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Frequency of occurrence of alleles and genotypes of CYP3A5 gene polymorphism (A6986G) in children with systemic lupus erythematosus

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ABSTRACT

The article presents the results of the analysis of the association of CYP3A5 polymorphism (A6986G) with the development of systemic lupus erythematosus (SLE) in children. Forty-five children with SLE and 72 healthy donors were examined. The frequency of the A allele was 88.9% in patients versus 93.75% in the control group, the differences are statistically insignificant (p> 0.05). The G/A genotype was found in 54.5% of patients and 47.2% of healthy people, and G/G in 35.6% of patients and 45.8% in the control, without significant differences (p> 0.05). The potential role of CYP3A5 polymorphism as a pharmacogenetic marker of sensitivity to glucocorticoid therapy in children with SLE is emphasized, which requires further studies with an expanded sample.

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Tizimli qizil yuguruk bilan og‘rigan bolalarda CYP3A5 geni polimorfizmining (A6986G) allellari va genotiplari uchrash chastotasi

Kalit so‘zlar:
tizimli qizil yuguruk,
bolalar,
CYP3A5,
A6986G,
glyukokortikoidlar,
farmakogenetika,
genotiplash,
immunogenetika.

ANNOTATSIYA

Maqolada bolalarda tizimli qizil volchanka (TQV) rivojlanishi bilan CYP3A5 (A6986G) polimorfizmi o‘rtasidagi bog‘liqlikni tahlil qilish natijalari keltirilgan. TQV bilan kasallangan 45 nafar bola va 72 nafar sog‘lom donor tekshiruvdan o‘tkazildi. A allelining chastotasi bemorlarda 88,9% ni, nazorat guruhida esa 93,75% ni tashkil etdi, bunda farqlar statistik jihatdan ahamiyatsiz (p> 0,05). G/A genotipi bemorlarning 54,5% ida va sog‘lom odamlarning 47,2% ida, G/G genotipi esa bemorlarning 35,6% ida va nazorat guruhining 45,8% ida aniqlandi, sezilarli farqlar kuzatilmadi (p> 0,05). TQV bilan og‘rigan bolalarda glyukokortikoid terapiyaga sezuvchanlikning farmakogenetik markeri sifatida CYP3A5 polimorfizmining potensial ahamiyati ta’kidlangan. Bu esa kengaytirilgan namuna bilan qo‘shimcha tadqiqotlar o‘tkazishni talab etadi.

Частота встречаемости аллелей и генотипов полиморфизма гена CYP3A5 (A6986G) у детей с системной красной волчанкой

Ключевые слова:
системная красная волчанка,
дети,
CYP3A5,
A6986G,
глюкокортикоиды,
фармакогенетика,
генотипирование,
иммуногенетика.

АННОТАЦИЯ

В статье представлены результаты анализа ассоциации полиморфизма CYP3A5 (A6986G) с развитием системной красной волчанки (СКВ) у детей. Были обследованы 45 детей с СКВ и 72 здоровых донора. Частота аллеля А составила 88,9% у пациентов против 93,75% в контрольной группе, различия статистически незначимы (p> 0,05). Генотип G/A был обнаружен у 54,5% пациентов и 47,2% здоровых людей, а G/G – у 35,6% пациентов и 45,8% в контрольной группе, без статистически значимых различий (p> 0,05). Подчеркивается потенциальная роль полиморфизма CYP3A5 как фармакогенетического маркера чувствительности к глюкокортикоидной терапии у детей с СКВ, что требует дальнейших исследований на расширенной выборке.

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by a wide range of clinical manifestations and involvement of multiple organs and systems. The features of the course of SLE in children include a more aggressive onset, high levels of immune activity, and frequent development of complications, which makes the search for prognostic markers especially important [1, 5, 11, 15]. In recent years, special attention has been paid to molecular genetic studies aimed at identifying predisposing factors for the development of SLE. Among them,

polymorphisms of genes involved in xenobiotic metabolism, regulation of the immune response and apoptosis are considered as potential biomarkers of the risk and severity of the disease [2, 6, 9, 14]. The CYP3A5 gene encodes one of the key cytochromes P450 enzymes involved in the metabolism of a large number of drugs and endogenous substrates [3, 7, 10, 13]. The A6986G (rs776746) polymorphism affects the expression of the CYP3A5 enzyme, changing its activity, which may be important both in pharmacogenetics and in the pathogenesis of immune diseases, including SLE. The study of CYP3A5 (A6986G) polymorphism in children with SLE can contribute to a deeper understanding of the genetic mechanisms of predisposition to the disease and can potentially be used in predicting the course, choosing therapy and assessing the response to treatment [4, 8, 12].

