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ADVANCES IN POTENTIAL BIOMARKERS FOR RHEUMATOID ARTHRITIS: SYSTEMATIC REVIEW

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Abstract

Introduction. Rheumatoid arthritis (RA) is a chronic autoimmune condition marked by continuous inflammation of the synovial membrane, gradual joint damage and involvement of internal organs. Its relapsing-remitting course leads to joint deformation, disability and impaired quality of life. The Institute for Health Metrics and Evaluation estimated the global prevalence of RA to exceed 18 million cases in 2019. Given the multifactorial nature of RA, increasing attention is being directed to the role of genetic predisposition, autoantibody formation and cytokine dysregulation in disease onset and progression. Understanding these elements is essential for developing tools for early diagnosis and therapy.

Objective. To analyze current achievements in genetic mutations, autoantibodies, and cytokine profiles involved in RA pathogenesis and assess their potential for early diagnosis of this disease.

Search Strategy. A systematic review was conducted using PubMed and Google Scholar databases. The search included full text articles in English, prioritizing peer-reviewed research, systematic review and meta-analysis. Search terms included “rheumatoid arthritis”, “genetic mutations”, “autoantibodies”, “cytokine production*”. Inclusion criteria:* studies focusing on human subjects, evaluating the role of genetic variants, cytokines or autoantibodies in RA pathogenesis. *Exclusion criteria:* abstracts without full text, animal studies.

Results. From 1990 to 2024, 33,908 publications on RA were identified, with 4,080 meeting the criteria. The findings highlight that RA has a multifactorial pathogenesis with a complex genetic background involving both HLA and non-HLA genes such as HLA-DRB1, STAT4, PADI4 and PTPN22. These gene alterations contribute to T-cell activation, increased cytokine production, including IL-6, TNF-α and IL-17, and subsequent osteoclast–mediated joint destruction. Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies are considered as key diagnostic biomarkers, often detectable years before the clinical onset of symptoms. Environmental triggers like smoking induce the formation of autoantibodies, activation of the complement system and sustained synovial inflammation. Together, these mechanisms underline the diagnostic and prognostic relevance of genetic, cytokine and autoantibody profiling in RA and support the development of diagnostic and therapeutic approaches.

Conclusion. Genetic susceptibility, cytokine dysregulation and autoantibody production act synergistically in rheumatoid arthritis, causing joint damage and systemic complications. Emerging biomarkers for RA show considerable promise in improving early diagnosis, prognosis, and personalized treatment approaches. While several candidates demonstrate strong potential, further validation and standardization are necessary before widespread clinical implementation. Continued research will be essential to translate these findings into routine practice.

Keywords: *rheumatoid arthritis, genes, antibodies, cytokines*.

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Резюме

ДОСТИЖЕНИЯ В ОБЛАСТИ ИССЛЕДОВАНИЯ ПОТЕНЦИАЛЬНЫХ БИОМАРКЕРОВ РЕВМАТОИДНОГО АРТРИТА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Введение. Ревматоидный артрит (РА) — это хроническое аутоиммунное состояние, характеризующееся продолжительным воспалением синовиальной мембраны, постепенным разрушением суставов с вовлечением в процесс внутренних органов. Рецедивирующий характер течения приводит к деформации суставов, с последующей инвалидизацией и снижением качества жизни пациентов. На 2019 год, согласно отчету Института измерения показателей и оценки состояния здоровья, распространенность РА превышает более 18 миллонов зарегестрированных случаев по миру. Учитывая мультифакториальную природу РА, все больше внимания уделяется роли генетической предрасположенности, образованию аутоантител и нарушению регуляции цитокинов в возникновении и прорессировании заболевания. Понимание этих факторов необходимо для разработки инструментов ранней диагностики и последующего лечения.

Цель исследования. Проанализировать современные достижения в области изучения генетических мутаций, аутоантител и цитокинов, участвующих в патогенезе РА и оценить их потенциал для ранней диагностики заболевания.

Стратегия поиска. Систематический обзор литературы был проведен с использованием баз данных PubMed и Google Scholar. Поиск включал полнотекстовые публикации на английском, в первую очередь исследования, опубликованные в рецензируемых журналах, систематические обзоры и мета-анализы. В поиск были включены термины «ревматоидный артрит», «генетические мутации», «аутоантитела», «продукция цитокинов». *Критерии включения* составляли исследования с участием людей, оценивающие роль вариантов генетических мутаций, цитокинов и спектр аутоантител при ревматоидном артрите. *Критерии исключения:* тезисы без полного текста, исследования на животных.

