ORIGINAL ARTICLE

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ASSOCIATION OF OSMR GENE VARIANTS RS2278329 AND RS2292016 WITH DERMATOMYOSITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS IN BULGARIAN PATIENTS

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Abstract. Introduction: *The precise nature of dermatomyositis (DM) and systemic lupus erythematosus (SLE) is not yet fully understood, although it is recognized that various genetic, hormonal or external factors play a significant role in the onset of autoimmune processes. This study aims to explore the link between two specific genetic variants of the oncostatin M receptor (OSMR) – rs2278329 (Asp553Asn) and rs2292016 (-100G/T) – and the predisposition to DM and SLE in Bulgarian patients.* ***Materials and methods:*** *A total of 126 individuals were included in the study – 62 patients with SLE, 64 with DM, and 95 healthy unrelated controls. Genotyping was performed using TaqMan assays.* ***Results:*** *The analysis revealed that the minor allele frequency was low. None of the genetic variants investigated showed any significant correlation with SLE, DM, or clinical characteristics associated with these conditions.* ***Conclusions:*** *Our findings suggest that none of the OSMR genetic variants investigated pose a significant risk for the development of dermatomyositis or systemic lupus erythematosus in Bulgarian patients.*

Key words: *systemic lupus erythematosus, dermatomyositis, OSMR rs2278329, OSMR rs2292016*

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INTRODUCTION

Dermatomyositis (DM) is an uncommon autoimmune disorder that falls under the category of idiopathic inflammatory myopathies [1]. This condition presents with muscle weakness and specific skin lesions, often accompanied by pruritus [2, 3]. A common characteristic of DM is its association with cancer, affecting around 30% of the patients diagnosed [4, 5].

Systemic lupus erythematosus (SLE) is also a potentially life-threatening autoimmune disease that targets multiple organs and systems [6]. While the exact nature of DM and SLE is not fully understood, it is clear that genetic, hormonal and environmental influences are crucial factors in initiating and sustaining autoimmune reactions. Numerous studies are focused on the role of interleukins, particularly IL-6, in the pathogenesis of both DM and SLE. In our previous research, we investigated IL-6 gene polymorphisms as potential factors contributing to the increased risk of these autoimmune disorders [7].

Oncostatin M (OSM) is a multifunctional cytokine that belongs to the interleukin-6 (IL-6) family. It is produced primarily by activated T lymphocytes and monocytes [8] and interacts with the heterodimeric oncostatin M receptor (OSMR). The OSMR gene, located on chromosome 5p13.1, encodes the OSMRβ subunit, which pairs with an IL-6 signal transducer to form a functional heterodimer [9, 10]. OSMR β-chain forms heterodimers with IL31 receptor α-chain to transduce IL-31 signals. Once assembled, this receptor complex activates Janus tyrosine kinases (JAKs), which subsequently trigger downstream signaling pathways involving signal transducer and activator of transcription (STAT) proteins, phosphatidylinositol-3 kinase (PI3K)/AKT (also known as protein kinase B or PKB), as well as mitogen-activated protein kinases (MAPKs) [8, 11].

The OSMRβ signaling axis was found important in the pathogenesis of inflammatory bowel disease [12, 14], pulmonary fibrosis [15], IL-31-mediated pruritus [16-18], diffuse cutaneous systemic sclerosis [19] and rheumatoid arthritis [20]. Interleukin-31 receptor is associated with chronic itch [20]. Elevated OSM expression has been associated with increased skin inflammation compared to normal tissue in diseases associated with chronic itch, such as psoriasis, atopic dermatitis, cutaneous T-cell lymphoma [17] and prurigo nodularis [18]. Recently, an anti–IL-31 receptor antibody was shown to significantly improve pruritus in patients with atopic dermatitis [22].

The aim of this research was to assess whether the OSMR gene variants rs2278329 (Asp553Asn) and rs2292016 (-100G/T) are associated with an increased susceptibility to developing DM and SLE among Bulgarians.

