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New aspects of the genetic disposition of various forms of chronic nephritic syndrome in children.

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Аннотация

В системе всеобщей диспансеризации детского населения рекомендуется выделить группу детей с хроническим нефритическим синдромом, обусловленным генетической предрасположенностью, как группу высокого риска и проведения диспансерного наблюдения. Выявленные ассоциации взаимосвязи генотипа GG гена MMP9 (A-8202G) rs11697325 с развитием болезни, в частности его нефротической и смешанной форм, служат важным диагностическим и прогностическим маркером данной патологии и подхода к своевременному лечение.

Ключевые слова: хронический нефритический синдром, металопротеиназа, генотип.

Annotation

Knowing hereditary predisposition, in the system of general medical examination of the child population, it is recommended to single out a group of children with chronic nephritic syndrome due to a genetic predisposition as a high-risk group and conduct dispensary observation.

The revealed associations of the relationship between the GG genotype of the MMP9 (A-8202G) rs11697325 gene and the development of the disease, in particular its nephrotic and mixed forms, serve as an important diagnostic and prognostic marker of this pathology and the approach to timely treatment.

Key words: chronic nephritic syndrome, metalloproteinase, genotype.

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Introduction. Matrix metalloproteinases (MMPs) are a 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 will be carried out in the immunoregulation laboratory of the Institute of Immunology and Human Genomics in Tashkent. In the DNA of blood leukocytes of patients and practically healthy, gene polymorphism will be determined. The isolated DNA will be carried out by the standard nucleosorb method using Diatom™ kits. Typing of DNA samples will be carried out using a specific oligonucleotide primer with gene regions. PCR analysis 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 .

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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%)		0.461 >0.704> 1.073
G	127 (62.25%)	66 (49.25%)	2.674 (p=0.101998)	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

As can be seen from Table. 4.1.1, 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; $\chi2$= 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; $\chi2$= 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; $\chi2$=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

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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; $\chi 2$=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.

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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