778		0.525	0.221	0.598		0.842

In patients with psoriasis, the frequency of the resistin +299 GA genotype was meaningfully higher compared with the control group (23.4% vs. 9.7%), whereas the frequency of the GG genotype was significantly higher in the controls (90.3% vs. 76.6%). The resistin +299 GA genotype was significantly associated with to psoriasis risk compared with the wild-type GG genotype (OR: 2.85; 95% CI: 1.28 vs. 6.25; *P*=0.008). Compared with controls, the frequency of the resistin +299 A allele increased in patients with psoriasis (11.7% vs. 4.9%), while the frequency of the resistin +299 G allele decreased (88.3% vs. 95.1%). Furthermore, subjects with the resistin +299 A allele had a significantly higher risk of developing psoriasis (OR: 2.59; 95% CI: 1.21- 5.54; *P*=0.01) (Table 3).

There was no significant relationship between the resistin -420C>G and +299 G>A genotypes and the patient characteristics (age, gender, age of onset of the disease, PASI) (*P*>0.05) (Table 4).

DISCUSSION

Considering the role of resistin in the pathogenesis of psoriasis, we hypothesized that polymorphisms in the promoter and intron regions of resistin may have a part in the development of psoriasis. Therefore, our study examined the promoter -420 C>G and intron +299 G>A in the resistin gene in patients with psoriasis and controls, and genotype and allele frequency distributions were compared. In the present study, we found a significant relationship between psoriasis and resistin polymorphisms -420 C>G and +299 G>A. To the best of our knowledge, this is the first study to examine the link between resistin gene polymorphisms and psoriasis, and there are therefore no reports in the literature with which to compare our results. However, this polymorphism has been investigated in different disease groups.

Comparing the patients with psoriasis and the control group, the frequency of resistin -420 C>G genotypes was observed to be substantially different. While the frequency of resistin -420 CC and GG genotypes was higher in patients with psoriasis than in controls, the frequency of CG genotypes was higher in the control group. Based on these results, it was determined that the CG genotype significantly reduced the risk of psoriasis. In a previous study, we found that the resistin -420 CC and GG genotypes were high and the CG genotype was low in patients with acne vulgaris. Similarly, we reported that -420 CG genotypes reduced the risk of acne vulgaris (19). The resistin -420 CG genotype was reported to be protective in obese individuals with acute coronary syndrome in another study performed in our nation (20). While the frequency of the -420 C allele was higher in patients with psoriasis than in controls, the frequency of the -420 G allele was lower, but the difference was not significant. In a meta-analysis study, it was stated that carrying the -420 G allele may be a risk factor for obesity (21). It has been reported that the G allele and GG genotype at resistin-420 C>G predispose to type 2 diabetes in Egyptian patients, which may contribute to cardiovascular disease complications (22).

The genotypes and alleles of the resistin +299 G>A polymorphism exhibited significant differences when comparing patients with psoriasis and controls. While the frequency of the resistin +299 GA genotype was significantly higher in patients with psoriasis compared with controls, the frequency of the GG genotype was higher in controls. Furthermore, compared with the wild-type GG genotype, the

resistin +299 GA genotype was found to dramatically enhance the risk of psoriasis. In patients with psoriasis, the frequency of the resistin +299 A allele was found to be significantly higher than in the controls, whereas the frequency of the resistin +299 G allele was found to be significantly lower. Furthermore, the resistin +299 A allele was found to be associated with a higher incidence of psoriasis. In a study involving patients with type 2 diabetes, a significant association was found between cerebrovascular disease and resistin -420 C>G and +299 G>A, and it was reported that GG and AA genotypes were found to have the highest frequency, respectively (23).

According to a study done in a Pakistani community, the polymorphisms of the resistin -420 C>G and +299 G>A had a significant association with the severity of acne vulgaris and acne vulgaris symptoms (16). However, we could not find a relationship between psoriasis severity and either polymorphism in our study.

In a study exploring the association between atopic dermatitis and resistin gene polymorphisms, it was reported that resistin +299 G>A gene polymorphism played a part in the development of atopic dermatitis specific to gender and age (24). In contrast, in our study, no correlation was observed between resistin +299 G>A and -420 C>G polymorphisms and age and gender in patients with psoriasis. Additionally, no relationship was found in our study between family history and the age of onset of the disease for either polymorphism.

We do not know the exact molecular mechanism of the association between psoriasis and resistin gene polymorphism identified in this study. It has been reported that polymorphisms in resistin affect plasma resistin concentration (16,25-27). In a meta-analysis study, high serum resistin levels were detected in patients with psoriasis, and it was reported that this could be used as a diagnostic and prognostic biomarker (15). Some studies in the literature have reported a relationship between resistin -420 and/or +299 and high serum resistin concentrations (25-28). The relationship between psoriasis and resistin gene polymorphisms in this study may be due to the changes in serum resistin levels.

There were a several limitations to our study. Firstly, our sample size was small, with just the Turkish population included. Secondly, we studied only the +299 G>A and -420 C>G polymorphisms in the resistin gene. Finally, because levels of serum resistin were not measured, the link between serum resistin levels and resistin polymorphism could not be established. Therefore, larger and more extensive investigations involving diverse populations are required to confirm the results of our study.

CONCLUSION

Our study determined the relationship between resistin polymorphisms at -420 C>G and +299 G>A and psoriasis in the Turkish community. For resistin -420 C>G, the high CG genotype was found to decrease the risk of psoriasis. In addition, the resistin +299 GA genotype and A allele were found to be related to a higher risk of psoriasis. Based on our results, we believe that resistin -420 C>G and +299 G>A may part a role in the etiopathogenesis of psoriasis. However, studies with larger sample sizes and in diverse ethnic groups are required to confirm our results.