Purpose of the study: to study the role of CYP3A5 gene polymorphism (A6986G) in the development of systemic lupus erythematosus in children.

Materials and methods of research: We selected 45 children with SLE for molecular genetic studies. The control group consisted of 72 practically healthy individuals of Uzbek nationality (data were provided by the leading researcher of the Department of Cellular Technologies of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan, Doctor of Medical Sciences Ruzibakieva M.R.)

The material for DNA extraction was 3-5 ml of venous blood from the cubital vein (Beckton-Dickinson vacutainers were used for blood collection) with an anticoagulant/preservative of 15% tripotassium EDTA (Ethendianin-tetraacetic acid). Genotyping of polymorphic regions of immune response genes was carried out by the polymerase chain reaction (PCR) method with allele-specific primers (NPF Litekh, Moscow) and electrophoretic detection of reaction products in agarose gel.

The distribution of genotypes in the studied polymorphic loci was studied using logistic regression analysis and checking for compliance with the Hardy–Weinberg equilibrium using the Fisher exact test. The correspondence of patients and control group individuals by gender and age was taken into account. Differences were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS

In the first stage, we presented comparative data on the frequency of alleles A and G in patients with SLE and in the control group, and also analyzed the association with the risk of developing the disease.

Table 1.

Frequency of occurrence of polymorphism of gene alleles CYP3A5 (A6986G) in the general sample and in the control group in children with SLE

Alleles	Cases	Controls	χ^2	*p*	*OR*	
	n = 45	n = 72			meaning.	95% CI
Allele G	0.889	0.938	1.75	0.19	0.53	0.21 – 1.37
Allele A	0.111	0.063			1.88	0.73 – 4.81

The results of the analysis of the frequency of alleles A and G of the CYP3A5 polymorphism (A6986G) in children with SLE compared with the control group are presented in Table 4.2. It was found that the frequency of the allele G in the group of patients was 88.9%, and in the control group – 93.8%. Despite the observed decrease in the frequency of the G allele in patients, the difference did not reach statistical significance ($\chi^2 = 1.75$; $p = 0.19$) (Table 1).

The relative risk (OR) estimate for carriage of the G allele was 0.53 (95% CI: 0.21–1.37), indicating a possible tendency towards a protective role of this allele, but the results are not statistically significant. In contrast, carriage of the A allele is associated with OR = 1.88 (95% CI: 0.73–4.81), which may indicate a potential increase in the risk of developing SLE, but this association is also not statistically confirmed.

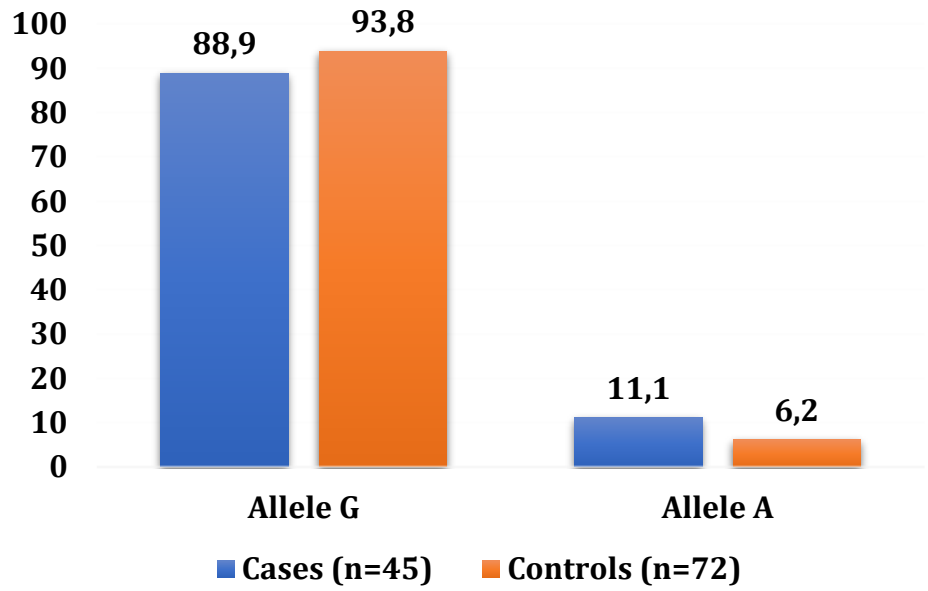

Fig. 1. Distribution of alleles in examined children with SLE

The frequency of the A allele of the CYP3A5 gene (A6986G) among children with SLE was 11.1%, while in the control group it was 6.2%. Despite the lack of statistical significance of differences ($\chi^2 = 1.75$; $p = 0.19$), there is a tendency towards an increased representation of the A allele in patients, which may indicate its potential role as a factor in genetic predisposition to the development of systemic lupus erythematosus (Fig. 1).