Результаты. С 1990 по 2024 год было выявлено 33 908 публикаций о РА, из которых 4080 соответствовали критериям. Исследования подчёркиваю, что РА имеет мультифакториальный патогенез со сложным генетическим фоном, включающим как HLA, так и не-HLA гены, такие как HLA-DRB1, STAT4, PADI4 и PTPN22. Эти генетические изменения способствуют активации Т-клеток, повышенной выработке цитокинов, включая IL-6, TNF-α и IL-17, и последующему разрушению суставов остеокластами. Аутоантитела, такие как ревматоидный фактор (РФ) и антитела к цитруллинированным белкам (АЦЦП) считаются ключевыми диагностическими биомаркерами, которые часто обнаруживаются за несколько лет до появления клинических симптомов. Факторы окружающей среды, такие как курение, вызывают цитруллинирование, способствуя образования аутоантител, активации системы комплимента и устойчивому воспалению синовиальной оболочки. В совокупности эти механизмы подчеркивают диагностическую и прогностическую значимость определения генов, цитокинов и аутоантител при РА и способствуют разработке диагностических и терапевтических подходов.

Заключение. Генетическая предрасположенность, дисрегуляция цитокинов и продукция аутоантител действуют синергетически при ревматоидном артрите, вызывая повреждение суставов и системные осложнения. Новые биомаркеры ревматоидного артрита демонстрируют значительный потенциал в улучшении ранней диагностики, прогноза и персонализированных подходов к лечению. Несмотря на высокую перспективность ряда кандидатов, необходима дальнейшая валидация и стандартизация перед их широким клиническим применением. Продолжение исследований имеет ключевое значение для внедрения этих находок в клиническую практику.

Ключевые слова: *ревматоидный артрит, гены, антитела, цитокины*

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Түйіндеме

РЕВМАТОИДТЫ АРТРИТ ҮШІН ЫҚТИМАЛ БИОМАРКЕРЛЕРДІ ЗЕРТТЕУДЕГІ ЖЕТІСТІКТЕР: ЖҮЙЕЛІ ШОЛУ

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Кіріспе. Ревматоидты артрит (РА) — бұл буындардың синовиальды мембранасының ұзақ мерзімді қабынуымен, ішкі ағзалардың бұзылысының біртіндеп қосылуымен сипатталатын ұзақ мерзімді аутоиммунды ауру. Ағымның қайталанатын сипаты буындардың деформациясына, кейін мүгедектікке және өмір сапасының төмендеуіне әкеледі. Денсаулық көрсеткіштерін өлшеу және бағалау институтының есебі бойынша 2019 жылы РА-тың таралуы бүкіл әлем бойынша 18 миллионнан асады. РА-тың мультифакторлық сипатын ескере отырып, аурудың пайда болуы мен дамуындағы генетикалық бейімділіктің, аутоантиденелердің және цитокиндердің реттелуінің бұзылуына көбірек көңіл бөлінеді. Бұл факторларды түсіну ерте диагностика және кейінгі емдеу құралдарын жасау үшін өте маңызды.

Зерттеудің мақсаты: РА патогенезіне қатысатын генетикалық мутацияларды, аутоантиденелерді және цитокиндерді зерттеудің заманауи жетістіктерін талдап, олардың ауруды ерте диагностикалаудағы әлеуетін бағалау.

Әдістер. Әдебиеттерге жүйелі шолу PubMed және Google Scholar дерекқорларының көмегімен жүргізілді. Іздеу ағылшын тіліндегі толық мәтінді басылымдарды, ең алдымен рецензияланған зерттеулерді, жүйелі шолуларды және мета-талдауларды қамтыды. Іздеуге "ревматоидты артрит", "генетикалық мутациялар", "аутоантиденелер", "цитокин өндірісі" терминдері қолданылды. *Іріктеу талаптары* ревматоидты артриттегі мутациялардың, цитокиндердің және аутоантиденелердің генетикалық нұсқаларының рөлін бағалайтын адамдарға қатысты зерттеулерді құрады. *Ескерілмейтін талаптар:* толық мәтінсіз тезистер, жануарларда жүргізілген зерттеулер.

