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THE ROLE OF THE TNF-α GENE POLYMORPHIC VARIANT IN THE DEVELOPMENT OF PSORIASIS IN CHILDREN

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Abstract

This study explores the genetic aspects of the etiopathogenesis of psoriasis in children. The research analyzed the distribution of alleles and genotypes of the single nucleotide polymorphism -308G>A of the TNF-α gene (rs1800629) in 107 affected children and 80 individuals in a control group. The results demonstrated a statistically significant prevalence of the heterozygous G/A genotype and the A allele in the patient group compared to the control group, which is associated with an almost twofold increase in the risk of disease development (OR=1.9). It was established that the presence of the A allele is associated with high TNF-α production and can serve as a genetic marker of susceptibility to psoriasis, whereas the G/G genotype plays a protective role. The findings suggest that the -308G>A polymorphism is a potential biomarker for risk prediction and assessment of psoriasis severity in pediatric practice.

Keywords: psoriasis, children, TNF-α gene, genetic polymorphism, pathogenesis, allele, genotype.

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ЗНАЧЕНИЕ ПОЛИМОРФИЗМА ГЕНА ФНО- α В ЭТИОПАТОГЕНЕЗЕ ДЕТСКОГО ПСОРИАЗА

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Аннотация.
Данная работа посвящена изучению генетических аспектов этиопатогенеза псориаза у детей. В ходе исследования был проведен анализ распределения аллелей и генотипов однонуклеотидного полиморфизма -308G>A гена ФНО- α (rs1800629) у 107 больных детей и 80 лиц контрольной группы. Результаты продемонстрировали статистически значимое преобладание гетерозиготного генотипа G/A и аллеля A в группе больных по сравнению с контролем, что сопровождается повышением риска развития заболевания почти в 2 раза (OR=1,9). Установлено, что наличие аллеля A ассоциировано с высокой продукцией ФНО- α и может выступать генетическим маркером предрасположенности к псориазу, в то время как генотип G/G выполняет протективную роль. Полученные данные позволяют рассматривать полиморфизм -308G>A как потенциальный биомаркер для прогнозирования риска и оценки тяжести течения псориаза в педиатрической практике.

Ключевые слова: псориаз, дети, ген TNF-α, ФНО- α, генетический полиморфизм, патогенез, аллель, генотип.

Introduction

Psoriasis is a chronic inflammatory skin disease with a complex genetic and immune pathogenesis [4]. Current data characterize it as an organ-specific autoimmune condition caused by aberrant proliferation of keratinocytes [1, 9, 14].

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Abnormal reactions of T-cells, dendritic cells, and overproduction of inflammatory cytokines are recognized as key mechanisms of disease development [2, 11, 15, 16].

The hereditary nature of psoriasis is confirmed by the association of numerous genetic variations with the risk of disease development [3, 5, 8, 17]. Special attention is paid to the role of keratinocytes, whose function depends on epigenetic factors, metabolism, and cytokine profile, particularly TNF-alpha and IL-17 [6, 10, 12, 18].

Despite the effectiveness of targeted therapy, the influence of single nucleotide polymorphisms (SNPs), especially the TNF-alpha -308G/A variant, on the development of psoriasis remains not fully understood [6, 10, 13]. Studying the genetic aspects of the TNF-alpha gene polymorphism is a necessary step for addressing unresolved issues of the disease etiopathogenesis.

Objective of the Study

To study the role of the polymorphic variant of the TNF-alpha gene in the development of psoriasis in children.

Materials and Methods

The study was conducted among 107 children with psoriasis aged 3 to 18 years, of whom 48 (44.9%) were boys and 59 (55.1%) were girls. By place of residence, rural residents predominated – 64 children (59.8%), while there were 43 urban patients (40.2%). The age distribution showed that children aged 3–5 years accounted for 16.8% (18 people), 6–10 years – 39.3% (42 people), and 11 years and older – 43.9% (47 people). A population control of 80 conditionally healthy donors from a DNA bank was used as a comparison group.

The complex of methods included anamnesis collection, physical examination, consultations with related specialists, and routine clinical and laboratory tests (CBC, UA, coprology). Biochemical blood tests and ultrasound of internal organs

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were performed as indicated. The specific part of the work included determination of serum cytokine levels by ELISA and DNA extraction from peripheral blood lymphocytes according to a modified technique.

Genotyping of the -308G>A polymorphism of the TNF-alpha gene (rs1800629) was performed by PCR on Corbett Research (Australia) and Applied Biosystems (USA) thermal cyclers using MedLab (Russia) test systems. Statistical data processing was carried out using the Microsoft Office Excel-2010 package. To assess the deviation of genotype distribution from the Hardy-Weinberg equilibrium, the specialized genetic data analysis computer program GenePop was used.

