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Molecular-Genetic Mechanisms of the Development of Juvenile Idiopathic Arthritis in Children

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Summary: The article presents clinical and genetic features and prognostic criteria for juvenile idiopathic arthritis. The clinical features of the disease, the results of laboratory analysis are important when choosing an effective method of treatment. Depending on the severity of the disease, the characteristics of the clinical course and the results of the functional laboratory analysis, drug and surgical treatment of joints is recommended.

Key words: juvenile idiopathic arthritis, diagnosis, prognosis.

Juvenile idiopathic arthritis (JIA) is the most common multifactorial rheumatic disease that develops in children under 16 years of age [1]. The International League of Rheumatological Associations distinguishes 7 variants of JIA: systemic, oligoarticular (persistent and spreading), polyarticular (positive or negative for rheumatoid factor), arthritis associated with enthesitis, psoriatic arthritis, and undifferentiated arthritis [2]. In Caucasians, oligoarticular JIA is the most common variant of the disease, diagnosed in 50% of cases [3]. The incidence of JIA in North America and Europe varies from 16 to 160 cases per 100,000 children, with an increase in the number of cases from 4 to 14 per year [3]. In patients with oligoarticular JIA, four or fewer joints are affected at the onset and during the first 3 months of the disease. At the same time, in some children, the disease progresses over time and acquires a polyarticular course. Rheumatoid factor (RF) negative polyarticular JIA is the second most common variant of the disease. It is diagnosed in 10–15% of JIA patients and is characterized by involvement of more than four joints at onset. RF-positive polyarticular JIA is clinically similar to adult rheumatoid arthritis (RA) and is rare. Systemic arthritis is the 3rd most common. In Caucasian populations, systemic arthritis in the structure of JIA is 5-15%, in Japan - 50%, in the Russian Federation - 22%. Since JIA combines subtypes that are heterogeneous in their clinical manifestation,

It should also be noted that JIA predisposition loci may be associated with other autoimmune diseases. This hypothesis is supported by cases of JIA associated with autoimmune diseases such as type 1 diabetes mellitus (DM) [4], autoimmune thyroiditis [5], and celiac disease [6]. The genetic component makes a significant contribution to the development of JIA. Twin methods of genetic analysis showed a 25–40% degree of JIA concordance in identical twins, which is significantly higher than the incidence of this disease in the general population, reaching an average of one case per 1000 people [7], while the incidence of JIA in sibling couples is approximately 15– 30 times higher than the prevalence of JIA in the general population [4].

Human major histocompatibility complex (HLA) genes are believed to be the main locus of predisposition to JIA, accounting for approximately 17% of familial clustering of the disease [8]. To date, many studies have been carried out regarding the evaluation of the role of HLA genes in the pathogenesis of JIA, and the association of several HLA loci has been confirmed in various ethnic groups. For example, for HLA class I genes, the association of HLA-A2 and HLA-B27 alleles in JIA patients with undifferentiated spondyloarthritis has been repeatedly demonstrated [9, 10]. Juvenile idiopathic arthritis predisposition genes found in population-based case-control studies. The candidate gene approach has been widely used in studies of genetic predisposition to JIA.

However, the success achieved with this approach has been very modest. The low performance of this type of study may be largely due to small sample sizes, which increase the risk of false positive results. For only two loci, a genetic association with disease has been demonstrated in more than two large-scale case-control studies. These are the genes for tyrosine phosphatase type 22 (PTPN22; marker rs2467701) and the α-subunit of the interleukin 2 receptor (IL2RA; rs2104286; In general, the T allele of the PTPN22 gene (polymorphism C1858T; rs2467701) showed the most significant association with JIA in European

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populations (OR = 1.311, p T of the PTPN22 gene leads to the amino acid substitution of arginine for tryptophan (R620W) in the molecule of lymphoid tyrosine phosphatase Lyp, which is specifically expressed in immune cells and plays a role in the inhibition of signals from T- and B-cell receptors. The Lyp 620W variant is more active than Lyp 620R, and this leads to a pronounced ability to suppress the signal from the T-cell receptor [14]. It has been shown that the presence of the high-risk allele 1858T in the PTPN22 gene is directly related to defects in the regulation and disturbances in the central and peripheral tolerance of B lymphocytes. In addition, the Lyp 620W variant is more sensitive to degradation by the cytoplasmic calpain protease, which ultimately leads to a reduced content of this variant and hyperactivity of T and B cells. Due to its key role in immune regulation, the presence of the predisposing 1858T allele of the PTPN22 gene may increase the risk of impaired immune tolerance,