Нәтижелер. 1990 жылдан 2024 жылға дейін РА туралы 33 908 басылым анықталды, оның 4080-і адам зерттеулері немесе жүйелі шолулар талаптарына сәйкес келді. Зерттеулер РА-тың HLA және HLA емес гендер HLA-DRB1, STAT4, PADI4, PTPN22 сияқты күрделі генетикалық фоны бар, көп факторлы патогенезі бар екенін атап көрсетеді. Бұл генетикалық өзгерістер Т-жасушаларды белсендіріп, IL-6, TNF-α және IL-17 цитокиндерін көбейтіп, нәтижесінде остеокласттар буындардың бұзылуына ықпал етеді. Ревматоидты фактор (РФ) және цитруллинденген ақуызға қарсы антиденелер (АЦЦП) клиникалық белгілер пайда болмай, бірнеше жыл бұрын кездесетін негізгі диагностикалық биомаркерлер болып саналады. Темекі шегу сияқты қоршаған орта факторлары цитруллинацияны тудырады, аутоантиденелердің пайда болуына, комплимент жүйесінің белсендірілуіне және синовиальды қабықтың тұрақты қабынуына ықпал етеді. Бұл механизмдердің бірігуі РА-те гендерді, цитокиндерді және аутоантиденелерді анықтаудың диагностикалық және болжамды маңыздылығын көрсетеді, диагностикалық және емдік тәсілдерді дамытуға ықпал етеді.

Қорытынды. Генетикалық бейімділік, цитокиндердің реттелуінің бұзылысы және аутоантиденелердің өндірісі ревматоидты артрит кезінде бірлесіп әсер етіп, буындардың зақымдалуына және жүйелік асқынуларға әкеледі. Ревматоидты артриттің жаңа биомаркерлері ерте диагностика, болжам жасау және жеке бағытталған ем тәсілдерін жетілдіруде үлкен әлеуетке ие. Генетикалық бейімділік, цитокиндердің реттелуінің бұзылысы және аутоантиденелердің өндірісі ревматоидты артрит кезінде бірлесіп әсер етіп, буындардың зақымдалуына және жүйелік асқынуларға әкеледі. Ревматоидты артриттің жаңа биомаркерлері ерте диагностиканы, болжамды және емдеудің жекелендірілген тәсілдерін жақсартуда айтарлықтай әлеуетті көрсетеді. Бірқатар кандидаттар жоғары перспективалы болғанымен, оларды клиникалық тәжірибеде кеңінен қолданбас бұрын, одан әрі валидациялау және стандарттау қажет. Зерттеулерді жалғастыру нәтижелерді клиникалық тәжірибеге енгізудің кілті болып табылады.

Түйінді сөздер: *ревматоидты артрит, гендер, антиденелер, цитокиндер*

Дәйексөз үшін:
Зарипова Л.Н., Байгенжин А.К., Болтанова А.А., Жабакова Ж.М., Соломадин М.В., Макимова Д.М., Садыкова Т.А. Ревматоидты артрит үшін ықтимал биомаркерлерді зерттеудегі жетістіктер: жүйелі шолу // Ғылым және Денсаулық сақтау. 2025. Vol.27 (5), Б. 191-202. *doi 10.34689/SH.2025.27.5.023*

Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disease characterized by the gradual development of inflammation in the joints, which can lead to cartilage degradation, bone erosion, and reduced mobility. Initially, only a few joints may be affected, usually small joints of the hand and wrist, but over time, the chronic inflammatory process causes the formation of rheumatoid nodules, vasculitis, and various other conditions, including cardiovascular, pulmonary, neurological, gastrointestinal, renal, and hematological problems [15]. Although the cause of RA is still unknown, research has shown that both genetic and environmental factors play a role in its occurrence.

The prevalence of RA differs depending on gender, ranging from 0.4% to 1.3% of the population. At the same time, the incidence is higher in women compared to men, and there is a growing trend among individuals over the age of 60. RA is a highly prevalent chronic inflammatory disease that affects millions worldwide, leading to joint pain, stiffness, and disability [56].

Like other autoimmune disorders, RAA is likely to be the result of a complex interplay between genetic and environmental factors. To begin with, individuals with genetic predisposition develop self-reactive T and B cells. Then, an initial event such as a viral or bacterial infection or tissue damage triggers the activation of antigen-presenting cells (APCs), which in turn activates these self-reactive lymphocytes. This process disrupts immune tolerance and leads to tissue and organ damage. Therefore, RA develops in individuals with a genetic predisposition due to a combination of genetic, epigenetic, and environmental factors, with an initial event playing a crucial role [38]. Due to remarkable advances in the pharmaceutical industry, innovative therapeutic approaches are becoming increasingly available. However, the challenge of discovering curative treatments persists, largely due to a limited understanding of the molecular mechanisms that regulate the behavior of antibodies, genes, and cytokines. The cornerstone of effective therapy is early diagnosis and the implementation of optimized pharmacological and non-pharmacological treatments, combined with regular assessment of therapeutic efficacy and safety. This necessitates a comprehensive diagnostic approach at the earliest stage, including not only immunological evaluation but also genetic analyses. Early and accurate diagnosis coupled with timely intervention, significantly improves disease outcomes and minimizes the risk of complications.

