көрсеткіштері мен шетелдік деректерге салыстырмалы талдау жасалды. Зерттеу нәтижесінде мектеп оқушылары арасында миопияның таралу деңгейі ресми статистика мәліметтерінен жоғары екендігі, сондай-ақ көруді түзету құралдарымен қамтамасыз етілу деңгейінің төмендігі анықталды. Ерте диагностиканың негізгі мәселелері ретінде скринингтік тексерулердің жеткіліксіз ұйымдастырылуы және мектеп медицина қызметкерлеріне түсетін жүктеменің жоғары болуы айқындалды. Алынған нәтижелер профилактикалық іс-шаралар жүйесін жетілдіру, ата-аналар мен педагогтардың ақпараттандырылуын арттыру, сондай-ақ балаларда миопияны ерте анықтау мен оның үдеуін баяулату бойынша жүйелі тәсілді енгізу қажеттілігін растайды.
Түйінді сөздер: миопия, аккомодация, көру өткірлігі, экран уақыты, профилактика.

Childhood myopia: challenges, diagnosis, and management strategies

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Abstract
This article examines current issues related to the prevalence of myopia among school-aged children, as well as the features of its early diagnosis and prevention in the context of increasing visual load. The author conducted a comprehensive analysis of risk factors contributing to the development of myopia, including screen time exposure, educational workload, reduced time spent outdoors, and genetic predisposition. The study employed a multilevel approach, including questionnaires administered to primary, middle, and high school students in Almaty city and Zhetysu region, as well as preventive examinations aimed at the early detection of refractive errors. To obtain objective data, descriptive statistical methods and comparative analysis of official statistical indicators of the Republic of Kazakhstan and foreign countries were used. The results revealed a high prevalence of myopia among schoolchildren, exceeding official statistical data, as well as a low rate of adequate vision correction. The main challenges in early diagnosis were identified, including insufficient organization of screening examinations and the high workload of school medical personnel. The findings confirm the need to improve preventive strategies, increase awareness among parents and teachers, and implement a systematic approach to early detection and slowing the progression of myopia in children.
Keywords: myopia, accommodation, visual acuity, screen time, prevention.

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IDENTIFICATION OF HUB GENES AND SIGNALING PATHWAYS IN REMISSION-STAGE JUVENILE IDIOPATHIC ARTHRITIS BY BIOINFORMATICS ANALYSIS

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Abstract
Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of chronic inflammatory joint disorders in children under 16, often resulting in disability, growth impairment, and systemic complications. Achieving clinical remission on medication (CRM) is a key treatment goal in JIA. However, transcriptomic data indicate that drug-induced remission may not restore immunological normalcy, necessitating biomarkers to identify this state and predict long-term stability. To identify hub genes and signaling pathways characterizing the persistent immune imbalance in the granulocyte transcriptome of patients with polyarticular JIA in CRM. Transcriptomic data from granulocytes (GSE41831) of patients with polyarticular JIA in CRM on combination therapy (methotrexate and etanercept) and healthy children were analyzed. Differentially expressed genes (DEGs) were identified using GEO2R with thresholds of adjusted p-value < 0.05 and $|\text{Log FC}| \geq 0.5$.

Functional enrichment analysis was performed using Enrichr through Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome databases. A protein–protein interaction (PPI) network was constructed using STRING and visualized in Cytoscape, with hub genes identified via the CytoHubba plugin with the maximal clique centrality (MCC) algorithm. The expression of top hub genes was statistically validated. A total of 232 DEGs were identified from 54,675 analyzed genes, of which 99 were downregulated and 133 upregulated. Functional enrichment analysis clustered into two major functional categories: reorganization of the actin cytoskeleton and dysregulation of amino acid metabolism alongside pro-inflammatory signalingю These processes align with the activated state of granulocytes, indicating persistent cellular activity even during clinical remission. The PPI network comprised 126 nodes and 498 edges. The MCC algorithm identified 10 hub genes, among which *HSP90AB1* and *HSP90AA1* were the most prominent, suggesting they act as key regulators of the observed molecular imbalance. Despite achieving clinical remission, patients with polyarticular JIA exhibit a persistent, activated transcriptomic profile in their granulocytes. The elevated expression of *HSP90AB1* and *HSP90AA1* indicates persistent cellular stress and may represent these genes as candidate biomarkers for subclinical immune imbalance and potential therapeutic targets to achieve deeper remission. The results obtained lay the foundation for further research aimed at translating fundamental discoveries into clinical practice.
Keywords: juvenile idiopathic arthritis, signaling pathways, hub genes, bioinformatics analysis, remission on medication.

Inrtoduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic inflammatory joint diseases in children and the most common rheumatic disorder in the pediatric population [Zaripova L.N. et al., 2021]. Among its subtypes, the polyarticular form, characterized by involvement of five or more joints, involves a complex pathogenesis engaging both innate and adaptive immunity [Zaripova L.N. et al., 2021]. Despite significant therapeutic advances, including disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate (MTX) and biologic agents, achieving sustained remission remains challenging. A substantial proportion of patients experience an incomplete response, drug resistance, or significant adverse events. Notably, MTX intolerance, manifesting as nausea, vomiting, and behavioral symptoms, affects up to 73% of patients and is a leading cause of poor treatment adherence [Wibrand C. et al., 2024]. This clinical challenge underscores the need for a deeper understanding of the molecular underpinnings of JIA to develop more personalized and effective therapeutic strategies.

