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THE ROLE OF GENOTYPE COMBINATIONS OF CANDIDATE GENES (TNF-A, IL-6, SOD2, AND IL-1) IN PREDICTING DERMATOPATHIES IN OBESE PATIENTS

Abstract. *In this population, polymorphisms TNF-α (G308A), IL-6 (C174G), and SOD2 (Ala16Val), as well as their combinations, were associated with an increased risk of dermatopathies in obese patients. The most significant predictive value was observed for the IL-6 + SOD2 combination, particularly in psoriasis. The IL-1 (C511T) polymorphism showed no significant role. These findings confirm the multifactorial nature of pathogenesis and emphasize the importance of genetic interactions in predicting and diagnosing dermatopathies in obesity.*

Keywords: *obesity, polymorphism, genes, psoriasis, vitiligo*

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РОЛЬ КОМБИНАЦИЙ ГЕНОТИПА КАНДИДАТОВЫХ ГЕНОВ (TNF-A, IL-6, SOD2, И IL-1) В ПРОГНОЗИРОВАНИИ ДЕРМАТОПАТИЧЕСКИХ ЗАБОЛЕВАНИЙ У ПАЦИЕНТОВ С ОЖИРЕНИЕМ

Резюме. *В исследуемой популяции выявлено, что полиморфизмы TNF-α (G308A), IL-6 (C174G) и SOD2 (Ala16Val), а также их сочетания, ассоциированы с повышенным риском развития дерматопатий у пациентов с ожирением. Наибольшую прогностическую ценность показала комбинация IL-6 + SOD2, особенно у пациентов с псориазом. Полиморфизм IL-1 (C511T) значимой роли не продемонстрировал. Полученные результаты подтверждают многофакторный характер патогенеза и подчёркивают необходимость учёта генетических взаимодействий при прогнозировании и ранней диагностике дерматопатий у пациентов с ожирением.*

Ключевые слова: *ожирение, полиморфизм, гены, псориаз, витилиго*

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СЕМИЗЛИК БЎЛГАН БЕМОРЛАРДА ДЕРМАТОПАТИЯЛАРНИ БАШОРАТ ҚИЛИШДА НОМЗОД (TNF-A, IL-6, SOD2 ВА IL-1) GENOTIP ГЕНОТИП БИРИКМАЛАРИНИНГ РОЛИ

Хулоса. *Тадқиқотда TNF-α (G308A), IL-6 (C174G) ва SOD2 (Ala16Val) полиморфизмлари ҳамда уларнинг комбинациялари семизликка чалинган беморларда дерматопатиялар ривожланиши билан боғлиқ экани аниқланди. Энг катта прогностик қиймат IL-6 + SOD2 комбинациясида кузатилди, айниқса псориаз билан оғриган беморларда. IL-1 (C511T) полиморфизми аҳамиятли роль кўрсатмади. Олинган натижалар патогенезнинг кўп омилли хусусиятини тасдиқлайди ва семизликда дерматопатияларни башорат қилиш ҳамда эрта ташхис қўйишда генетик ўзаро таъсирларни ҳисобга олиш зарурлигини кўрсатади.*

Калит сўзлар: *семизлик, полиморфизм, генлар, псориаз, витилиго*

Introduction.

Currently, obesity is considered one of the major global health threats due to its rapid increase worldwide. Obesity-associated inflammation represents the body's response to excessive accumulation of metabolic products. This process is accompanied by the activation of genes encoding cytokines and other mediators of inflammation. Chronic inflammation alters adipose tissue function and impairs immune cell activity, contributing to the development of insulin resistance [3].

Tumor necrosis factor alpha (TNF-α) plays an active role in the regulation of immune processes, apoptosis, and energy homeostasis; therefore, it is considered one of the key candidate genes associated with obesity [11]. The G-308A variant is associated with obesity and metabolic disorders [12], although in some studies (e.g., Kochetova O.V. et al., 2022) no

significant differences were found. Another important pro-inflammatory cytokine is IL-6, whose levels are elevated in dyslipidemia and insulin resistance [4; 10].