The relative risk (OR) calculation for carriage of the A allele showed a value of 1.88 (95% CI: 0.73–4.81), indicating an almost twofold increase in the chance of developing SLE in the presence of this allele. However, the wide confidence interval and $p > 0.05$ indicate the absence of a significant association, which is probably due to insufficient sample power.

Thus, the obtained data allow us to assume the possible involvement of the A allele in the pathogenesis of SLE in children, however, confirmation of this hypothesis requires further research on larger and ethnically homogeneous samples.

Table 2.

Frequency of occurrence of gene polymorphism genotypes CYP3A5 (A6986G) in the general sample and in the control group in children with SLE

Genotypes	Cases	Controls	χ^2	*p*	*OR*	
	n = 45	n = 72			meaning.	95% CI
Genotype G/G	0.778	0.889	4.01	0.13	0.44	0.16 – 1.21
Genotype G/A	0.222	0.097			2.65	0.93 – 7.58
Genotype A/A	0.000	0.014			0.52	0.02 – 13.14

Analysis of the distribution of CYP3A5 (A6986G) genotypes among children with SLE and healthy donors showed differences in the frequency of variants. The G/G genotype was the most common in both groups, but its frequency was lower in patients with SLE (77.8%) compared to the control group (88.9%). Despite the tendency to a decrease in the proportion of this genotype among patients, the difference did not reach statistical significance (χ^2 = 4.01; p = 0.13). At the same time, the calculation of the odds ratio (OR = 0.44; 95% CI: 0.16–1.21) may indicate a possible protective role of homozygous carriage of the G allele, although the results are not reliable (Table 2).

The frequency of the heterozygous genotype G/A was higher among patients (22.2% versus 9.7% in the control). The calculation of OR = 2.65 (95% CI: 0.93–7.58) indicates an almost three-fold increase in the risk of developing SLE in the presence of a heterozygous combination, which may reflect the potential role of the A allele in the manifestation of the disease. However, despite the pronounced trend, statistical significance was also not achieved (p > 0.05), which may be due to the limited number of observations.

The homozygous genotype A/A was not detected in any patient with SLE, while in the control group its frequency was 1.4%. The obtained OR = 0.52 (95% CI: 0.02–13.14) with an extremely wide confidence interval does not allow us to draw reasonable conclusions about the significance of this genotype in the pathogenesis of the disease (Fig. 2).