Aim. To analyze current achievements in genetic mutations, autoantibodies and cytokine profiles involved in RA pathogenesis and assess their potential for early diagnosis of this disease.

Search Strategy. Potential genetic mutations, autoantibodies, and cytokines implicated in autoimmune aggression during RA were identified through a systematic review of biomedical literature and comparison with genetic panels offered by leading global manufacturers. The literature search was conducted using the PubMed and Google Scholar platforms, employing a combination of targeted keywords, including “rheumatoid arthritis”, “genetic mutations”, “autoantibodies”, “cytokine production”, “sequencing”, “NGS” and “exome.” The review included full-text English publications that focused on the prevalence of genetic variations, autoantibodies, and cytokine profiles associated with autoimmune diseases. Articles were screened for relevance, and studies providing detailed information on these parameters were prioritized. Exclusion criteria included literature reviews, abstracts, and other forms of limited publications. Peer-reviewed studies, systematic reviews, and meta-analyses were prioritized for inclusion. Additionally, the Ion AmpliSeq™ Designer gene repository was used to identify disease-associated genes relevant to RA pathogenesis. This approach ensured a comprehensive and evidence-based selection of molecular targets for further analysis. A schematic search strategy is shown in Figure 1.

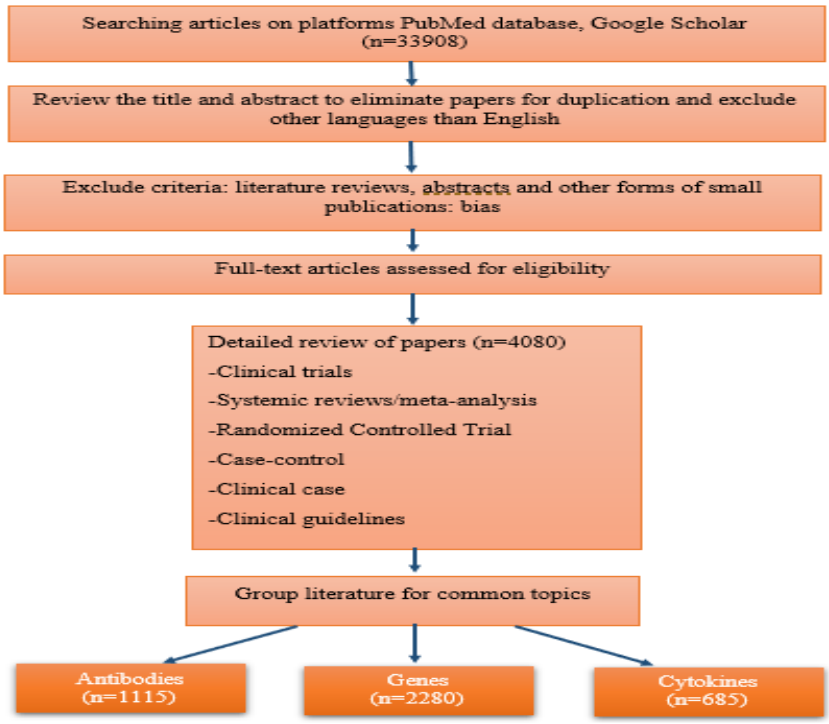

Figure 1. Search strategy (n – number of articles).

Results

The literature search covering the years 1990–2024 yielded 33,908 publications. After applying predefined inclusion criteria - human studies, original investigations, and systematic reviews - a total of 4,080 articles were included in the final analysis.

The importance of antibodies in RA

In contemporary diagnostic procedures, the presence of antibodies such as rheumatoid factor (RF) and antibodies to anticitrullinated proteins (ACPA) serves as a diagnostic tool for rheumatoid arthritis [28]. Novel autoantibodies targeting post-translationally modified proteins—such as carbamylated or acetylated epitopes—are increasingly used to improve diagnostic sensitivity and specificity. Anti-carbamylated protein antibodies (anti-CarP) can also serve as biomarkers, helping stratify patients based on serological profile. This enables the prediction of the disease progression and the selection of the most suitable treatment approach [57].