Juvenile idiopathic arthritis predisposition genes identified by screening for loci previously associated with rheumatoid arthritis. Using the method of whole genome scanning, a lot of genetic variants have been discovered, each of which is involved in the pathogenesis of several autoimmune diseases. Since the molecular mechanism of the pathogenesis of autoimmune and inflammatory diseases has a number of similar features, they may also share common susceptibility genes. In this regard, geneticists began to study the loci, for which association with such an autoimmune disease as RA was proved, for a possible connection with JIA. Subsequent genetic studies have shown the presence of loci involved in the etiology of both JIA and RA. TRAF1/C5 (tumor necrosis factor receptor-associated factor 1/complement component 5). In a primary analysis of nine loci previously associated with RA, two (STAT4 and TRAF1/C5) were found to be strongly associated with JIA [21]. For the other two loci (TNFAIP3 and PRKCQ), the observed association was not as significant. In early studies regarding the association of the TRAF1/C5 gene with JIA, mixed results were obtained. The marker rs10818488 showed an association with polyarticular JIA (OR = 1.46, p = 0.004) in the Dutch [22], while a weak association between the marker rs3761847 and JIA was described in US Caucasians (OR = 1.45, p = 0.03551) [23]. However, when analyzing an independent sample of North American Caucasians, the relationship between the marker rs3761847 and JIA was not confirmed [16]. Thus, the results obtained by Hinks et al. [31] confirmed the association of the TRAF1/C5 locus with JIA. The TRAF1 and C5 genes lie next to each other on chromosome 9q33-34. The former encodes factor 1, which binds to the tumor necrosis factor receptor TNFR and is a member of the TRAF family of proteins that mediate signal transduction from various TNFR family receptors. The heterodimeric TRAF1/TRAF2 complex controls the activation of MAPK8/JNK protein kinases and the nuclear transcription factor NF-κB as a result of the stimulatory effect of tumor necrosis factor (TNF) α. As a result of this activation, NF-κB is translocated into the nucleus, which is accompanied by subsequent induction of the expression of numerous pro-inflammatory and anti-apoptotic genes [24]. The TRAF1/TRAF2 complex also interacts with the apoptosis inhibitor proteins IAP, leading to stimulation of the anti-apoptotic response. As is known, TNF-α acts as one of the most important regulators of the acute inflammatory response in patients with JIA. Thus, as mediators of the pro-inflammatory signaling mechanism induced by TNF-α, the TRAF1 gene can be considered as a functional candidate for association with the development of JIA. The C5 gene encodes the fifth component of complement, which plays an important role in the processes of inflammation and death of foreign cells. During activation, proteolysis of C5 occurs with the formation of the C5a peptide, called anaphylotoxin, which has a powerful antispasmodic and chemotoxic effect, and C5b, which is a component of the complement membrane attack complex. Significant activation of the complement system in the synovial fluid of patients with oligoarticular JIA was shown [5]. Thus, the C5 gene could also be considered as a possible candidate for JIA association. Among the markers associated with JIA at the TRAF1/C5 locus, two (rs10818488 and rs2900180) are located between these genes, while the third (rs3761847) is located in intron 1 of the TRAF1 gene. The functional significance of these markers is unknown. It is suggested that the A allele of the rs10818488 marker, which predisposes to JIA, is involved in the creation of the EP300 binding site, a histone acetyltransferase that regulates transcription through chromatin remodeling [6]. The absence of the A allele can disrupt the binding of the transcription activator EP300 to this DNA region. The EP300 factor may be involved in the regulation (activation) of both the TRAF1 gene and the C5 gene. Therefore, the rs10818488 marker can claim the role of a possible etiological variant in the TRAF1/C5 locus.

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Conclusion. JIA is a polygenic disease that develops with the participation of many genes located outside the HLA locus and for the most part demonstrate a weak genetic effect on predisposition to this disease. Also for this disease, many genes have been identified that are involved in the pathogenesis of other autoimmune diseases, especially JIA. Most of the genes predisposing to JIA are involved in the regulation of the immune system and the regulation of inflammation, which indicates the main role of impaired immune homeostasis. Differentially expressed genes can be used to identify major subtypes of JIA in the early stages of the disease [7]. This is most noteworthy as no clear clinical criteria have been developed to distinguish between these subtypes. Gene expression profiles can also be useful for predicting disease outcome or response to therapy [12]. Pharmacogenetics and pharmacogenomics should be more widely used to identify molecular markers (genes, SNPs) that influence the therapeutic efficacy of anti-inflammatory and other classes of drugs used in the treatment of JIA. For example, the association of the rs3763980 marker in the SLC16A7 gene with a weak response of JIA patients to methotrexate treatment was shown [8]. The pharmacogenetic approach will make it possible to discover signaling and metabolic pathways and genes that will help control the effectiveness of drugs used in the treatment of childhood arthritis, as well as to choose an individual strategy to achieve the greatest effectiveness of therapy. Discovery of new JIA susceptibility genes such as JMJD1C and NAA25,

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