Achieving clinical remission on medication (CRM) is a primary goal in JIA management. However, accumulating evidence suggests that CRM is not equivalent to full restoration of immunological homeostasis. The transcriptomic study by Jiang K. et al. (2013), based on dataset GSE41831, convincingly demonstrated that patients with polyarticular JIA in remission on either MTX monotherapy or MTX combined with a TNF-α inhibitor (etanercept) still show significant deviations in peripheral blood gene expression profiles compared with healthy children [Jiang K. et al., 2013]. This indicates a persistent subclinical immune imbalance that may underlie the risk of flare and determine long-term outcomes. Consequently, identifying the specific molecular mechanisms and regulatory hub genes that sustain this state of "controlled inflammation" remains a critical and insufficiently explored challenge.

In this context, granulocytes (neutrophils) are of particular interest. As primary effector cells of innate immunity, they play a pivotal role in initiating and sustaining inflammation in arthritis, with growing evidence implicating their active participation in JIA pathogenesis [Zaripova L.N. et al., 2021]. Recent studies further indicate that neutrophils in JIA exist in a state of chronic "priming" or heightened readiness. Their abnormal activity, reflected by sustained elevated levels of specific granular proteins such as HNL and MPO, persists despite effective drug suppression of clinical activity and correlates with low-grade inflammatory activity [Backlund M. et al., 2021]. Notably, in the work by Jiang K. et al. (2013), the most pronounced transcriptomic deviations from normal were found precisely in the granulocytes of patients who achieved CRM on the MTX and etanercept combination [Jiang K. et al., 2013]. This makes a targeted analysis of the granulocyte transcriptome

in this clinical state especially relevant for identifying molecular determinants of the persistent imbalance.

Modern bioinformatics approaches offer a powerful and objective toolkit for this task. Big data analysis methods, including identification of differentially expressed genes (DEGs), functional enrichment of biological pathways (GO, KEGG, Reactome), and construction of protein-protein interaction (PPI) networks followed by hub gene identification, enable the systematic discovery of key molecular patterns associated with pathological states [Nagaraj K. et al., 2018]. Applying these methods to well-characterized public datasets like GSE41831 represents a valuable hypothesis-generating strategy. Applying an independent, modern bioinformatics pipeline to re-analyze this data offers an opportunity not only to verify earlier findings but also to potentially discover new regulatory networks and key genes associated with "remission without normalization." Our re-analysis provides a complementary methodological perspective. It should be noted that in Kazakhstan, bioinformatics analysis for identifying key genes and signaling pathways has already been successfully applied to the study of other conditions. An example is the work by Abilbayeva A.A. et al., where a similar methodological pipeline (GEO2R, Enrichr, STRING, Cytoscape) was used to identify hub genes and pathogenic pathways in bronchopulmonary dysplasia in preterm neonates [Abilbayeva A.A. et al., 2025]. The present study continues this methodological line, adapting a proven approach to investigate the molecular basis of juvenile idiopathic arthritis, thereby highlighting the versatility and reproducibility of this bioinformatics method.

This study hypothesized that a comprehensive bioinformatics re-analysis of granulocyte transcriptomic data from patients with polyarticular JIA who achieved CRM on combined MTX and etanercept therapy would identify specific hub genes and signaling pathways characterizing the persistent immune imbalance in this state. Accordingly, the objective of this study was to identify these key hub genes and signaling pathways associated with persistent immune imbalance in the granulocyte transcriptome of such patients through comprehensive bioinformatics analysis.

Materials and Methods

Data collection and cohort characterization

Transcriptomic data associated with JIA were obtained from the publicly accessible Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (NCBI). The dataset GSE41831, generated on the GPL570 platform (Affymetrix Human Genome U133 Plus 2.0 Array), was selected for analysis. The primary study associated with this dataset [Jiang K. et al., 2013] aimed at the genomic characterization of remission in JIA and included samples of peripheral blood mononuclear cells (PBMCs) and granulocytes from patients who achieved clinical remission on therapy.

For this secondary analysis, we purposefully selected a subset of samples. Only granulocyte (neutrophil) samples were included. The study group consisted of 12 patients with the polyarticular (rheumatoid factor-negative) subtype of JIA who were in a state of CRM on background combination therapy with MTX and a tumor necrosis factor-α inhibitor (etanercept). The control group comprised 13 samples from healthy children.

Identification of Differentially Expressed Genes (DEGs)

The GSE41831 data were processed using the GEO2R web application, which performs analysis based on R software to identify differentially expressed genes between sample groups. P-values were adjusted using the Benjamini-Hochberg method, and the threshold criteria for DEG selection were an adjusted p-value < 0.05 and an absolute log fold change $|\log FC| \geq 0.5$. GEO2R provided visual outputs including volcano plots, UMAP, box plots, and Venn diagrams. The primary analysis identified 300 differentially expressed probes. After conversion to gene symbols and filtering out non-coding and non-annotated transcripts, a final working set of 232 unique DEGs was formed and used for all subsequent analyses.

Gene Ontology and pathway enrichment analysis

To elucidate the biological functions and molecular mechanisms, a comprehensive enrichment analysis of the DEGs was performed. Gene Ontology (GO) enrichment analysis characterized the associated molecular functions, biological processes, and cellular components. Pathway analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome databases complemented the picture by identifying key metabolic and signaling pathways. This analysis was conducted using the bioinformatics platform Enrichr, with result visualization performed using its built-in tools.

Protein-Protein Interaction (PPI) network analysis and hub gene identification

The online tool STRING was used to analyze and predict interactions between proteins encoded by the identified DEGs. The analysis of the 232 DEGs was performed with a minimum required interaction confidence threshold of 0.4. The resulting network was exported and visualized in Cytoscape (version 3.10.3). The CytoHubba plugin was used to identify the most significant network nodes (hub genes). Analysis was conducted using the Maximal Clique Centrality (MCC) algorithm, which was selected for final ranking based on its results. Consequently, the top 10 hub genes were identified, among which *HSP90AB1* and *HSP90AA1* demonstrated the highest significance.