According to Suzuki K. et al. [13], the IL-1 polymorphism is associated with obesity: carriers of the TT genotype had a higher risk compared to those with the CC genotype.Superoxide dismutase 2 (SOD2 Ala16Val) is involved in the neutralization of reactive oxygen species. This gene polymorphism is associated with the risk of metabolic syndrome and oxidative stress [1; 9].

Thus, obesity acts as a trigger not only for metabolic complications but also for dermatopathies. Identifying genetic predisposition factors allows for a better understanding of pathogenesis mechanisms and the development of predictive models.

Objective of the study: to determine the significance of polymorphisms in the TNF-α, IL-6, SOD2, and IL-1 genes and their combinations in forming susceptibility to dermatopathies in obese patients.

Materials and Methods

The study included 39 obese patients aged 47 to 66 years (mean age 54.8 ± 4.1 years), of whom 22 were men (56.4%) and 17 were women (43.6%). All patients had obesity accompanied by inflammatory dermatopathies: psoriasis, vitiligo, or atopic dermatitis. The duration of obesity ranged from 10 to 23 years (mean 14.3 ± 3.3 years). The control group consisted of 34 healthy donors (15 men and 19 women) without signs of acute or chronic inflammatory, autoimmune, or endocrine diseases. The mean age in the control group was 48.4 ± 14.3 years.

Inclusion criteria: confirmed diagnosis based on clinical examination, laboratory, and instrumental studies in accordance with international protocols; age over 18 years; written informed consent to participate.

Exclusion criteria: acute infectious processes, oncological diseases, severe somatic diseases in the stage of decompensation, refusal to participate.

All participants were informed in advance about the purpose of the study and signed written consent in accordance with the requirements of the Declaration of Helsinki. Diagnoses were established on the basis of clinical, laboratory, and instrumental methods according to international standards and protocols.

To minimize the influence of ethnic heterogeneity, only citizens of the Republic of Uzbekistan residing in Tashkent and the Tashkent region were included.

The molecular genetic analysis was performed at the Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, Department of Cell Therapy.

Genotyping of TNF (G308A), IL-6 (C174G, rs1800795), SOD2 (Ala16Val, rs4880), and IL-1 (C511T) polymorphisms was carried out using allele-specific PCR with primers and reagents from NPF “Litekh” (Moscow, Russia).

Primary data processing, including clinical and biochemical parameters, genotypes, and the distribution of patients into study groups (obesity, control, type of dermatopathy), was performed using Microsoft Excel 2019 (Microsoft Corporation, USA). The main statistical analysis was conducted using Python 3.11 (Python Software Foundation, USA) with specialized libraries: pandas, numpy, scipy, and matplotlib.

In cases where the frequency of certain genotypes was low (including zero), the Haldane–Anscombe correction was applied to avoid division by zero and to obtain valid statistical estimates. For calculating odds ratios (OR) with 95% confidence intervals, as well as for testing Hardy–Weinberg equilibrium (HWE), built-in scipy functions and specialized online calculators were used: calc.pcr24.ru and OpenEpi (version 3.01, https://www.openepi.com). Differences were considered statistically significant at $p < 0.05$.

Results.

The analysis of genotype frequency distribution for TNF (G308A), IL-6 (C174G, rs1800795), SOD2 (Ala16Val, rs4880), and IL-1 (C511T) in obese patients and in the control, group showed that in obese patients, the major GG genotype of the TNF-α gene occurred less frequently than in the control group (59.0% vs. 82.4%; OR 0.31; $p = 0.03$, Haldane–Anscombe correction applied). The frequency of GA heterozygotes did not differ significantly (OR 1.61; $p = 0.41$). The homozygous mutant AA variant was identified in 15.4% of obese patients and was absent in the control group (OR 13.39; $p = 0.03$). In the dominant model (GA+AA vs. GG), carriage of the A allele was associated with an increased risk of dermatopathies (OR 3.25; $p = 0.03$).

In obesity, the homozygous major GG genotype of the IL-6 gene was significantly less frequent compared to the control group (41.0% vs. 82.4%; OR 0.15; $p = 0.0001$).