Additional autoantibodies reported in RA include anti–acetylated vimentin, anti-PAD4, anti-PTX3, and antibodies to DUSP11, although their clinical utility requires further validation [5, 30, 31, 57]. These autoantibodies can be identified primarily in the blood and synovial fluid of individuals with RA years before symptom onset [20]. Upon clinical manifestation of the disease, a broad spectrum of autoantibody isotypes is typically detected. This suggests that, in individuals genetically or environmentally predisposed to RA, specific immunological processes are initiated well in advance of symptom onset, leading to the early production of autoantibodies. The detection of these autoantibodies may serve as a valuable predictive tool for identifying individuals at elevated risk of developing RA.

The key serological markers in RA are RF and ACPA. Beyond their diagnostic utility, these autoantibodies are also instrumental in predicting disease progression and therapeutic outcomes. ACPAs and RF contribute to pathogenesis by forming immune complexes with citrullinated proteins, which subsequently activate macrophages and stimulate the release of pro-inflammatory cytokines. This cytokine-driven inflammatory cascade plays a central role in the initiation and progression of RA.

The cytokines signature

The role of cytokines in the development of RA has been actively studied for many years. Scientific research has confirmed their significant involvement in both the pathogenesis of the disease and its relationship with other systemic disorders.

In the affected joint, infiltrating immune cells in the synovium produce a range of pro-inflammatory cytokines, which are key mediators of cellular differentiation, inflammation, immune pathology, and immune response [32]. Tumor necrosis factor-alpha (TNF-α), mainly secreted by synovial macrophages, B-cells, and NK-cells, is a key driver of inflammatory process [38]. The significance of IL-17A produced by Th17 cells is also emphasized, as it promotes secretion of pro-inflammatory cytokines such as IL-6, IL-8, and GM-CSF, contributing to bone erosion, cartilage damage, and the neoangiogenesis in patients with RA [33]. Additionally, Interleukin 1 has been linked to interstitial lung damage [41], while interleukin 17 has been associated with atherosclerosis [61].

Cytokines could be effective targets for early diagnosis and treatment of RA with targeted biologic therapies. Biologic agents that inhibit TNF-α or block the IL-6 receptor have substantially improved clinical outcomes in RA. Detailed cytokine characteristics are summarized in Table 1.

Table 1.

Cytokines involved in the development of rheumatoid arthritis.

N	Cytokine abbreviation	Cytokine name	Summary (role, mechanism of working, findings)	Reference
1	2	3	4	5
1	TNF-α	tumor necrosis factor alpha	TNF-α is involved in the development and advancement of rheumatoid arthritis (RA) by controlling the growth and development of lymphocytes, promoting the growth of synovial cells, releasing metalloproteinases and cytokines, and inhibiting the function of regulatory T cells.	[1, 27]
2	IL-6	interleukin-6	A distinctive feature of IL-6 is its dual signaling process, known as classical and trans-signaling. In classical IL-6 signaling, IL-6 binds to the membrane-bound form of the IL-6-specific receptor α subunit (IL-6Rα), causing it to interact with the signal-transducing gp130 receptor subunit through the membrane-bound IL-6 receptor. Trans-signaling occurs through the soluble IL-6 receptor. In this case, IL-6 binds to the soluble form of the receptor, which then interacts with the gp130 subunit through the membrane.	[54]
3	IL-7	interleukin-7	IL-7 enhances the differentiation of Th1 cells in RA and increases the secretion of interferon gamma (IFNγ). This process can directly stimulate the expression of the myeloid interleukin-7 receptor (IL-7R), which can exacerbate the inflammatory and erosive effects of IL-7 on joints. Additionally, IL-7 promotes angiogenesis in joints by increasing the production of pro-angiogenic factors by macrophages and endothelial cells in RA.	[45]
4	IL-17	interleukin-17	IL-17 includes several subtypes, such as IL-17A, IL-17B, IL-17C, IL-17D, IL-25, and IL-17F. Patients with RA often have an increased level of IL-17 in their synovial tissues, which suggests that this cytokine may play a role in the inflammatory processes that occur in the joints.	[61]

Continuation of Table 1.