Statistical validation of key hub gene expression

For independent statistical verification of the expression of the key hub genes *HSP90AB1* and *HSP90AA1*, an additional analysis was performed based on raw expression data from the GSE41831 dataset using IBM SPSS Statistics software (version 29). Data normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The non-parametric Mann-Whitney U test was applied to compare the main and control groups. The level of statistical significance was set at $p < 0.05$. Based on the analysis results, box plots were constructed to visually represent the distribution of expression levels for these genes.

Results

Sample data information

To assess data distribution and identify differences between the group of patients with polyarticular JIA in CRM and the control group, the GSE41831 dataset was analyzed. Visual inspection of box plots confirmed adequate data normalization. UMAP analysis results showed that samples from the patient and healthy control groups formed clearly separable clusters on a two-dimensional plot, indicating profound transcriptomic differences between the groups that persist even in a state of clinical remission (Figure 1).

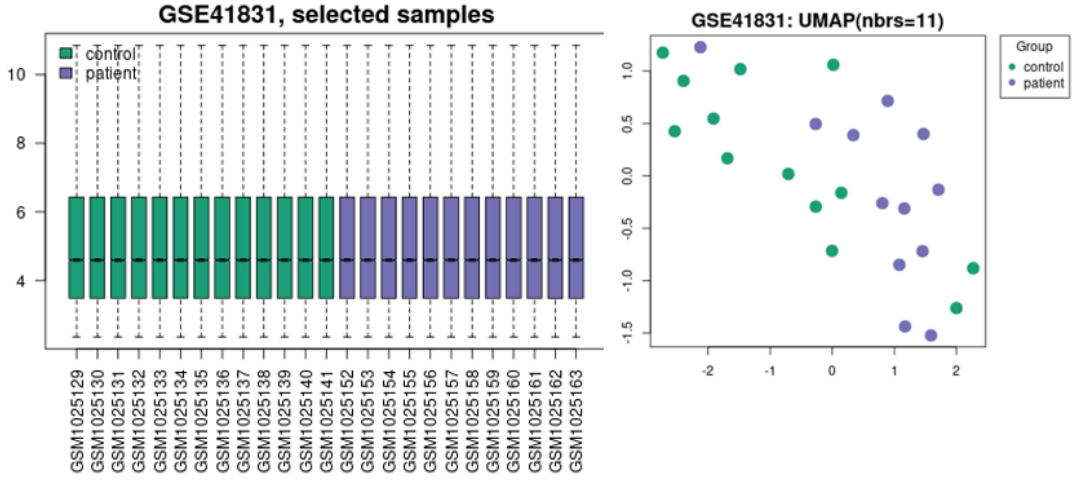

Figure 1. Gene set assessment. A box-and-whisker plot with samples on the horizontal axis and log2-transformed gene expression values on the vertical axis. UMAP analysis performed for the two groups

DEG analysis

Analysis using GEO2R identified 232 DEGs out of 54,675 analyzed genes. Among these, 99 genes were downregulated, and 133 were upregulated. A volcano plot clearly illustrates the distribution of DEGs according to the degree of expression change and statistical significance (Figure 2).

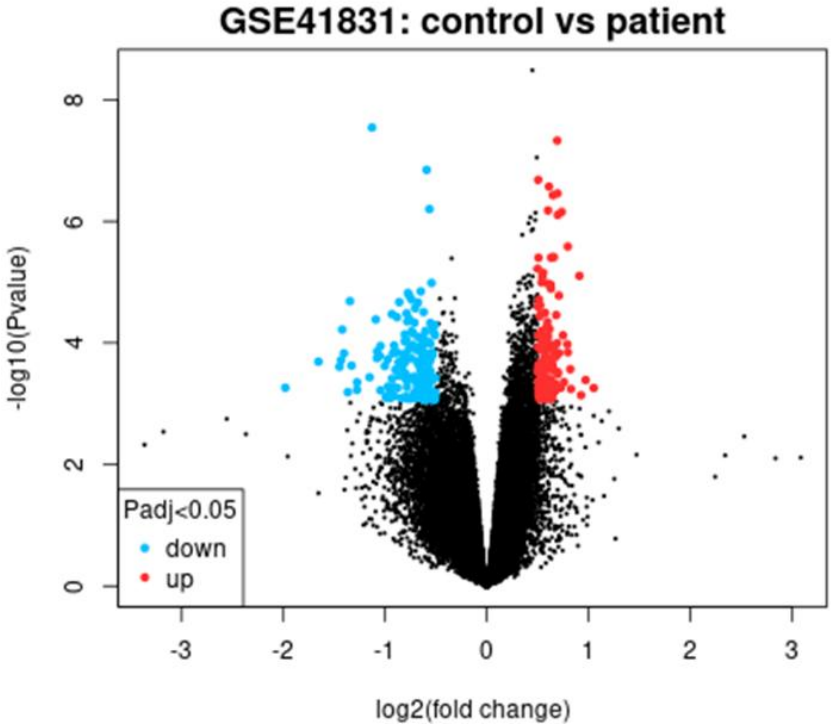

Figure 2. Results of differential gene expression analysis. A volcano plot illustrating gene expression in the two groups. The horizontal axis represents log2FC values, and the vertical axis represents -log10 (adjusted p-value) values. Upregulated genes are highlighted in red, downregulated genes in blue, and genes that do not meet the significance criteria ($p < 0.05$ and $|\text{Log FC}| \geq 1$) are shown in black

Pathway enrichment analysis

To identify biological functions and signaling pathways associated with the identified DEGs, a comprehensive functional enrichment analysis was performed using the Enrichr platform. The analysis was conducted separately for genes with upregulated and downregulated expression.