The heterozygous CG variant was more common (38.5% vs. 17.6%) and was at the threshold of significance (OR 2.92; $p = 0.05$). The homozygous CC variant was absent in the control group but occurred in 20.5% of obese patients (OR 18.62; $p = 0.008$). In the dominant model, carriage of the C allele was associated with a high risk (OR 4.67; $p = 0.003$).

Among obese patients, the homozygous Ala/Ala genotype of the SOD2 gene was significantly less frequent than in the control group (48.7% vs. 82.4%; OR 0.20; $p = 0.003$), indicating a potential protective effect. The Ala/Val variant was more com-

mon in obese patients (43.6% vs. 11.8%) and was associated with a risk of dermatopathies (OR 5.80; p = 0.003). The Val/Val variant was rare and did not show significant differences (OR 1.33; p = 0.76).

The distribution of IL-1 (C511T) genotypes did not reveal statistically significant differences between obese patients and the control group. The mutant TT genotype was registered in only one control subject (2.9%) and was not found among obese patients.

In the univariate analysis, statistically significant associations with the risk of developing dermatopathies in obesity were identified for three genes — TNF-α, IL-6, and SOD2 — whereas the IL-1 polymorphism did not show significant differences (Table 1).

Table 1.

Results of univariate and multivariate analysis of studied polymorphisms in obese patients

Polymorphism	Univariate Analysis OR (95% CI)	p	Multivariate Analysis OR (95% CI)	p
TNF-α	3.25 (1.09–9.64)	0.03	1.55 (0.38–6.36)	0.54
IL-6	4.67 (1.69–12.92)	0.003	3.85 (1.08–13.70)	0.04
SOD2	4.91 (1.66–14.50)	0.004	5.12 (1.60–16.33)	0.006
IL-1	0.86 (0.20–3.72)	0.84	–	–

In the multivariate model, which accounted for the combined influence of multiple genetic factors, IL-6 and SOD2 remained independent predictors of dermatopathy risk in obese individuals. At the same time, TNF-α lost statistical significance.

This may indicate that its effect on the development of dermatopathies is not direct but mediated through other mechanisms, or that its association with dermatopathies is due to close linkage with IL-6 and SOD2.

Therefore, we analyzed the frequency of different gene combinations in order to identify the most informative ones that can be used for early diagnosis of dermatopathies in obese patients. The results are presented in Table 2.

Table 2.

Association of gene combinations with the development of dermatopathies in obese patients

Combination	Obesity	Control	OR	95% CI	p (Fisher)	p (χ^2)
TNF + IL-6	15	4	4.69	1.37 – 15.98	0.0151	0.0095
IL-6 + SOD2	12	1	14.67	1.79 – 120.07	0.0019	0.0019
TNF + SOD2	8	1	8.52	1.01 – 72.09	0.0316	0.0227
IL-6 + IL-1	3	0	N/A	N/A	0.2432	0.0986
TNF + IL-1	1	0	N/A	N/A	1.0000	0.3471

The most significant combination was identified for the IL-6 + SOD2 genes, which demonstrated a very strong association with the risk of dermatopathy development in obesity (OR 14.67; p = 0.0019). This indicates the key role of the combined influence of these polymorphisms in shaping predisposition to skin manifestations in the context of obesity.

A moderate significant association was linked to the TNF + IL-6 combination (OR 4.69; p = 0.0151), which may reflect the combined impact of pro-inflammatory cytokines on skin inflammation. Another significant combination was TNF + SOD2 (OR 8.52; p = 0.0316), suggesting the importance of interactions between inflammatory and oxidative pathways. Combinations involving IL-1 were very rare and cannot be used in predictive modeling.

The results indicate that the most valuable diagnostic predictors for dermatopathies in obese patients are IL-6 + SOD2, as well as TNF + IL-6 and TNF + SOD2. The most powerful predictor is the IL-6 + SOD2 pair, underscoring the importance of considering both inflammatory and antioxidant mechanisms in the development of skin pathology.

The analysis showed that psoriasis was the absolute leader in terms of the number of gene combinations (Table 3).

Table 3.