1	2	3	4	5
5	IL-21	interleukin-21	IL-21 has a complex impact on the immune system and plays a crucial role in B-cell function, including responsiveness, proliferation, plasma differentiation, and antibody production. As a result, the effects of IL-21 on B cells may contribute to the development of autoimmune diseases.	[8]
6	IL-1α	interleukin-1 α	The production of IL-1α results in the immune and inflammatory response. Elevated IL-1α correlated with extra-articular manifestations - particularly - interstitial lung disease (ILD) associated with RA.	[41, 48]
7	IL-23	interleukin-23	IL-23 is predominantly produced by macrophages and dendritic cells that are activated and located in peripheral tissues, including skin, intestinal mucosa, joints, and lungs.	[51]
8	IL-1β	interleukin-1β	The level of IL-1β was substantially elevated in individuals with rheumatoid arthritis.	[37]
9	IL-18	interleukin-18	The levels of IL-18 and TNF-α in individuals with RA can be used as reliable indicators of disease progression. IL-18 plays a crucial role in the development and maintenance of inflammatory joint conditions.	[49, 60]
10	IL-33	interleukin-33	In RA IL-33 plays a critical role in the development of the disease. It influences the behavior of several types of immune cells, such as circulating monocytes, tissue macrophages, synovial fibroblasts, mast cells, dendritic cells, neutrophils, T cells, B cells, and endothelial cells.	[39]
11	GM-CSF	Granulocyte-macrophage colony-stimulating factor	GM-CSF is a small cytokine that plays a crucial role in stimulating the growth and development of myeloid cells derived from bone marrow stem cells.	[3]
12	IL-2	interleukin-2	IL-2 plays a fundamental role in maintaining cartilage damage and severe joint destruction by unregulated activation of the immune system.	[35]
13	IL-12p40	Interleukin-12 subunit beta	The Bulgarian RA patients had a significant increase in the blood levels of both IL-12p40 and IL-23 in patients with RA.	[42]
14	IL-17A	Interleukin-17A	They stimulate movement, activation of the gene responsible to produce chemokines, and the ability of synovial membrane cells to penetrate into other tissues. These processes contribute to the transition of the disease into a chronic form, preventing death of synovial cells and increasing production of enzymes that destroy cartilage tissue.	[22]
15	IL-17F	Interleukin-17F		
16	IL-3	Interleukin-3	IL-3 controls growth of Th17 cells by inhibiting the activation of STAT3.	[50]
17	IL-4	Interleukin-4	The research revealed that the IL-4-590 T gene variant is linked to an increased risk of developing RA in individuals of Spanish and Chinese descent.	[26]
18	IL-1	Interleukin-1	It plays a role in the development of RA. IL-1, primarily produced by activated macrophages, is one of the earliest cytokines involved in the inflammatory cascade of RA. Beyond promoting synovial inflammation, IL-1 enhances the expression of adhesion molecules, facilitates leukocyte recruitment, and stimulates fibroblast-like synoviocytes to produce matrix metalloproteinases, thereby accelerating cartilage degradation. IL-1 also drives osteoclast differentiation through RANKL-mediated pathways, contributing directly to bone erosion. Elevated IL-1 levels correlate with disease activity, radiographic progression, and extra-articular manifestations - particularly ILD.	[6]
19	IL-10	Interleukin-10	IL-10 is a versatile anti-inflammatory cytokine produced by various types of immune cells, including macrophages, regulatory T cells, B cells, and mast cells. Decrease in IL-10 levels triggers a severe inflammation response in RA greatly accelerating the progression of the disease.	[10]
20	IL-8	interleukin-8	IL-8 is a powerful chemoattractant that plays a central role in attracting neutrophils to the synovial fluid. IL-8 is activated by TNF-α, IL-1β, and IL-6 and binds to the CXCR1 and CXCR2 receptors on neutrophils, causing their migration and activation. IL-8 is also involved in angiogenesis by promoting the formation of new blood vessels in the synovial membrane, which supports chronic inflammation. Additionally, it stimulates the release of TNF-α and IL-6 creating a vicious cycle of inflammation	[17]

The relevance of genes in RA

Numerous epidemiological investigations have been carried out to identify the elements that make individuals more susceptible to RA, with a particular emphasis on genetic factors. In 2007, the first genomic association studies (GWAS) initiated the investigation of genetic variants in RA [46] . Herein, we analyzed 2,280 articles and identified 32 genes that may predispose to the disease and 12 associated with RA activity. A crucial genetic link in RA is the major histocompatibility complex, particularly the HLA-DR molecule. Variations in the HLA-DRB1 gene containing the shared epitope sequence are linked to an increased likelihood of developing RA and its severe manifestations [16]. In addition to HLA genes, attention has also been focused on non-HLA gene variations like STAT4, PADI4, and TRAF6 that influence the risk of developing rheumatoid arthritis [18, 21, 44]. The genetic profile of the patient can also determine the clinical manifestation of RA, including the presence of rheumatoid factor and antibody-mediated cellular cytotoxicity, as well as the speed at which erosive changes occurs in the joints [32, 46].