Results and Discussion

Although information exists regarding the role of tumor necrosis factor alpha (TNF-alpha) in the pathogenesis of psoriasis [6, 10, 17], regional studies of this cytokine in children have not been conducted previously. Given the prevalence of single nucleotide polymorphisms in the TNF-alpha gene (rs361525, rs1800629, rs1799724), studying the 308G>A (rs1800629) variant in pediatric psoriasis remains a relevant task. In the course of the study, the pathogenetic significance of the genotypic variants of this locus was analyzed in 187 subjects, including 107 children with psoriasis and 80 individuals in the control group.

The results showed that the normal G allele predominated in both groups against a background of low frequency of the functionally deficient A allele. In the control group, the prevalence of the A allele was 6.9% (11/160), and the G allele was 93.1% (149/160). Among the sick children, the frequency of the A allele was 9.4% (20/214), and the G allele was 90.6% (194/214).

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https://eurekaoa.com/index.php/5

Group	Allele frequency				Genotype frequency distribution					
	G		A		G/G		G/A		A/A	
	abs	%	abs	%	abs	%	abs	%	abs	%
Main group of patients n=107* (214**)	194	90,6	20	9,4	85	79,5	21	19,6	1	0,9
Limited form n=11* (22**)	19	86,4	3	13,6	8	72,7	2	18,2	1	9,1
Disseminated form n=96* (192**)	175	91,1	17	8,9	77	80,2	19	19,8	0	0
Control group n=80* (160**)	149	93,1	11	6,9	69	86,2	11	13,8	-	0

Note: n* is the number of individuals and genotypes studied, n** is the number of alleles studied

Table 2. Expected and observed frequencies of genotype distribution of the TNF-alpha gene rs1800629 polymorphism according to HWE in the group of children with psoriasis.

Genotypes	Genotype frequency		χ^2	P	df
	Observed	Expected			
G/G	0,75	0,76	0,008	0,4	1
G/A	0,24	0,23	0,121		
A/A	0,01	0,01	0,431		
Total	1,0	1,00	0,561		

Table 3. Expected and observed frequencies of genotype distribution of the TNF-alpha gene rs1800629 polymorphism according to HWE in the control group.

Genotypes	Genotype frequency		χ^2	P	df
	Observed	Expected			
G/G	0,86	0,87	0,002	0,5	1
G/A	0,14	0,12	0,056		
A/A	0,00	0,01	0,378		
Total	1,0	1,00	0,436		

Similar patterns in the distribution of alleles and genotypes of the TNF-alpha 308G>A (rs1800629) polymorphism were maintained in the analysis based on the clinical form of psoriasis. In the genotype structure of the main group, the

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Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)
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G/G variant predominated (79.5%), while the proportion of the heterozygous G/A genotype was 19.6%. In the control group, the frequencies of these genotypes were 86.2% and 13.8%, respectively.

Population genetic analysis revealed that in the group of patients, the level of observed heterozygosity (H_0=0.24) slightly exceeded the theoretically expected level (H_e=0.23), while deviations from the Hardy-Weinberg equilibrium were statistically insignificant (χ^2 =0.121; p=0.4). In the control group, no significant deviations from the HWE were found either (χ^2 =0.436; p=0.5). The excess of observed heterozygosity over expected heterozygosity in both samples is confirmed by a positive Wright's fixation index (D=+0.04 and +0.08). The predictive efficacy of the AUC marker was 0.55, with sensitivity (SE) of 0.24 and specificity (SP) of 0.86.

It is known that the A allele (TNF-alpha 2) is associated with the HLA-A1-B8-DR3-DQ2 haplotype and is a potent transcriptional activator, increasing cytokine expression by 6–7 times. This accounts for the association of this polymorphism with a more severe course of the disease. Comparative analysis showed that the frequency of the mutant A allele in sick children is higher than in the control (9.4% vs 6.9%). According to the odds ratio calculation, the presence of the functionally unfavorable A allele increases the risk of developing psoriasis by almost 2 times (OR=1.9; RR=1.7; p=0.07).

A statistically significant increase in the frequency of the heterozygous 308G/A genotype in the main group (19.6% vs 13.7% in the control) also confirms an increase in the risk of developing the pathology by 1.7 times (OR=1.9; RR=1.7; p=0.1). Meanwhile, the homozygous 308G/G genotype was significantly more frequent in the control group (86.2% vs 79.5%). The results obtained allow the TNF-alpha -308G/A polymorphism to be considered as a potential biological marker for evaluating the prognosis of psoriasis in children, regardless of its clinical form.

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Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)
ISSN 2760-4942 (Online) Volume 2, Issue 3, March 2026

https://eurekaoa.com/index.php/5

Conclusion

The data obtained indicate that the presence of the heterozygous 308G/A genotype (and potentially the 308A/A genotype) increases the risk of psoriasis in children, meaning this polymorphism serves as a genetic marker for an elevated risk of the disease. In contrast, the G/G genotype may perform a protective function. Furthermore, the rs1800629 polymorphism affects the transcription of the TNF-alpha gene and is associated with the risk of psoriasis, which should be taken into account during diagnosis.

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https://eurekaoa.com/index.php/5

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Eureka Journal of Health Sciences & Medical Innovation (EJHSMI)

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https://eurekaoa.com/index.php/5

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