GO enrichment analysis for upregulated genes identified 1057 significant annotations in the Biological Process (BP) category, 110 in the Cellular Component (CC) category, and 216 in the Molecular Function (MF) category. Among the most significant biological processes were those related to the regulation of response to external and biotic stimuli, cytoskeleton reorganization, and defense response. Enriched cellular component terms were associated with the actin cytoskeleton and specific neutrophil granules, while molecular function terms included JUN kinase binding and ATP binding.

For downregulated genes, GO analysis revealed 733 significant BP annotations, 112 CC annotations, and 145 MF annotations. Enriched biological processes were linked to the regulation of lamellipodium morphogenesis and mitochondrial membrane permeability (Figure 3).

KEGG pathway analysis identified 135 significant pathways for upregulated genes and 158 for downregulated genes (Figure 4). The most significant pathways for upregulated genes included the NOD-like receptor (NLR) signaling pathway, necroptosis, and Th17 cell differentiation, while for downregulated genes, they included platelet activation, the insulin signaling pathway, and epidermal growth factor receptor (ERBB) signaling pathways.

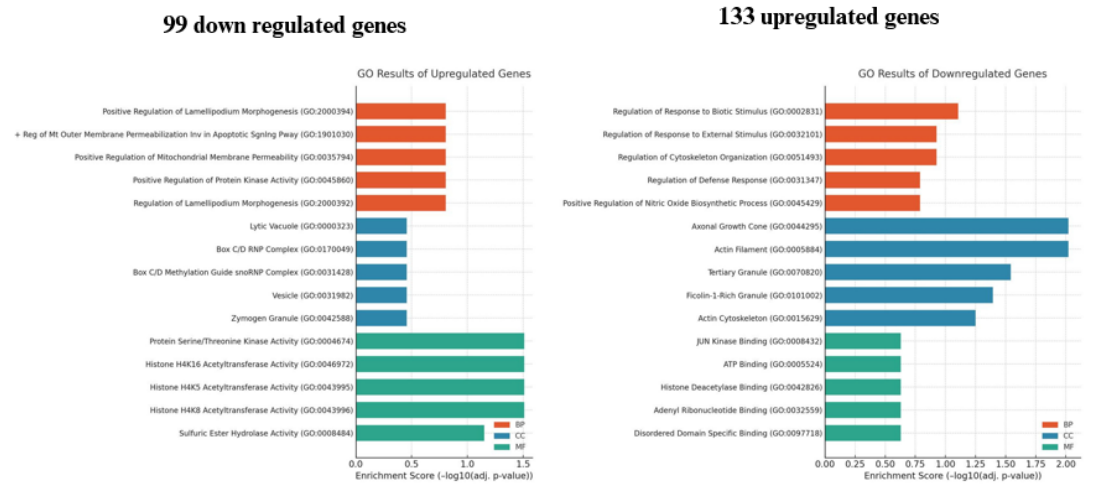

Figure 3. Graphical representation of Gene Ontology (GO) enrichment analysis. The top five genes associated with each GO category (BP – Biological Process; CC – Cellular Component; MF – Molecular Function) for the downregulated and upregulated gene sets

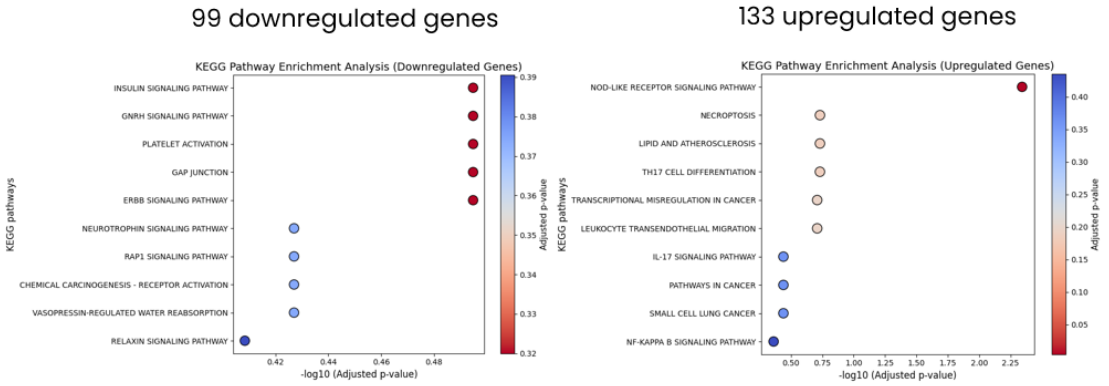

Figure 4. Graphical representation of KEGG pathway enrichment analysis. The 10 most significantly enriched KEGG pathways for the downregulated and upregulated gene sets

Reactome pathway analysis identified 496 significant pathways for upregulated genes and 459 for downregulated genes (Figure 5). For the upregulated group, pathways such as branched-chain amino acid metabolism, inflammasome function, and innate immune system activation were prominent. For the downregulated group, pathways involving intracellular signaling mediated by AKT, erythropoietin, and integrins were highlighted.