Active RA is marked by a distinct molecular profile characterized by upregulation of genes involved in inflammation and immune regulation. During disease flares, genes encoding pro-inflammatory mediators show increased expression, reflecting heightened immune activation. Genes participating in intracellular signaling cascades, particularly those associated with the JAK-STAT pathway (STAT1), are also elevated, underscoring their role in perpetuating cytokine-driven inflammation. The immune response is further intensified by enhanced expression of co-stimulatory molecules such as CD40, indicating active antigen presentation. Collectively, these genetic signatures mirror the pathological mechanisms underlying active RA and may aid in identifying disease activity and guiding targeted therapeutic approaches. Table 2 provides complete information about the genes involved in RA including genes increased during active disease.

Table 2.

The genetic factors involved in the development of rheumatoid arthritis: a review of recent findings.

N	Gene abbreviation	Gene name	Summary (role, mechanism of working, findings)	Reference
1	2	3	4	5
Significant genes associated with susceptibility to the development of RA				
1	AFF3	ALF Transcription Elongation Factor 3	The AFF3 gene is located at 2q11.2 locus and encodes a protein consisting of 1,227 amino acids. This gene is predominantly expressed in lymphoid tissues and is linked to their development. However, low levels of expression have also been observed in other tissues such as the brain and lungs.	[2]
2	FCGR2A	Fc Gamma Receptor IIa	The FCGR2A and FCGR3A genes variations have been discovered to be associated with RA in individuals of European descent, but not in those of Asian ancestry.	[36]
3	IL2 / IL21	Interleukin 2 / Interleukin 21	The IL2/IL21 genes are potential contributors to the development of RA.	[40]
4	IRAK1	Interleukin 1 Receptor Associated Kinase 1	IRAK1 serves as a pivotal controller of the inflammatory environment in joints which depends on IL-1β and represents a promising therapeutic target for inflammatory arthritis.	[23]
5	PIP4K2C	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Gamma	These are hereditary features that increase the likelihood of developing rheumatoid arthritis.	[58]
6	SPRED2	Sprouty Related EVH1 Domain Containing 2	The SPRED2 gene plays a role in controlling the inflammatory process, white blood cells infiltration, and local chemokines synthesis.	[47]
7	IL2RA	Interleukin 2 Receptor Subunit Alpha	The IL2RA gene is located on the shorter segment of chromosome 10 (10q15-q14), also known as CD25. This gene is highly expressed in CD4+CD25+ regulatory T cells and plays a critical role in maintaining immune balance and suppressing autoimmune responses.	[64]
8	ARID5B	AT-Rich Interaction Domain 5B	The variant in the intron of the ARID5B gene, which is associated with an increased risk of RA, may lead to elevated levels of IL-6 production.	[53]
9	TRAF6	TNF Receptor Associated Factor 6	The study revealed a link between a specific TRAF6 gene variant and low bone mineral density in patients with RA.	[21]
10	CD28	CD28 Molecule	CD28 and CTLA-4 are crucial in controlling the stimulatory and inhibitory signals in T cells.	[19]
11	GATA3	GATA Binding Protein 3	GATA3 is directly involved in the process of differentiation and work of Th17 cells.	[59]
12	IL2RB	Interleukin 2 Receptor Subunit Beta	As is known, variations in the IL-2RA and IL-2RB genes can affect the predisposition to RA among Europeans.	66]

Continuation of Table 2.

