

# Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility

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**Tumour microenvironment has an important effect on the progression of cutaneous T-cell lymphomas. Using PCR with sequence-specific primers, this study analysed single-nucleotide polymorphisms in the interleukin-17 genes of 150 patients with cutaneous T-cell lymphoma. GG homozygote rs8193036 A/G of interleukin-17A gene occurred less commonly in the cutaneous T-cell lymphoma group; however, patients with this single-nucleotide polymorphism experience significantly intense pruritus. Conversely, the rs2397084 AG heterozygote of interleukin-17F is more common in the lymphoma population. In addition, there were significant differences in the frequencies of interleukin-17 genotypes when comparing early (Ia to IIa) and advanced stages (IIB, III and IV) of this neoplasms. A similar result has been shown in comparison between Sézary syndrome and mycosis fungoides. The current data may serve as a possible explanation for the increased bacterial infection rates in the course of cutaneous T-cell lymphoma, especially caused by *Staphylococcus aureus*. In summary, specific single-nucleotide polymorphisms occur with different frequencies between cutaneous T-cell lymphoma and healthy patients. Moreover, genetic predisposition of several interleukin-17 single-nucleotide polymorphisms may be a factor causing impaired immune defence in cutaneous lymphomas.**

**Key words:** cutaneous lymphoma; mycosis fungoides; Sézary syndrome; cytokine; interleukin-17; lymphoma pathogenesis; single-nucleotide polymorphism.

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Cutaneous T-cell lymphomas (CTCLs) belong to a group of rare, lymphoproliferative disorders, which have their origin in skin (1). Interleukin (IL)-17 has been implicated in the pathogenesis of these tumours, but the exact mechanism remains unclear (2–4). Various single-nucleotide polymorphisms (SNPs) of IL-17 genes have previously been associated with increased risk and worse

## SIGNIFICANCE

Cutaneous T-cell lymphomas are a rare entity of lymphoproliferative disorders. This study presents genetic predisposition of some single-nucleotide polymorphic variants in the context of developing cutaneous T-cell lymphomas. Moreover, the results show some single-nucleotide polymorphisms of interleukin-17A and interleukin-17F to be significantly associated with pruritus intensity. These results may explain the increased susceptibility and rates of skin infections in the course of cutaneous T-cell lymphomas. Analysis of the current data and the literature may lead to improved care and management of patients with cutaneous T-cell lymphomas.

course of autoimmune and neoplastic diseases (5–12). Other cytokines have been studied in this context in CTCL (13, 14). The aim of this study was to elucidate whether the frequency of selected SNPs of IL-17 genes are associated with susceptibility to the CTCL.

## MATERIALS AND METHODS

The study was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland. A total of 150 blood samples of patients with CTCL: 139 MF in stages IA (44 cases), IB (38 cases), IIA (3 cases), IIB-IV (54 cases), and 11 Sézary syndrome (SS) diagnosed and treated at the Department of Dermatology of the Medical University in Gdansk and a control non-CTCL group of 196 unrelated healthy individuals within similar age and sex distribution, without personal or family history of chronic skin diseases, without pruritus and without personal history of malignancy were included in the study. Patients had been diagnosed on the basis of clinical, histopathological and immunohistochemical findings, according to the European Organization of Research and Treatment of Cancer (EORTC) criteria (1). Pruritus intensity was evaluated according to visual analogue scale (VAS) and numeric rating scale (NRS) and correlated with IL-17 gene polymorphisms.

### DNA extraction/genotyping

Genomic DNA was isolated from all blood samples with the Blood Mini A&A Biotechnology (A&A Biotechnology, Gdansk, Poland) according to the instructions of the manufacturer. Analysis of the polymorphic variants IL-17A (rs2275913, rs3819024, rs8193036) and IL-17F (rs763780, rs2397084) were analysed by PCR with sequence-specific primers (SSP-PCR). Graphical visualization of this method is shown in Appendix S1.

**Table I. Polymorphism rs8193036 A/G of interleukin (IL) 17A and rs2397084 A/G of interleukin 17F**

Genotypes	Cutaneous T-cell lymphoma n = 150 n (%)	Control group n = 196 n (%)
rs8193036 A/G of IL-17A		
AA	45 (30.00)	45 (22.96)
AG	84 (56.00)	98 (50.00)
GG	<b>21 (14.00)</b>	53 (27.04)
rs2397084 A/G of IL-17F		
AG	<b>133 (88.67)</b>	146 (74.49)
GG	17 (11.33)	50 (25.51)

Bold indicates statistical significance  $p < 0.05$ .

