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NEW ASPECTS OF THE GENETIC DISPOSITION OF VARIOUS FORMS OF CHRONIC NEPHRITIC SYNDROME IN CHILDREN

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Таянч сўзлар: сурункали нефритик синдром, металлопротеиназа, генотип.
Ключевые слова: хронический нефритический синдром, металопротеиназа, генотип.

The medicine of the 21st century is considered to be medicine that involves the prevention of various diseases, including chronic kidney disease, taking into account the genetic predisposition. Children with chronic nephritic syndrome due to genetic predisposition are recommended to be allocated to a separate high-risk group in the general dispensary system of the child population and to conduct regular dispensary monitoring of them. In the development of the disease, especially its nephrotic and mixed forms, it interacts with the GG genotype of the MMP9 (A-8202G) rs11697325 gene, it is an important diagnostic and prognostic factor for above-mentioned pathology and requires early treatment.

БОЛАЛАРДА СУРУНКАЛИ НЕФРИТИК СИНДРОМНИНГ ТУРЛИ ШАКЛЛАРИДА ГЕНЕТИК МОЙИЛЛИКНИНГ ЯНГИ ЖИҲАТЛАРИ

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XXI аср тиббиёти - ирсий мойилликларни англаган ҳолда турли касалликларнинг, шу жумладан сурункали буйрак касалликларнинг профилактикасини назарда тутувчи тиббиёт саналади. Аҳолининг болалар ёшидаги қисмини умумий диспансеризацияси тизимида, ирсий мойиллик туфайли келиб чиқувчи сурункали нефритик синдром билан оғриган болаларни, алоҳида юқори хавф гуруҳи сифатида ажратиш ва уларда доимий диспансер кузатувини ўтказиш тавсия этилади. Касалликни, хусусан унинг нефротик ва аралаш шаклларини ривожланиши, MMP9 (A-8202G) rs11697325 генининг GG генотипи билан ўзаро алоқадорликка эга эканлиги, ушбу патологиянинг муҳим диагностик ва прогностик белгиси ҳисобланади ва ўз вақтида даволашни тақозо этади.

НОВЫЕ АСПЕКТЫ ГЕНЕТИЧЕСКОЙ РАСПОЛОЖЕННОСТИ РАЗЛИЧНЫХ ФОРМ ХРОНИЧЕСКОГО НЕФРИТИЧЕСКОГО СИНДРОМА У ДЕТЕЙ

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Медициной XXI века принято считать медицину, предполагающую профилактику различных заболеваний, в том числе хронических заболеваний почек, с учетом генетической предрасположенности. Детей с хроническим нефритическим синдромом, обусловленным генетической предрасположенностью, рекомендуется выделять в отдельную группу высокого риска в общей диспансерной системе детского населения и проводить за ними регулярное диспансерное наблюдение. В развитии заболевания, особенно его нефротической и смешанной форм, имеет взаимодействие с генотипом GG гена MMP9 (A-8202G) rs11697325, что является важным диагностическим и прогностическим фактором данной патологии и требует своевременного лечения

Introduction. Matrix metalloproteinases (MMPs) are the family of zinc-dependent proteolytic enzymes responsible for the renewal and remodeling of the extracellular matrix (they include the families of collagenases, gelatinases, stromelysins, matrilysins, etc). Under various pathological conditions, MMPs are a component of a nonspecific inflammatory response. Natural inhibitors of MMPs in in vivo are tissue inhibitors of metalloproteinases (TIMP) and α2-macroglobulin. One of the promising markers for early diagnosis of kidney damage is matrix metalloproteinase-9 (MMP-9). In the adult kidney, matrix MMP-9 is predominantly expressed in collecting duct cells and to a lesser extent in proximal tubules and podocytes. Matrix metalloproteinases are endopeptidases that not only cleave extracellular matrix (ECM) components, but also modify non-ECM molecules, including various growth factors and their binding proteins .

MMP9 also promotes invasion into the basement membrane of cells involved in the pathogenesis of inflammation (T cells, mononuclear phagocytes, synovial fibroblasts, etc). Therefore, the study of the association of various polymorphic variants of MMP genes with clinical manifestations of glomerulonephritis in children is of great practical interest.

The purpose of the study. To study aspects of the genetic disposition of various forms of chronic nephritic syndrome in children.

Materials and methods. DNA isolation. Genetic studies of genes and their tissue inhibitors was carried out in the immunoregulation laboratory of the Institute of Immunology and Hu-

Table 1.