References:

1. Santus P, Rizzi M, Radovanovic D, Airoldi A, Cristiano A, Conic R, *et al.* Psoriasis and respiratory comorbidities: the added value of fraction of exhaled nitric oxide as a new method to detect, evaluate, and monitor psoriatic systemic involvement and therapeutic efficacy. BioMed Res Int. 2018;2018:1-10.
2. Dizen-Namdar N, Akcilar R, Bayat Z. Association between vaspin rs2236242 gene polymorphism and psoriasis vulgaris. Skin Pharmacol Physiol. 2020;33:317-22.
3. Raychaudhuri SK, Maverakis E, Raychaudhuri SP. Diagnosis and classification of psoriasis. Autoimmun Rev. 2014;13:490-5.
4. Levine D, Gottlieb A. Evaluation and management of psoriasis: an internist's guide. Med Clin. 2009;93:1291-303.
5. Gerdes S, Rostami-Yazdi M, Mrowietz U. Adipokines and psoriasis. Exp Dermatol. 2011;20:81-7.
6. Kovács D, Fazekas F, Oláh A, Törőcsik D. Adipokines in the skin and in dermatological diseases. Int J Med Sci. 2020;21:1-29.
7. Kyriakou A, Patsatsi A, Sotiriadis D, Goulis DG. Serum leptin, resistin, and adiponectin concentrations in psoriasis: a meta-analysis of observational studies. Dermatology. 2017;233:378-89.
8. Gisondi P, Lora V, Bonauguri C, Russo A, Lippi G, Girolomoni G. Serum chemerin is increased in patients with chronic plaque psoriasis and normalizes following treatment with infliximab. Br J Dermatol. 2013;168:749-55.
9. Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol. 2010;314:1-16.

10. Curat, CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, *et al.* Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. Diabetologia. 2006;49:744-7.
11. Jaworek AK, Szepietowski JC, Szafraniec K, Jaworek M, Hałubiec P, Wojas-Pelc A, *et al.* Adipokines as biomarkers of atopic dermatitis in adults. J Clin Med. 2020;9:1-12.
12. Wong Y, Nakamizo S, Tan KJ, Kabashima K. An update on the role of adipose tissues in psoriasis. Front Immunol. 2019;10:1-7.
13. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol. 2005;174:5789-95.
14. Yıldırım Y, Polat M, Serin E, Parlak AH. Serum TNF-α, IL-6 and resistin levels in chronic plaque psoriasis. Turkderm-Turkish Archives of Dermatology and Venereology. 2012;46:138-42.
15. Huang H, Shen E, Tang S, Tan X, Guo X, Wang Q, *et al.* Increased serum resistin levels correlate with psoriasis: a meta-analysis. Lip Health Dis. 2015;14:1-9.
16. Younis S, Blumenberg M, Javed Q. Resistin gene polymorphisms are associated with acne and serum lipid levels, providing a potential nexus between lipid metabolism and inflammation. Arch Derm Res. 2016;308:229-37.
17. Hu WW, Tang CH, Sun Y, Lu TT, Jiang P, Wu YM, *et al.* Correlation between resistin gene polymorphism and clinical aspects of lung cancer. Medicine. 2017;96:1-6.
18. Louden BA, Pearce DJ, Lang W, Feldman SR. A Simplified Psoriasis Area Severity Index (SPASI) for rating psoriasis severity in clinic patients. Dermatol Online J. 2004;10:1-7.
19. Akcılar R, Dizen-Namdar N, Arslan-Utku S. Association between resistin gene (– 420 C> G) polymorphism and acne vulgaris. J Cosm Dermatol.. 2022;21:1651-5.
20. Arat A, Yılmaz Ü, Yılmaz N, Fazlıoğulları O, Çelik F, Başaran C, *et al.* Effects of Leptin, resistin, and ppar-gama gene variants on obese patients with acute coronary syndrome in the turkish population. J Acad Res Med. 2020;10:166-74.
21. Zhu ZL, Yang QM, Li C, Chen J, Xiang M, Chen MM, *et al.* Association between the resistin gene-420C> G polymorphism and obesity: an updated meta-analysis. Eur Rev Med Pharmacol Sci. 2016;20:4922-9.
22. Motawi TM, Shaker OG, El-Sawalhi MM, Abdel-Nasser ZM. Visfatin-948 G/T and resistin-420 C/G polymorphisms in Egyptian type 2 diabetic patients with and without cardiovascular diseases. Genome. 2014;57:259-66.
23. Kunnari A, Ukkola O, Kesäniemi YA. Resistin polymorphisms are associated with cerebrovascular disease in Finnish Type 2 diabetic patients. Diabetic Med. 2005;22:583-9.
24. Banihani SA, Abu-Alia KF, Khabour OF, Alzoubi KH. Association between resistin gene polymorphisms and atopic dermatitis. Biomolecules. 2018;8:1-11.
25. Suriyaprom K, Tungtrongchitr R, Namjuntra P. Associations of resistin levels with resistin gene polymorphism and metabolic syndrome in Thais. J Med Biochem. 2015;34:170-8.
26. Cho YM, Youn BS, Chung SS, Kim KW, Lee HK, Yu KY, et al. Common genetic polymorphisms in the promoter of resistin gene are major determinants of plasma resistin concentrations in humans. Diabetologia. 2004;47:559-65.
27. Menzaghi C, Trischitta V. Genetics of serum resistin: a paradigm of population-specific regulation? Diabetologia. 2010;53:226-8.
28. Lau CH, Muniandy S. Adiponectin and resistin gene polymorphisms in association with their respective adipokine levels. Ann Hum Genet. 2011;75:370-82.