### Statistical analysis

Statistical calculations were made with Statistica, version 12.0 (StatSoft, Inc. 2015, Tulsa, Oklahoma, USA). Analysis of qualitative features was made with the  $\chi^2$  test in the Pearson method. Independent variables fulfilling the assumptions for parametric tests were analysed with the Student's t-test. Independent variables that did not meet the parametric test assumptions were analysed with non-parametric tests (analysis of variance (ANOVA) equivalents): Mann-Whitney U test (comparison of 2 tests) or Kruskal-Wallis test (comparison of many samples). Odds ratios (ORs) with 95% confidence intervals (95% CI) were determined by a logistic regression. In all tests,  $p < 0.05$  was considered a significant level of statistical significance.

## RESULTS

Genotype distribution of the studied SNPs (AA, AG, and GG) of IL-17A and IL-17F in which significant differences between studied groups in the distribution of alleles were found are shown in **Tables I–III**.

### Interleukin-17A gene polymorphisms

Of the 3 studied loci, the only polymorphism which occurred significantly different in comparison with healthy controls was rs8193036 A/G of interleukin 17A. The presence of the IL-17A GG genotype has been found to be less frequent in the current CTCL population (odds ratio (OR) 0.4392, 95% CI 0.2512–0.7679 and  $p = 0.0039$ ) (Table I). The pruritus intensity regarding our group has also been studied. Medium NRS in IL-17A rs8193036 polymorphism appeared to be significantly higher when the GG homozygote was present, in comparison with other genotypes ( $p = 0.03$ ) (Table II). Moreover, the distinction between pruritus level GG and other polymorphisms has also been discovered to be significant ( $p = 0.005$ ) (Appendix S1).

### IL-17F gene polymorphisms

Of the 2 studied loci of the IL-17F gene, the only polymorphism that occurred significantly more commonly in comparison with the control group was rs2397084 AG (OR 2.6793, 95% CI 1.4729–4.8739 and  $p = 0.0009$ ) (Table I). As before, it is also the only polymorphism of IL-17F

**Table II. Medium numerical rating scale score in comparison with rs8193036 A/G of interleukin 17A**

Genotype	Cutaneous T-cell lymphoma n = 140	Medium numerical rating scale score	SD
AA	44	3.22	3.20
AG	77	3.64	3.25
GG	19	<b>4.95</b>	2.58

SD: standard deviation.

Bold indicates statistical significance  $p < 0.05$ .

in the current study, in which the visual analogue scale (VAS) pruritus levels have differed significantly between AG and GG ( $p = 0.01$ ) (Appendix S1).

### Stage of a lymphoma and IL-17 polymorphisms

Several distinctions were found between the distribution of certain genotypes in the various stages of the CTCL. The distribution of polymorphisms in the early stage (Ia to IIa) and advanced (IIb and higher) stages of lymphomas were analysed. Presence of IL-17A AG and GG genotypes of the rs2275913 polymorphism were respectively more (OR 2.1081, 95% CI 1.0285–4.3210 and  $p = 0.0417$ ) and less (OR 0.3391, 95% CI 0.1678–0.6852 and  $p = 0.0026$ ) frequent in IIb, III and IV stage CTCL compared with early stages (Table III). The analysis was significant, although not reliable due to the small group size with the AA genotype. Similar observations have been made concerning rs3819024 A/G polymorphism of interleukin 17A. The AA genotype was less frequent in advanced CTCL (OR 0.4447, 95% CI 0.2268–0.8718 and  $p = 0.0183$ ), while the GG homozygote was more common in the mentioned group (OR 4.6815, 95% CI 1.7099–12.817 and  $p = 0.0027$ ) (Table III). Significant differences were found in the frequency of polymorphism rs2275913 A/G of interleukin 17A genotypes when comparing patients with SS with those with mycosis fungoides (MF). The GG homozygote was found more often in MF than in SS (OR 0.2763, 95% CI 0.0768–0.9939 and  $p = 0.0489$ ) (Table III). No significant distinctions were found when analysing other polymorphisms in that manner (Appendix S1).

**Table III. Polymorphism rs2275913 A/G and rs3819024 A/G of interleukin 17A frequency difference between disease stages and subtypes**

Genotypes	Stages and subtypes			
	Stage Ia-IIa CTCL n = 85 n (%)	Stages IIb-IV CTCL n = 61 n (%)	MF n = 135 n (%)	SS n = 11 n (%)
rs2275913 A/G of IL-17A				
AA	1 (1.18)	6 (9.84)	5 (3.70)	2 (18.18)
AG	20 (23.53)	<b>24 (39.34)</b>	39 (28.89)	5 (45.45)
GG	<b>64 (75.29)</b>	31 (50.82)	<b>91 (67.41)</b>	4 (36.36)
rs3819024 A/G of IL-17A				
AA	<b>49 (57.65)</b>	23 (37.70)		
AG	30 (35.29)	22 (36.07)		
GG	6 (7.06)	<b>16 (26.23)</b>		

CTCL: cutaneous T-cell lymphoma; MF: mycosis fungoides; SS: Sezary syndrome. Bold indicates statistical significance  $p < 0.05$ .