Distribution of allele and genotype frequencies of the MMP9 (A-8202G) gene in sick and healthy children

Gene MMP 9 (A-8202G)	Main group n=102 (%)	Control group n=67 (%)	χ2	OR (95% CI)
A	77 (37.75%)	68 (50.75%)	2.674 (p=0.101998)	0.461 >0.704> 1.073
G	127 (62.25%)	66 (49.25%)		0.932 >1.421> 2.167
AA	13 (12.75%)	16 (23.88%)	3.527 (p=0.060)	0.207 >0.466> 1.045
AG	51 (50.0%)	36 (53.73%)	0.225 (p=0.634)	0.464 >0.861> 1.597
GG	38 (37.25%)	15 (22.39%)	4.152 (p=0.041)	1.021 >2.058> 4.148

Note: χ 2 – Pearson confidence indicator; O R – relative risk.

man Genomics in Tashkent. In the DNA of blood leukocytes of patients and practically healthy, gene polymorphism was determined. The isolated DNA was carried out by the standard nucleosorb method using Diatom™ kits. Typing of DNA samples was carried out using a specific oligonucleotide primer with gene regions. PCR analysis was provided by using a PCR amplification kit.

Results. MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 in the group of patients and a comparative analysis of the obtained results with data from practically healthy individuals were carried out .

Table 1 presents the results of studies on the distribution of allele and genotype frequencies of the MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 genes in the general group of children with CGN.

As can be seen from Table 1, a significantly significant GG genotype of the MMP 9 gene (A -8202G) rs 11697325 was detected 1.66 times more often in the group of patients than in the control (OR= 2.058; χ2= 4.152 (p=0.041584); 95% CI: 0.464 >0.861> 1.597). The AA genotype of the MMP 9 (A-8202G) rs 11697325 gene tended to be significant. Our results also showed that the presence of the AA genotype of the MMP 9 gene (A-8202G) rs 11697325 had a protective effect, it was more common in the control group (OR=0.466; χ2= 3.527 (p=0.060362); 95% CI: 0.207 >0.466 > 1.045), however, as can be seen from the obtained data, the obtained data did not reach Pearson's reliability. According to the analysis of the results, the presence of the AG genotype of the MMP9 gene (A-8202G) rs11697325 did not have a significant association with the disease, and it occurred to the same extent in the main and control groups (OR=0.861; χ2=0.225 (p=0.634); 95% CI: 0.464 > 0.861 > 1.597).

When analyzing the A and G alleles of the MMP 9 gene (A-8202G) rs 11697325, it was found that the G allele is more common in patients with CNS (62.25% and 49.25%, respectively), and A alleles are most noted in healthy individuals. The frequency distribution of the A and G alleles of the MMP 9 (A-8202G) rs 11697325 gene did not give statistically significant results, but the presence of the G allele of the MMP 9 (A-8202G) rs 11697325 gene tended to be significant (OR=1.42; χ2=2.674 (p = 0.101998); 95% CI: 0.932 > 1.421 > 2.167).

An analysis of literature data did not reveal any studies on the analysis of possible associations between MMP9 (A8208G) and TIMP2 (C5367) gene polymorphisms and the development of chronic nephritic syndrome in children. However, several studies have been found to study associations between genetic polymorphisms of these genes and calcified aortic stenosis in the adult population, as well as the development of spontaneous abortions in the first trimester in pregnant women. For example, in a study by Mashkina et al. (2016), it was found that the presence of pathological genotypes of the MMP9 gene (rs11697325) increases the risk of spontaneous abortions in pregnant women in the first trimester. These results indicate an increased risk of developing pathological changes in the body of individuals with MMP9 gene polymorphism (rs11697325), which is confirmed by the results of this study.

MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 was carried out in a group of sick children with nephrotic form of glomerulonephritis and a comparative analysis of the obtained results with data from practically healthy individuals.

Table 2 presents the results of studies on the distribution of frequencies of alleles and genotypes of the gene MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 in the group of children with nephrotic form.

In the studied subgroup of patients, a significantly significant GG genotype of the MMP 9

Table 2.

Distribution of allele and genotype frequencies of the MMP9 (A-8202G) gene in patients with nephrotic form and healthy children

MMP 9 gene (A-8202G)	Patients , n=36 (%)	Control, n=67 (%)	χ2	OR (95% CI)
A	27 (37.50)	68 (50.75)		0.324 >0.582> 1.045
G	45 (62.50)	66 (49.25)	3.307 (p=0.068982)	0.957 >1.717> 3.083
AA	6 (16.67)	16 (23.88)	0.726 (p=0.394338)	0.225 >0.638> 1.805
AG	15 (41.67)	36 (53.73)	1.364 (p=0.242922)	0.271 >0.615> 1.394
GG	15 (41.67)	15 (22.39)	4.216 (p=0.04004)	1.03 >2.476> 5.952

Note: χ 2 – Pearson confidence indicator; O R – relative risk.