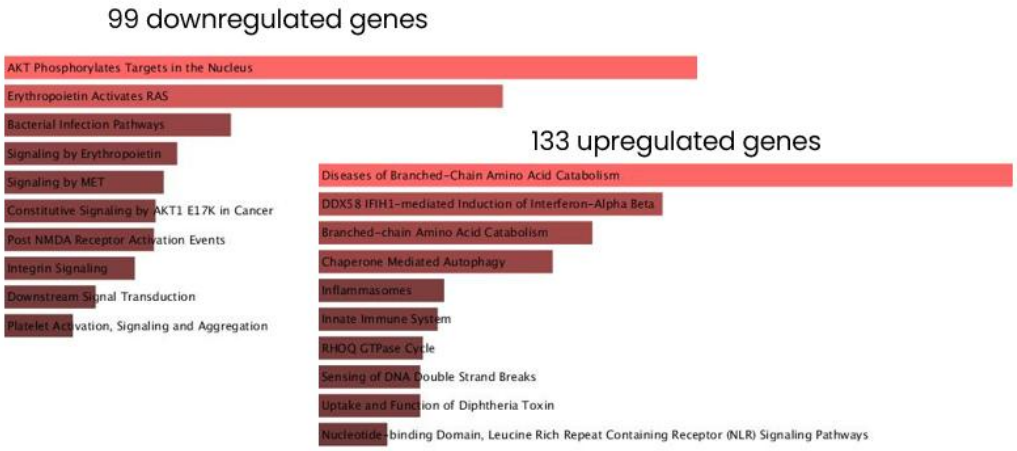

Figure 5. Graphical representation of Reactome pathway enrichment analysis. The 10 most significantly enriched Reactome pathways for the downregulated and upregulated gene sets

PPI network construction and hub gene identification

To study functional relationships among the 232 identified DEGs, a molecular interaction network was constructed using the STRING database. The resulting network consisted of 126 nodes and 498 edges (Fig. 6). Application of the MCC algorithm identified 10 key hub genes likely to play central roles in the observed pathological processes: *HSP90AB1, HSP90AA1, SRC, ATM, FOXO1, RPS6KB2, SNRNP70, RBM25, HNRNPU, EZR*. Particular attention in this study is given to the genes *HSP90AB1* and *HSP90AA1*, whose products are key participants in the protein-protein interactions (highlighted in red in Figure 6).

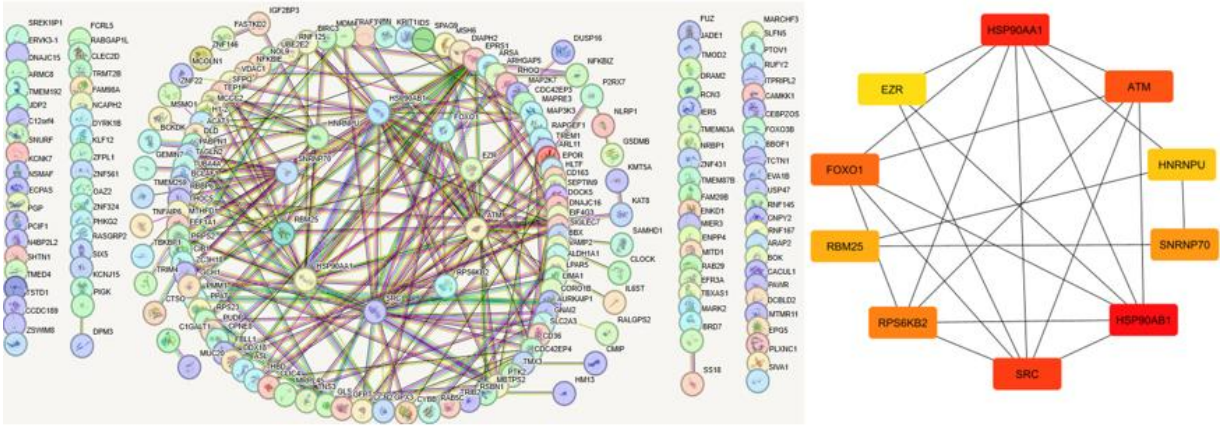

Figure 6. PPI network analysis and hub gene identification. PPI network analysis based on the STRING database. The ten hub genes identified using the MCC ranking method

Statistical validation of key hub gene expression

The statistical significance of the differential expression of the two main hub genes, *HSP90AB1* and *HSP90AA1*, was independently confirmed based on raw data using the non-parametric Mann-Whitney U test. The expression level of both genes was significantly higher in the patient group compared to the control group (for *HSP90AB1* $p < 0.001$, for *HSP90AA1* $p = 0.004$). The distribution of expression levels is presented in Figure 7 (box plots).

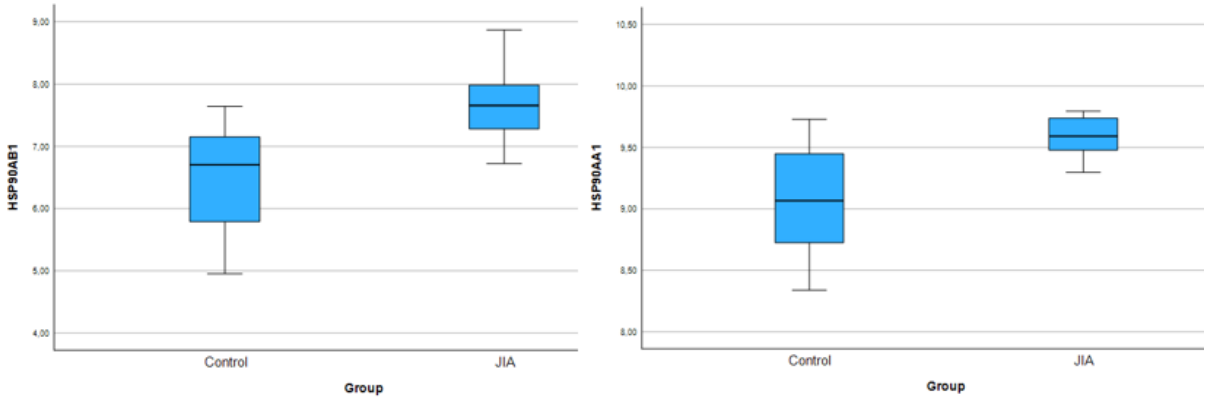

Figure 7. A box-and-whisker plot demonstrating the expression levels of the identified hub genes between the case and control groups

Discussion

Achieving CRM remains a primary, yet not always definitive, goal in treating polyarticular JIA. The pioneering study by Jiang K. et al. established a fundamental paradox. The state of CRM is not equivalent to restored immunological homeostasis and is characterized by significant, persistent deviations in the peripheral blood transcriptome, which are most pronounced in granulocytes [Jiang K. et al., 2013]. This phenomenon of "remission without normalization" creates a necessity to

understand the molecular basis of the persistent immune imbalance that may determine the risk of flare. The present study aims to provide an in-depth characterization of this imbalance through comprehensive bioinformatics analysis of the GSE41831 dataset, with a focus on the granulocyte transcriptome [Nagaraj K. et al., 2018].