## DISCUSSION

To our knowledge this is the first study of IL-17 SNPs in primary CTCL. Several SNPs of IL-17 genes were associated with susceptibility to CTCL. The GG homozygote of rs8193036 A/G of interleukin 17A occurred less often in the CTCL group (Table I); however, patients with this polymorphism experienced significant pruritus (Table II). The rs2397084 AG heterozygote of IL-17F was more common in the CTCL population (Table I). Moreover, statistically significant differences between rs2275913 A/G and rs3819024 A/G of interleukin 17A have also appeared when comparing early and advanced CTCLs (Table III). That result may explain the more rapid progression to advanced stages of CTCLs in some patients. It is well known that several patients present stable disease for years. GG homozygote in rs2275913 A/G of interleukin 17A has been more common in the group of non-SS patients (Table III). It may suggest that this genotype has a lower predisposition to develop this aggressive, fast-spreading, leukaemic cutaneous lymphoma.

The role of IL-17 in CTCL is complex and not fully understood. It has been reviewed recently in the context of introducing new agents, such as bimekizumab, brodalumab, ixekizumab and secukinumab, in the treatment of psoriasis (15). IL-17A and IL-17F belong to the IL-17 family and are thought to have pro-inflammatory activity (16). They have been important in promoting the answer against extracellular bacteria and fungi (16). The IL-17A and IL-17F SNPs have been previously proven to increase the risk of asthma and rheumatoid arthritis (9–11). Similar correlation has been found in the Spanish cohort of psoriatic patients, but not in the Polish population (8, 12). SNP may play a role as a prognostic factor (6). Moreover, a link between IL-17 functions and carcinogenesis has been implicated in several different neoplasms; for example, in colorectal cancer, but also in the non-melanoma skin cancers (17, 18). Furthermore, several SNPs of IL-17A and IL-17F have been shown to be significantly associated with higher risk of gastric, lung and cervical cancer (5, 7, 19). SNPs have been studied in the context of cutaneous lymphomas, showing that some variants of IL-2 and IL-13 could be estimated as a risk factor, while IL-10 and tumour necrosis factor alpha (TNF- $\alpha$ ) have a protective effect against developing CTCL (13).

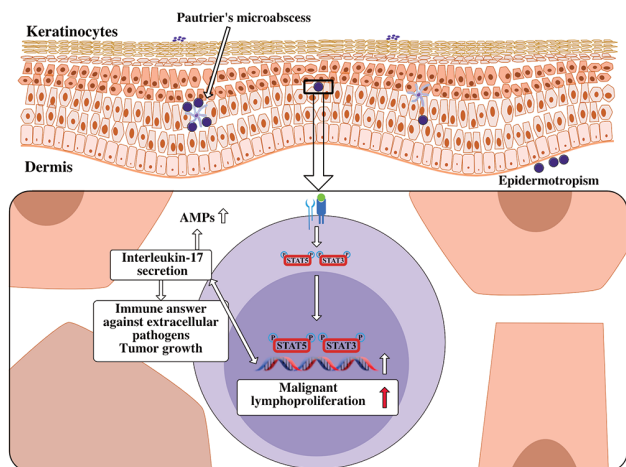
The exact pathogenesis of CTCL is unknown despite extensive previous research (20). Interestingly, recent studies of the mouse model have shown that T-cell receptor engagement is an important factor of malignant transformation in CTCL (20). Moreover, progression of the disease also appeared to be dependent on microbiota (20, 21). In addition, *Staphylococcus aureus* is known as the most common aetiological factor in infections in patients with CTCL, who are colonized by this bacteria

in 44% up to 76% (22). *S. aureus* superantigens may exacerbate and/or perpetuate the clonal expansion of the lymphoma concomitantly with spreading cutaneous inflammation (21, 23). In addition, staphylococcal enterotoxin A isolates have been shown to induce signal transducer and activator 3 (STAT3) activation and expression of IL-17, which pathway has been hypothesized as one of the oncogenic factors in CTCL (3, 24). Recently, another link between staphylococcal enterotoxins and progression of the lymphoma has been noted: they have been shown to induce STAT5 and microRNA-155 (miR-155) (25). STAT3, STAT5 and miR-155 have been previously associated with CTCL pathogenesis (14). Cobomarsen, an inhibitor of miR-155 expression, is thought to be one of the promising novel therapies in CTCL, currently undergoing phase first-in-human clinical studies (26). The constant responses of both malignant and benign lymphocytes to the *S. aureus* inflammation may contribute to carcinogenesis, which would explain why transient, aggressive antibiotic therapy may slow the tumour progression in some cases (22, 27). *S. aureus* eradication may be a novel treatment for advanced MF/SS in the future (21, 28).