Frequency of gene combinations among patients with dermatopathies (n, %)

Genotype Combination	Atopic Dermatitis	Vitiligo	Psoriasis
IL-6 + SOD2	–	2 (28.6%)	10 (45.5%)
TNF + IL-6	2 (20.0%)	3 (42.9%)	10 (45.5%)
TNF + SOD2	–	1 (14.3%)	7 (31.8%)
TNF + IL-6 + SOD2	–	1 (14.3%)	7 (31.8%)

Practically all studied combinations occurred in patients with this disease. Almost half (45.5%) of patients with psoriasis carried the IL-6 + SOD2 and TNF + IL-6 combinations. The triple combination (TNF + IL-6 + SOD2) was present in 31.8% of psoriasis patients, indicating its high significance for the formation of strong predisposition.

In vitiligo, the same gene combinations were observed, but with lower frequencies. The most common was TNF + IL-6 (42.9%), while other combinations occurred less frequently — from 14.3% to 28.6%.

In patients with atopic dermatitis, no pronounced genetic combinations were detected. Only 20% of patients showed the TNF + IL-6 combination, while other combinations were absent.

Psoriasis is thus characterized by the greatest genetic predisposition in terms of the studied polymorphisms.

The most significant combinations were IL-6 + SOD2 and TNF + IL-6, highlighting the role of inflammatory and antioxidant mechanisms in disease development. The triple combination occurred relatively often, making it a potential marker of high risk.

For vitiligo, the TNF + IL-6 combination was the most relevant, but overall, the frequency of all combinations was lower than in psoriasis, suggesting less involvement of these genes in disease pathogenesis.

Atopic dermatitis did not demonstrate significant association with the studied polymorphisms. Likely, other molecular mechanisms and genetic markers, not covered in this study, play a dominant role in its development.

Thus, the study demonstrated that the key genetic determinants of dermatopathies in obesity are the polymorphisms TNF-α (G308A), IL-6 (C174G), and SOD2 (Ala16Val). The minor alleles of these genes and their combinations were associated with an increased risk of dermatopathies, particularly psoriasis, where the highest frequency of combinations was observed. The most valuable predictive marker was the IL-6 + SOD2 combination, followed by TNF + IL-6 and TNF + SOD2. Moderate associations were identified for vitiligo, mainly with the TNF + IL-6 combination. Atopic dermatitis did not show significant associations, suggesting that other genetic and molecular factors may be involved in its pathogenesis.

These findings confirm that obesity and dermatopathies share common pathogenetic mechanisms, including inflammatory and oxidative stress pathways. The obtained results may be applied to develop a predictive model for the early identification of patients at high risk of dermatopathies, which would enable timely preventive and therapeutic interventions.

Discussion.

Obesity is accompanied by chronic inflammation and metabolic disturbances, associated with the activation of adipokines and pro-inflammatory cytokines [6].

Leptin and mediators, including TNF-α and IL-6, contribute to the chronic inflammatory state, promoting the development of dermatological diseases [2; 5; 7; 14].

In our study, associations were identified between TNF-α (G308A), IL-6 (C174G), and SOD2 (Ala16Val) polymorphisms and an increased risk of dermatopathies in obese patients. The minor alleles of these genes were associated with dermatopathies, whereas the major homozygous variants appeared to exert a protective effect.

Of particular importance was the IL-6 + SOD2 combination, which showed the highest predictive value (OR 14.67). Moderate associations were also found for TNF + IL-6 and TNF + SOD2. The IL-1 (C511T) polymorphism did not demonstrate significant differences, indicating its limited role.

The strongest genetic predispositions were observed in psoriasis, where IL-6 + SOD2 and TNF + IL-6 were most frequent, along with the triple combination TNF + IL-6 + SOD2. In vitiligo, TNF + IL-6 was the leading combination, but with lower frequencies. Atopic dermatitis showed no significant associations, suggesting other mechanisms are involved.

These findings underscore the importance of multigenic predictive models that account for both individual polymorphisms and their interactions.

Conclusion.

The polymorphisms TNF-α (G308A), IL-6 (C174G), and SOD2 (Ala16Val), as well as their combinations, are associated with an increased risk of dermatopathies in obese patients. The IL-6 + SOD2 combination demonstrated the strongest predictive value, particularly in psoriasis. The IL-1 (C511T) polymorphism did not play a significant role.

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