Our targeted selection of granulocytes as the object of analysis is based on their recognized key role in JIA pathogenesis as primary effectors of innate immunity [Zaripova L.N. et al., 2021]. This choice is further supported by data indicating the greatest magnitude of transcriptomic abnormalities precisely in this cellular population in patients who achieved CRM on combination therapy [Jiang K. et al., 2013]. The relevance of this approach has received direct experimental support. It has been shown that neutrophils in JIA exist in a state of chronic "priming," manifested by persistently elevated levels of specific granular proteins regardless of drug suppression of clinical activity [Backlund M. et al., 2021]. Thus, analysis of the granulocyte transcriptome allows for deciphering the molecular mechanisms of this activated state.

The conducted analysis identified 232 DEGs in the granulocytes of patients in CRM. Detailed enrichment analysis of biological processes revealed important directions of imbalance characteristic of both upregulated and downregulated expression. Among upregulated genes, the most significant processes were the regulation of response to biotic and external stimuli, regulation of defense response, and positive regulation of nitric oxide (NO) biosynthesis. These data align with a state of chronic granulocyte "priming," where cells maintain heightened readiness to respond to pathogens and stress. Furthermore, NO production may sustain a pro-inflammatory background even in the absence of overt clinical activity. In the group of downregulated genes, dominant processes were related to the positive regulation of lamellipodium morphogenesis and mitochondrial membrane permeability involved in apoptotic signaling. This may reflect complex adaptive changes, such as suppression of excessive mobility and modulation of apoptosis. These changes are possibly aimed at preventing excessive tissue destruction or may result from prolonged exposure to anti-inflammatory therapy. Together with the activation of cytoskeleton reorganization pathways, this points to a profound restructuring of fundamental cellular programs in granulocytes upon achieving clinical remission.

Clustering of these genes via functional enrichment indicated two primary processes. The first is the reorganization of the actin cytoskeleton, and the second is the dysregulation of amino acid metabolism, particularly of branched-chain amino acids (BCAAs). The revealed activation of cytoskeleton-related pathways holds key biological significance, considering the central role of a dynamic actin scaffold in executing primary neutrophil functions. These functions include phagocytosis, chemotaxis, and the formation of pro-inflammatory extracellular traps [Mylvaganam S. et al., 2021]. This allows the observed transcriptomic changes to be viewed as a molecular correlate of a primed, rapidly activatable cell phenotype. Concurrent dysregulation of metabolic pathways, especially of BCAAs, is consistent with the modern paradigm of immunometabolism. According to this paradigm, metabolic reprogramming is not merely a consequence but an active regulator of immune cell functional state [Yahsi B., Gunaydin G., 2022]. Dysregulation of BCAA metabolism is considered an important mechanism of immunometabolic remodeling. BCAA signaling via mTOR can modulate immune cell functions and help maintain granulocyte "priming" during chronic inflammation [Mansoori S. et al., 2025]. Our results, obtained via an independent analytical pipeline, thus not only confirm the conclusion of Jiang K. et al. regarding profound transcriptomic imbalance in remission [Jiang K. et al., 2013] but also specify it by pointing to potential cell-biological mechanisms.

The most significant result was the identification via network analysis of HSP90AB1 and HSP90AA1 as key hub genes, whose elevated expression was statistically confirmed. The role of HSP90 as a master regulator of cellular proteostasis and stress response is well-known. However, contemporary data reveal its exceptional complexity under pathological conditions [Chiosis G. et al., 2023]. In chronic inflammation, HSP90 can undergo structural changes, forming stable oligomeric complexes (epichaperomes). These complexes function not as classic chaperones but as pathological molecular

scaffolds that stabilize activated states of signaling pathways [Chiosis G. et al., 2023]. We propose that elevated HSP90 expression in the granulocytes of JIA patients may reflect the formation of such dysfunctional complexes, contributing to the maintenance of persistent priming. This hypothesis finds support in data from other arthritides. In rheumatoid arthritis, shifts in the expression of several HSP family members have been identified, correlating with enhanced NF-κB and JAK-STAT signaling and chronic inflammatory activity [Fouani M. et al., 2023]. At the same time, contemporary systematic reviews emphasize the dual role of HSPs. On one hand, they maintain proteostasis and cell survival. On the other hand, they participate in the activation of inflammatory cascades and intercellular signaling [Zhao B. et al., 2025]. Experimental data directly confirm the therapeutic potential of targeting HSP90 in inflammation. Selective blockade of HSP90 ATPase leads to the dissociation of the HSP90–COX-2 complex and ubiquitin-mediated degradation of COX-2. This is accompanied by reduced production of pro-inflammatory cytokines [Wang W. et al., 2024], proving that "Targeting HSP90 is a viable strategy to inhibit inflammation" [Wang W. et al., 2024]. Furthermore, an understanding of the role of HSPs in the neuro-immune axis in chronic inflammation is emerging [Fouani M. et al., 2025].