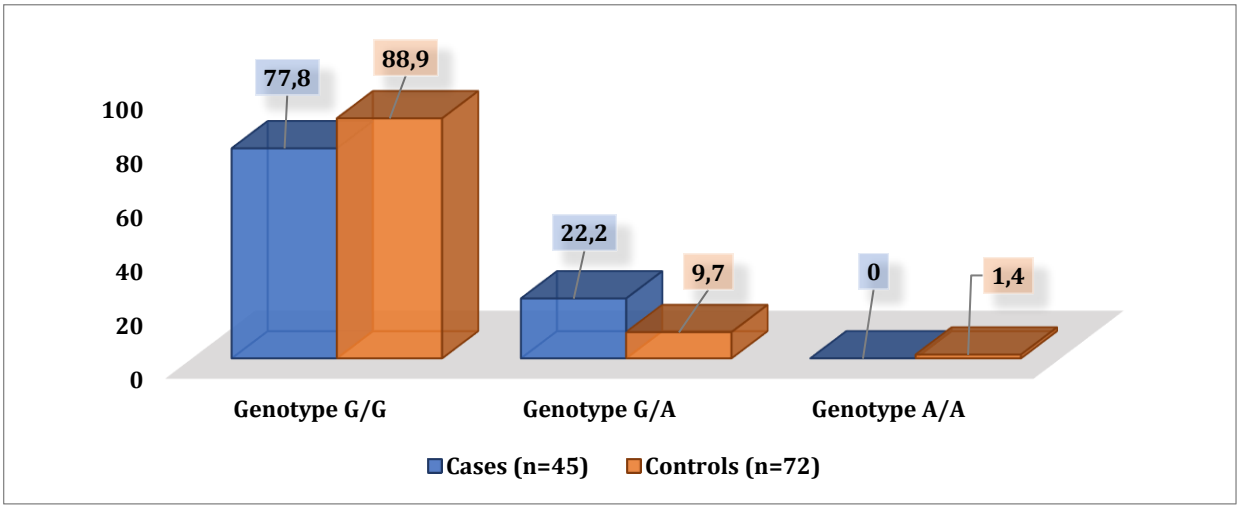

Fig. 2. Distribution of genotypes in examined children with SLE

The obtained data indicate a tendency to an increase in the frequency of carriage of the A allele in patients with SLE, which can be considered as a potential factor of genetic predisposition to the disease. Considering that the A6986G polymorphism affects the splicing of the CYP3A5 gene mRNA, a decrease in the expression of the functional protein in carriers of the A allele may have pathophysiological significance. The CYP3A5 enzyme, which belongs to the cytochrome P450 system, is involved not only in the metabolism of xenobiotics and drugs, but also in the biotransformation of steroid hormones, including glucocorticoids. Glucocorticoids are known to play a key role in immunoregulation, inhibiting the production of proinflammatory cytokines and modulating the activity of T- and B-cells.

Decreased CYP3A5 activity in A-allele carriers may contribute to the accumulation of active forms of endogenous glucocorticoids or, conversely, to disruption of their metabolism, leading to an imbalance between anti-inflammatory and pro-inflammatory mediators. This, in turn, may enhance immune disorders characteristic of SLE. In addition, decreased CYP3A5 activity may affect the pharmacokinetics of exogenous glucocorticoids widely used in the treatment of SLE, causing variability in the response to therapy: carriers of the A allele may have accelerated drug metabolism, which increases the risk of side effects, but may also contribute to a weaker therapeutic effect.

Thus, the identified differences in the frequency of CYP3A5 (A6986G) genotypes between children with SLE and the control group suggest the involvement of this gene in the pathogenesis of the disease due to changes in glucocorticoid metabolism and an indirect effect on immune homeostasis.

Table 3.

Distribution of CYP3A5 gene polymorphism (A6986G) genotypes by severity of SLE

CYP3A5(A6986G)	1 degree n = 5	2 degree n = 24	3 degree n = 16	Total n = 45
GG	0 (0.0%)	19 (79.2%)	16 (100.0%)	35 (77.8%)
GA	5 (100.0%)	5 (20.8%)	0 (0.0%)	10 (22.2%)
AA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

To assess the possible relationship between the CYP3A5 polymorphism (A6986G) and the clinical activity of systemic lupus erythematosus (SLE) in children, an analysis of the distribution of genotypes by the degree of disease activity was performed. According to the international classification (PRINTO, 2021), the first degree corresponds to the most severe course, the third – to the least pronounced activity of the process.

The results of the analysis showed a clear differentiation of genotypes by the degree of activity. In the group with the highest SLE activity (grade 1), 100% of patients had the heterozygous genotype G/A, while homozygous G/G was not found in this group. In the group with moderate activity (grade 2), the genotype G/G prevailed (79.2%), and G/A was found in 20.8% of patients. At the same time, in the group with the least pronounced activity (grade 3), exclusively all patients (100%) had the homozygous genotype G/G, and carriage of the A allele (G/A or A/A) was completely absent (Table 3).

Thus, carriage of the A allele (genotype G/A) is associated with a more severe course of the disease, while the homozygous for the G allele genotype G/G is characteristic mainly of patients with milder clinical activity. Such a distribution can be explained by the pharmacogenetic effect of CYP3A5 polymorphism on the metabolism of glucocorticoids – key drugs in the therapy of SLE.

It is known that the A allele causes accelerated expression of the functional enzyme CYP3A5, which leads to faster metabolism and elimination of glucocorticoids from the body. This, in turn, can reduce their therapeutic effectiveness, especially in patients with an active inflammatory process. In conditions of insufficient duration of glucocorticoid action, autoimmune inflammation increases, which is clinically manifested by increased disease activity.

Particular attention should be paid to patients with the second degree of SLE activity and heterozygous genotype G/A. These children can be considered as a high-risk group for disease progression with transition to the first degree of activity, which is due to insufficient sensitivity to glucocorticoid therapy due to accelerated metabolism of the drug. Given this, these patients require more careful monitoring of immunoinflammatory parameters and possible correction of the treatment regimen.

CONCLUSION

Thus, the identified association between the G/A genotype and a more severe course of SLE emphasizes the importance of molecular genetic typing of CYP3A5 in children with SLE as a potential criterion for predicting response to therapy, assessing the risk of progression and developing personalized approaches to treatment.

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