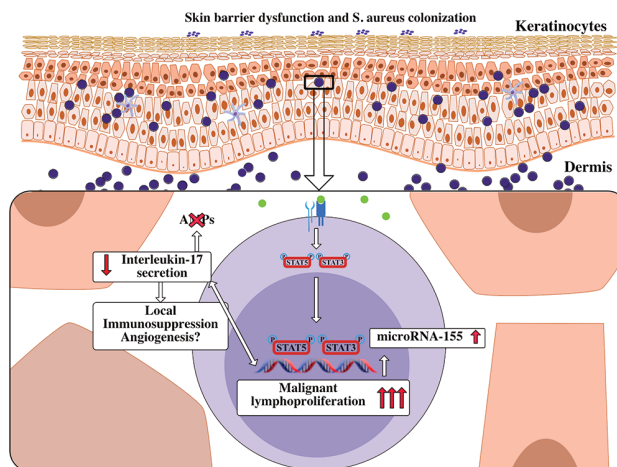
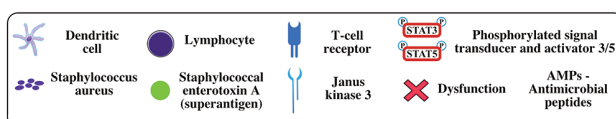
The disturbances in skin barrier also related to extensive inflammation in patients with lymphoma have been described previously (29, 30). Dysfunction of antimicrobial peptides secretion, which is induced by proinflammatory IL-17 cytokines, has been also observed (29, 30). The impaired skin function in case of infection can promote strong immune system defence. Despite elevated IL-17 levels in CTCL in several cases, such a state may lead to local immunosuppression caused by described mechanisms (2, 4, 24, 28, 31). We have summarized data on the possible pathogenic role of IL-17 in CTCL (Fig. 1). The results may provide a possible explanation for this phenomenon, as this study has revealed statistically significant differences in IL-17A rs8193036 GG and IL-17F rs2397084 AG SNPs in CTCL (Table I). In the case of IL-17A rs8193036 GG, more severe pruritus has been observed (Table II). Severe pruritus correlates with lower quality of life and both have been observed in advanced stages of MF and in SS (32). The statistical differences between early and advanced CTCL stages may also be an explanation of the fact that the pace of progression of the CTCL is individual. Bearing in mind that IL-17 belongs to a group of proinflammatory cytokines, and that Th2 profile is specific for advanced MF and SS, the rs2275913 A/G of interleukin 17A may protect switching from Th1 to Th2 profile in the CTCL microenvironment (Table III).

The study is limited by its design to test the specific SNPs instead of using new methods, such as next gene sequencing combined with the use of neural networks, which are currently shown in similar papers. It was not possible to perform them. However, the results of the current study seem to be important, especially in light of the

## a) CTCL I stage



## b) CTCL IV stage

**Th1 > Th2****Microenvironment****Th1 < Th2****Microenvironment**

**Fig. 1. Possible pathogenic role of interleukin-17 (IL-17) in cutaneous T-cell lymphoma (CTCL).** (a) An early stage of a CTCL is shown in the first panel. There is a domination of T helper 1 (Th1) microenvironment with the contribution of IL-17, which plays role in promoting cytotoxic answer against extracellular pathogens (bacteria and fungi). Staphylococcal enterotoxins (superantigens) promote immunological dysregulation by causing benign lymphocytes to stimulate malignant clones. IL-17 has also been shown to promote the oncogenic pathway by stimulation janus kinase 3 (JAK3), which activates signal transducer and activator 3 (STAT3). (b) A late stage of CTCL is presented in the second panel. A clear domination of T helper 2 (Th2) microenvironment has been shown. The secretion of IL-17 may be reduced in that stage leading to local immunosuppression. Also, the antimicrobial peptides (AMPs) have been shown to be reduced and dysfunctional in CTCL. In case of microbiota colonization of the skin, dysfunction of AMPs is one of the crucial elements of impaired skin function. Angiogenesis is signed with a question mark on this figure, because of a possibility, that IL-17 may promote formation of new vessels thorough all stages of the disease. The resistance to anti-VEGF drugs in other lymphomas, lung and colorectal cancer has been previously shown to be promoted by Th-17 subset of cells.

pathogenetic influence of *S. aureus* in CTCL. As shown previously, blocking IL-17 by numerous new biologic drugs used in the therapy of, for example, psoriasis, may cause a progression and/or unmasking of the disease (15).

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The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (decision number NKBBN/313/2017)

Informed consent was obtained from all subjects involved in the study.

The data presented in this study are available in Appendix S1.

*The authors have no conflicts of interest to declare.*

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