The clinical significance of our findings becomes particularly evident in the context of current challenges in JIA therapy. The high prevalence of intolerance to methotrexate, a key anchor drug, is a serious limitation for long-term disease control [Wibrand C. et al., 2024]. Furthermore, JIA is a disease with high heterogeneity in clinical outcomes. A significant proportion of patients experience long-term problems and functional limitations. This underscores the need to develop methods for molecular monitoring and risk stratification during remission [Ramos F.O. et al., 2024]. The identification of HSP90 as a potential mediator of sustained immune imbalance opens new perspectives. Modern developments in HSP90 inhibitors demonstrate that selective targeting of isoforms or pathological epichaperomes can reduce toxicity and selectively suppress pathological signaling complexes [Liang X. et al., 2024]. This makes the strategy of modulating HSP90 promising for achieving deeper immunological remission in JIA. The identified granulocyte transcriptomic profile, particularly the expression level of HSP90AB1 and HSP90AA1, could serve as a basis for developing a biomarker panel. Such an approach aligns with the general rheumatology trend advocating the use of multiparameter panels. These panels combine serological markers, molecular signatures, and imaging data for risk stratification and therapy personalization [Şahin D. et al., 2024]. The practical feasibility of such strategies is already proven. Biomarker-stratified approaches to therapy selection are implementable and can improve outcomes in chronic inflammatory diseases [Noor N.M. et al., 2024]. Our data are also consistent with the results of large-scale studies where neutrophil activation is defined as a key process common to various molecular subtypes of JIA [Baek I.W. et al., 2025]. Additionally, transcriptomic analysis of neutrophils in rheumatoid arthritis reveals complex regulatory networks, including miRNAs linked to disease severity [Alarcon M.F. et al., 2025]. This highlights the commonality of mechanisms across related diseases.

The present study has several limitations. First, its retrospective design, based on secondary analysis of the publicly available GSE41831 dataset, does not allow for the establishment of causal relationships. Second, the exclusive focus on granulocytes, while justified, does not provide a complete picture of the immune imbalance, which likely involves other cellular populations. An important methodological limitation is the incompleteness of clinical and demographic data in the original dataset. Variables such as precise age, sex, disease duration before remission, and comorbid conditions of the patients could have modulated the transcriptomic profile.

Furthermore, the relatively small sample size necessitates caution in interpreting the results. It requires confirmation of the identified signatures, particularly the role of HSP90AB1 and HSP90AA1 genes, in larger independent cohorts. Finally, the bioinformatics analysis based on microarray data reflects changes at the mRNA level. This is important but not conclusive proof of functional changes at the protein level. Thus, further validation in independent clinical cohorts is necessary to confirm and deepen the obtained results.

Conclusion

Conducted bioinformatics analysis supports the notion that clinical remission on medication in patients with polyarticular JIA does not necessarily reflect a restoration of immunological homeostasis. A persistent molecular imbalance is evident in the granulocytes of patients in CRM, represented by 232 DEGs, with dominant signatures of cytoskeletal remodeling and disturbances in amino acid metabolism. *HSP90AB1* and *HSP90AA1* emerged as key hub genes and potential regulators of persistent granulocyte priming. Their elevated expression was statistically confirmed. These genes represent promising candidates for further proteomic and prospective validation as markers of subclinical activity and possible therapeutic targets. Our data lay the groundwork for subsequent research aimed at translating molecular signatures of remission into clinical tools for risk stratification and personalized management of patients with JIA.

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Биоинформатикалық талдау арқылы ремиссия сатысындағы ювенильді идиопатиялық артрит кезіндегі гендер-концентраторлар мен сигналдық жолдарды анықтау

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Аңдатпа
Ювенильді идиопатиялық артрит (ЮИА) 16 жасқа дейінгі балаларда кездесетін созылмалы қабыну буын ауруларының гетерогенді тобы, олар жиі мүгедектікке, өсудің тежелуіне және жүйелі асқынуларға әкеледі. Медикаментозды терапия фонында клиникалық ремиссияға қол жеткізу ЮИА емдеудің негізгі мақсаты болып табылады. Алайда, транскриптомдық деректер дәрілік-индукцияланған ремиссия иммунологиялық норманың қалпына келуін білдірмеуі мүмкін екенін көрсетеді, бұл осы күйді айқындау және ұзақмерзімді тұрақтылықты болжау үшін биомаркерлерді іздеу қажеттілігін туындатады. Зерттеудің басты мақсаты – медикаментозды емдеу кезінде ремиссия жағдайындағы полиартикулярлы ЮИА бар пациенттердің гранулоциттер транскриптомындағы персистентті иммундық теңгерімсіздікті сипаттайтын гендер-концентраторлар мен сигналдық жолдарды анықтау. Ол үшін комбинацияланған терапия (метотрексат және этанерцепт) фонында ремиссияға қол жеткізген полиартикулярлы ЮИА бар пациенттер мен сау балалардың гранулоциттерінің транскриптомдық деректері (GSE41831) талданды. Дифференциалды экспрессияланатын гендер (DEG) GEO2R құралының көмегімен түзетілген p-value < 0,05 және |Log FC| ≥ 0,5 шекті мәндерімен идентификацияланды. Функционалды байыту талдауы Enrichr платформасында Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) және Reactome дерекқорларын пайдалана отырып орындалды. Ақуыз-ақуыз өзара әрекеттесу (PPI) желісі STRING дерекқорының көмегімен құрылып, Cytoscape бағдарламасында визуализацияланды. Гендер-концентраторлар CytoHubba плагині арқылы максималды орталықтылық клик (MCC) алгоритмін қолданып идентификацияланды. Жетекші гендер-концентраторлардың экспрессиясы статистикалық түрде расталды. Талданған 54 675 геннің ішінен 232 DEG идентификацияланды, оның 99-ы төмендетілген және 133-і жоғарылатылған экспрессияға ие болды. Функционалды байыту талдауы екі негізгі функционалды категорияны бөліп көрсетуге мүмкіндік берді: актинді цитоскелеттің реорганизациясы және қабынулық сигналды жолмен қатар аминқышқылдары метаболизмінің дерегуляциясы. Бұл үдерістер гранулоциттердің белсендірілген күйіне сәйкес келеді, бұл клиникалық ремиссия жағдайында да персистентті жасушалық белсенділікті көрсетеді. PPI желісі 126 түйін мен 498 жиекті қамтыды. MCC алгоритмінің көмегімен 10 ген-концентратор анықталды, олардың ішінде HSP90AB1 және HSP90AA1 ең маңызды болып шықты, бұл олардың байқалған молекулалық теңгерімсіздіктің негізгі реттеушілері ретіндегі рөлін болжауға мүмкіндік береді. Клиникалық ремиссияға қол жеткізгеніне қарамастан, полиартикулярлы ЮИА бар пациенттерде гранулоциттерде персистентті белсендірілген транскриптомдық профиль сақталады. HSP90AB1 және HSP90AA1 гендерінің жоғарылатылған экспрессиясы сақталатын жасушалық стрессті дәлелдейді және осы гендерді субклиникалық иммундық теңгерімсіздіктің кандидатты биомаркерлері және тереңірек ремиссияға қол жеткізу үшін әлеуетті терапевтік нысаналар ретінде қарастыруға мүмкіндік береді. Алынған нәтижелер одан арғы клиникалық тәжірибеге бағытталған басқа да зерттеулерге негіз бола алады.
Түйін сөздер: ювенильді идиопатиялық артрит, сигналды жолдар, гендер-концентраторлар, биоинформациялық анализ, медикаментозды терапия негізіндегі ремиссия.