MATERIALS AND METHODS

Clinical Material

A total of sixty-four individuals diagnosed with DM were enrolled in this study, all meeting the revised classification criteria proposed by Targoff et al. [23]. Among these patients, 23 were men and 41 were women. The median age at the time of enrollment was 52 years, with an age range from 18 to 82 years. Participants had been monitored for approximately 10 years at the Department of Dermatology and Venereology, in collaboration with the Clinic of Rheumatology, Medical University – Sofia, Bulgaria.

Additionally, sixty-two patients (51 women and 11 men) with SLE were included in a second group. Their median age was 40 years, with an age range from 15 to 78 years. These patients had also been under observation for about 10 years at the Department of Nephrology, Medical University – Sofia. All individuals with SLE fulfilled the SLICC classification criteria [24], and renal biopsy results confirmed lupus nephritis ranging from classes I to VI.

A control group of ninety-five healthy volunteers, unrelated to the patients and matched by sex, age, and ethnicity, was selected for genetic testing. These control samples were obtained from the BioBank of the Molecular Medicine Center and the National Genetic Laboratory.

Genetic Analysis

This research was conducted in full compliance with the principles outlined in the Declaration of Helsinki for studies involving human participants. Ethical approval was granted by the local institutional ethics committee. All participants provided written informed consent prior to inclusion in the study, and venous blood samples were collected for DNA extraction. Genomic DNA was isolated from peripheral blood using the DNA purification kit with the Magnetic Separation Module I (Chemagen AG).

Single Nucleotide Polymorphism Analysis

Genotyping of the OSMR variants rs2278329 (Asp553Asn) and rs2292016 (-100G/T) was performed using the ThermoFisher TaqMan genotyping assay kit, following the manufacturer's protocol. Allelic discrimination was conducted using the version 2.0.5 of Applied Biosystems 7500 software.

Statistical Analysis

Allele and genotype frequencies were compared between SLE, DM and control groups with SPSS 22.0 software (SPSS Inc, Chicago, USA) using the chi-square (χ^2) statistic with Fisher's exact test, odds ratios (OR) with exact 95% confidence and Hardy-Weinberg equilibrium.

RESULTS

Both polymorphisms are in Hardy-Weinberg equilibrium. However, the rs2278329A appears with a frequency of about 3% and the frequency of the rs2292016T is even lower – about 1%. No gender selectivity was observed neither among the patients, nor among the controls.

The two polymorphisms showed similar allele distribution (DM: p<0.5, OR 1.2, 95% CI 0.3-4.5, SLE: p<0.5, OR 0.6, 95% CI 0.1-3.2) and genotype distribution (DM: p<0.5, OR 1.2, 95% CI 0.3-4.6, SLE: p<0.5, OR 0.6, 95% CI 0.1-3.2) among the patients and the controls.

The data are presented in Table 1 and 2. The low frequency of the minor alleles does not allow us to study their association with the clinical features.

DISCUSSION

OSMRβ is widely expressed in various tissues and cells, such as epithelial cells, fibroblasts, blood vessels, nerve cells, respiratory tissues, adipose tissues, and lymph nodes. It plays a role in keratinocyte proliferation, differentiation, and inflammatory responsiveness [25]. It is known that the presence of SNPs could affect the gene expression and thus influence the disease susceptibility and severity. However, unlike the Asian population, where the rs2292016 and rs2278329 minor alleles occur at a frequency of about 25% [26-28], their frequency in the Bulgarian population is between 1 and 3%, respectively (Table

Table 1. Demographic and clinical data

Disease	**DM**		**SLE**	
Demographic parameters	Female/male	41/23	Female/male	51/11
	Age, mean ± SD years	52 ± 14,7	Age, mean ± SD years	40 ± 12,4
Clinical parameters	Cutaneous disease Muscle weakness Elevated muscle enzymes EMG findings Photosensitivity Autoantibodies	43 (67.2%) 38 (59.4%) 27 42.2%) 26 (40.6%) 29 (45.3%) 18 (28.1%)	Malar rash Discoid rash Arthritis Oral ulcer Photosensitivity Serositis Renal disease Neurological disease Haematological disease Immunological disease ANA	34 (54.8%) 11 (17.7%) 36 (58.1%) 4 (6.5%) 39 (62.9%) 12 (20.4%) 64 (100%) 12 (19.4%) 22 (35.5%) 38 (61.3%) 41 (66.1%)