(A-8202G) rs 11697325 gene was detected 1.86 times more often than in the control group (OR= 2.476; χ2= 4.216 (p=0.04004); 95% CI: 1.03 >2.476 > 5.952).). According to the analyzes, the presence of the AG genotype of the MMP9 gene (A-8202G) rs11697325 did not have a significant association with the disease, but it was slightly more common in healthy controls (OR=0.615; χ2= 1.364 (p=0.242922); 95% CI: 0.271 >0.615> 1.394).

In contrast with the general group, the AA genotype of the MMP 9 (A-8202G) rs 11697325 gene did not tend to be significant. However, as can be seen from the data obtained, allelic variants tended to be significant but did not reach the true significance according to Pearson. Thus, the presence of the GG genotype of the MMP 9 (A-8202G) rs 11697325 gene can serve as a predictor of the development of nephrotic glomerulonephritis in children. When analyzing the A and G alleles of the MMP 9 gene (A-8202G) rs 11697325, it was found that the G allele more common in patients with nephrotic form of CNS (62.50% and 49.25%, respectively), and the A allele was more often observed in healthy individuals. The frequency distribution of the A and G alleles of the MMP 9 (A-8202G) rs 11697325 gene did not reveal statistically significant results, however, the presence of the G allele of the MMP 9 (A-8202G) rs 11697325 gene tended to be significant (OR=1.717; χ2=3.307 (p =0.068982), 95% CI: 0.957>1.717>3.083).

Thus, the presence of the GG genotype of the MMP 9 (A-8202G) rs 11697325 gene can serve as a predictor of the development of the nephrotic form of the disease in children.

MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 was carried out in a group of sick children with hematuric form of glomerulonephritis and a comparative analysis of the results obtained with practically healthy individuals. Table 3 presents the results of studies on the distribution of frequencies of alleles and genotypes of the gene MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 in the group of children with hematuric form of the disease.

No significant associations were found in the studied subgroup of patients. The GG genotype of the MMP 9 gene (A-8202G) rs 11697325 was equally detected in both groups (OR= 1.387; χ2= 0.475 (p=0.490661); 95% CI: 0.546>1.387>3.52). According to the analyzes, the presence of the AG genotype of the MMP9 gene (A-8202G) rs11697325 did not have a significant association with the disease, but it was slightly more common in patients with hematuric CNS compared with the control group (OR=1.292; χ2= 0.366 (p=0, 54495); 95% CI: 0.564>1.292>2.96). In contrast to the general group, the AA genotype of the MMP 9 (A-8202G) rs 11697325 gene did not tend to be significant. However, as can be seen from the data obtained, allelic variants tended to be significant, but did not reach the true significance according to Pearson.

Table 3.

Distribution of allele and genotype frequencies of the MMP9 (A-8202G) gene in patients with hematuria and in healthy children.

MMP 9 gene (A-8202G)	Patients , n=35 (%)	Control, n=67 (%)	χ2	OR (95% CI)
A	29 (41.43)	68 (50.75)		0.383 >0.687> 1.231
G	41 (58.57)	66 (49.25)	1.601 (p=0.205812)	0.812 >1.457> 2.612
AA	4 (11.43)	16 (23.88)	2.261 (p=0.132633)	0.126 >0.411> 1.343
AG	21 (60.00)	36 (53.73)	0.366 (p=0.54495)	0.564 >1.292> 2.96
GG	10 (28.57)	15 (22.39)	0.475 (p=0.490661)	0.546 >1.387> 3.52

Note: χ 2 – Pearson confidence indicator; O R – relative risk.

Conclusions.

When analyzing the A and G alleles of the MMP 9 gene (A-8202G) rs 11697325 in patients with hematuric CNS, it was found that the G allele more often occurs in patients with hematuric form of CNS (58.57% and 49.25%, respectively), and the A allele is more common in healthy individuals. The distribution of A and G allele frequencies of the MMP 9 gene (A-8202G) rs 11697325 did not reveal statistically significant results (OR=1.457; $\chi 2$=1.601 (p=0.205812); 95% CI: 0.812 >1.457>2.612).

Thus, the presence of the GG genotype of the MMP 9 (A-8202G) rs 11697325 gene in this study was not associated with the development of the hematuric form of glomerulonephritis in children.

MMP 9 (A-8202G) rs 11697325 and TIMP 2 (C536T) rs 11551797 was carried out in a group of sick children with a mixed form of glomerulonephritis and a comparative analysis of the results obtained with data from practically healthy individuals.

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