Идентификация генов-концентраторов и сигнальных путей при ювенильном идиопатическом артрите в стадии ремиссии с помощью биоинформатического анализа

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Аннотация
Ювенильный идиопатический артрит (ЮИА) представляет собой гетерогенную группу хронических воспалительных заболеваний суставов у детей в возрасте до 16 лет, которые часто приводят к

инвалидизации, задержке роста и системным осложнениям. Достижение клинической ремиссии на фоне медикаментозной терапии является ключевой целью лечения ЮИА. Однако транскриптомные данные свидетельствуют о том, что лекарственно-индуцированная ремиссия может не означать восстановления иммунологической нормы, что обуславливает необходимость поиска биомаркеров для идентификации этого состояния и прогнозирования долгосрочной стабильности. Цель исследования – идентифицировать гены-концентраторы и сигнальные пути, характеризующие персистирующий иммунный дисбаланс в транскриптоме гранулоцитов у пациентов с полиартикулярным ЮИА в состоянии ремиссии при медикаментозном лечении. Для этого были проанализированы транскриптомные данные гранулоцитов (GSE41831) пациентов с полиартикулярным ЮИА, достигших ремиссии на фоне комбинированной терапии (метотрексат и этанерцепт), и здоровых детей. Дифференциально экспрессируемые гены (DEG) были идентифицированы с помощью инструмента GEO2R с пороговыми значениями скорректированного p-уровня < 0,05 и |Log FC| ≥ 0,5. Анализ функционального обогащения был выполнен в платформе Enrichr с использованием баз данных Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) и Reactome. Сеть белок-белковых взаимодействий (PPI) была построена с помощью базы данных STRING и визуализирована в программе Cytoscape. Гены-концентраторы идентифицировали с помощью плагина CytoHubba, используя алгоритм максимальной кликовой центральности (MCC). Экспрессия ведущих генов-концентраторов была статистически подтверждена. Из 54 675 проанализированных генов было идентифицировано 232 DEG, из которых 99 обладали пониженной и 133 – повышенной экспрессией. Анализ функционального обогащения позволил выделить две основные функциональные категории: реорганизация актинового цитоскелета и дерегуляция метаболизма аминокислот наряду с провоспалительным сигналингом. Данные процессы соответствуют активированному состоянию гранулоцитов, что указывает на персистирующую клеточную активность даже в состоянии клинической ремиссии. Сеть PPI включала 126 узлов и 498 ребер. С помощью алгоритма MCC были идентифицированы 10 генов-концентраторов, среди которых наиболее значимыми оказались HSP90AB1 и HSP90AA1, что позволяет предположить их роль в качестве ключевых регуляторов наблюдаемого молекулярного дисбаланса. Несмотря на достижение клинической ремиссии, у пациентов с полиартикулярным ЮИА в гранулоцитах сохраняется персистирующий активированный транскриптомный профиль. Повышенная экспрессия генов HSP90AB1 и HSP90AA1 свидетельствует о сохраняющемся клеточном стрессе и позволяет рассматривать эти гены в качестве кандидатных биомаркеров субклинического иммунного дисбаланса и потенциальных терапевтических мишеней для достижения более глубокой ремиссии. Полученные результаты закладывают основу для дальнейших исследований, направленных на трансляцию фундаментальных открытий в клиническую практику.
Ключевые слова: ювенильный идиопатический артрит, сигнальные пути, гены концентраторы, биоинформатический анализ, ремиссия при медикаментозном лечении.

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РАЗРАБОТКА ЛАКТОЗОСВОБОДНЫХ ПРОДУКТОВ, ОБОГАЩЕННЫХ ПРОБИОТИКАМИ И КАЛЬЦИЕМ

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Аннотация
В современном мире проблема лактазной недостаточности приобретает все большую остроту. По данным ВОЗ, более 65% взрослого населения мира страдают различными формами непереносимости лактозы. Вследствие этого миллионы людей вынуждены исключать из своего рациона молочные