SD = standard deviation, EMG = electromyography, ANA = antinuclear antibodies

Table 2. Genotype and allele frequencies of OSMR rs2278329 and OSMR rs2292016 SNPs in patients with DM, SLE and controls

Genotype	**Dermatomyositis**		**Systemic lupus erythematosus**		**Controls**	
rs2278329						
GG	60	(93.7%)	60	(96.8%)	90	(94.7%)
GA	4	(6.3%)	2	(3.2%)	5	(5.3%)
AA	0	(0.0%)	0	(0.0%)	0	(0.0%)
G	124	(96.9%)	122	(98.4%)	185	(97.4%)
A	4	(3.1%)	2	(1.6%)	5	(2.6)
rs2292016						
GG	63	(98.4%)	62	(100.0%)	93	(97.9%)
GT	1	(1.6%)	0	(0.0%)	2	(2.1%)
TT	0	(0.0%)	0	(0.0%)	0	(0.0%)
G	128	(99.2%)	124	(100.0%)	188	(98.9%)
T	1	(0.8%)	0	(0.0%)	2	(1.1%)

2). The low incidence of the polymorphic alleles and the small number of patients analyzed does not allow us to confirm their role in the susceptibility of DM and SLE Nevertheless, OSMR polymorphic variants were found associated with various autoimmune and inflammatory diseases. The OSMR rs2292016T alters ICSBF transcription factor binding, that is an important mediator for the development of SLE. [26]. The rs2292016 G/T+T/T genotypes were with an increased risk of SLE in Taiwanese population [26].

The polymorphism did not relate to the susceptibility to rheumatic arthritis but to its clinical manifestations, such as the sicca syndrome and the presence of anti-Ro/SSA antibodies [26].

The rs2292016 polymorphism was found to be associated with delayed cardiomyopathy and its poor prognosis in Chinese Han population [29].

Missense mutations in the OSMR β gene were identified in the patients of familial primary localized cutaneous amyloidosis (FPLCA), which is a hereditary skin disease associated with severe pruritus and amyloid material deposition in the dermis [30, 31].

Germline biallelic loss-of-function OSMR variants were found to cause severe allergic disease [32].

Several in vitro studies have demonstrated that Oncostatin M possesses tumor-suppressive properties by inhibiting the proliferation of various cancer cell lines, including ovarian, lung, human cerebral meningioma, mammary epithelial, and melanoma cells [33]. In certain cancer patients, disease progression has been linked to a loss of responsiveness to OSM [34]. The OSMR rs2292016 and the rs2278329 polymorphisms were found to be associated with higher recurrence in bladder cancer [28] and lung cancer [35] in the Chinese population. The rs2278329 was found to be associated with clinicopathologic characteristics of the tumor growth and multifocality development in papillary thyroid cancer in the Korean population [27].

OSM has also been identified as a potent mitogen for cells derived from Kaposi's sarcoma, which is associated with acquired immunodeficiency syndrome (AIDS) [36]. Notably, numerous cases of autoimmune diseases, such as DM and systemic lupus erythematosus SLE, complicated by Kaposi's sarcoma, have been reported [37].

Most of the studies conducted to date have focused on Asian populations. This research is the first one to address European populations. However, due to the low occurrence of the two specific genetic variations studied and the small sample size, their role for susceptibility to these diseases could not be definitively established. Still, their functional significance suggests they could contribute to a larger genetic pattern that affects disease susceptibility.

CONCLUSION

Our study did not confirm the independent impact of the OSM receptor (OSMR) single nucleotide polymorphisms on the susceptibility or clinical progression of DM and SLE in Bulgarians. A primary limitation of this study is the relatively small sample size, which limits the statistical power of the findings. Larger future studies with more patients will be needed to better understand the role of these genetic variations in the development and clinical manifestations of systemic lupus erythematosus and dermatomyositis.

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Ethics Approval: *This research was conducted in full compliance with the principles outlined in the Declaration of Helsinki for studies involving human participants. Ethical approval was granted by the local institutional ethics committee. All participants provided written informed consent prior to inclusion in the study, and venous blood samples were collected for DNA extraction.*

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

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