1	2	3	4	5
13	IRF8	Interferon Regulatory Factor 8	IRF8, a member of the IRF family, is produced by various cells, such as B cells, dendritic cells, macrophages, and activated T cells. Its role in regulating innate and adaptive immune responses has been demonstrated.	[59]
14	RBPJ	Recombination Signal Binding Protein for Immunoglobulin Kappa J Region	RBPJ may play a role in controlling the activation of T cells, the differentiation of lymphocytes and mononuclear cells, and regulating cell-to-cell adhesion.	[11]
15	PRKCQ	Protein Kinase C Theta	They are directly involved in the process of differentiation and the work of Th17 cells.	[59]
16	CCL21	C-C Motif Chemokine Ligand 21	The monokines activated by CCL21 can transform naive T cells into Th17, which contributes to the development of osteoclasts in RA.	[55]
17	IL6ST	Interleukin 6 Cytokine Family Signal Transducer	The IL6/IL6ST signaling pathway is a crucial factor in the development of RA.	[4]
19	NFKBIL1	NFKB Inhibitor Like 1	NFKBIL1 contributes to the development of RA, at least in part, by influencing the activity of dendritic cells.	[12]
20	IKZF3	IKAROS Family Zinc Finger 3	Engaged in the process of differentiation and operation of Th17 cells.	[59]
21	PTPRC	Protein Tyrosine Phosphatase Receptor Type C	The existence of LGALS9, PTPRC, and CD44 in platelets could potentially serve as a diagnostic marker for RA.	[65]
22	RUNX1	RUNX Family Transcription Factor 1	Engaged in the process of differentiation and operations of Th17 cells.	[59]
23	TNFRSF14	TNF Receptor Superfamily Member 14	TNFSF14 is part of the tumor necrosis factor family and serves as messenger for TR2 and lymphotoxin (LT)-β.	[29]
24	CCR5	C-C Motif Chemokine Receptor 5	The CCR5 receptor and its ligands play a crucial role in the development of RA and systemic lupus erythematosus.	[43]
25	ARG1	Arginase 1	ARG1 produces enzyme arginase, which is a key component of the urea cycle in liver cells. Arginine metabolism has been shown to play a critical role in both innate and adaptive immune responses.	[62]
26	TYMS	Thymidylate Synthetase	TYMS is a gene that encodes thymidylate synthase, an enzyme that catalyzes the methylation of deoxyuridine monophosphate to form thymidine monophosphate (dTMP). dTMP is crucial for DNA repair and replication and its deficiency leads to damage to DNA. Therefore, TYMS is targeted by some medications, such as methotrexate used to treat RA to inhibit cell proliferation.	[62]
27	SORT1	Sortilin 1	SORT1 is a gene producing the protein sortilin involved in intracellular transport processes.	[62]
28	OLFM4	Olfactomedin 4	The gene OLFM4 produces olfactomedin 4, which has been demonstrated to play a role in various cellular processes, including the innate immune system and the inflammatory response.	[62]
29	BIRC5	Baculoviral Inhibitor of Apoptosis Repeat Containing 5	BIRC5 plays a key role in pulmonary fibrosis.	[62]
30	MS4A4A	Membrane Spanning 4-Domains A4A	MS4A4A is a gene that produces a tetraspan surface protein, which is primarily expressed in white blood cells, particularly macrophages. This protein is essential for activating the immune system's inflammatory response when it detects an infection.	[62]
31	CLEC12A	C-type Lectin Domain Family 12 Member A	CLEC12A is a gene that codes for a member of the C-type lectin domain family 12. In addition to its functions in cell adhesion and intercellular communication, CLEC12A is expressed in alveolar macrophages. It has been implicated in the development of fibrotic lung diseases.	[62]
32	STAT4	Signal Transducer and Activator of Transcription 4	STAT4 is a regulatory protein that participates in the signaling cascades of cytokines and T-cell subsets development. Numerous investigations have shown a correlation between variations in STAT4 and autoimmune disorders.	[18]

Continuation of Table 2.

1	2	3	4	5
33	STAT3	Signal Transducer and Activator of Transcription 3	STAT3 is involved in a pathway that regulates Th17 cell differentiation. Increased activity of STAT3 in T-cells leads to suppression of Treg cells and stimulation of inflammation. STAT3 also affects the inhibition of the expression of FOXP3, which is main transcription factor for Treg cells. Recent studies have shown that suppression of FOX3 in RA disrupts the function of Treg cell, contributing to autoimmune responses.	[26]
34	STAT 6	Signal Transducer and Activator of Transcription 6	STAT6 is a dominant transcription factor for Th2 cell differentiation, activated when IL-4 binds to its receptor. It promotes the expression of genes associated with Th2 differentiation. Disruption of the STAT6 pathway in RA can impair Th2 cell function and result in expand inflammation through Th1 and Th17 cells. Recent research confirms that disturbances in STAT6 lead to decreased Th2 activation and worsening inflammatory responses.	[34]
Genes increased during active disease				
1	CD2	CD2 Molecule	The synovial area of joints in individuals with RA exhibits an elevated level of co-stimulatory molecules.	[14]
2	TRAF1	TNF Receptor Associated Factor 1	TRAF1 is a member of the TRAF protein family that can transmit a signal by interacting with various protein kinases and adapter proteins for different receptors in the TNF superfamily, including TNF-α.	[25]
3	TAGAP	T Cell Activation RhoGTPase Activating Protein	The TAGAP protein activates Rho GTPases in T cells, is involved in various autoimmune diseases, including RA, and is closely linked to the development of Th17 cells.	[52]
4	CD40	CD40 Molecule	CD40 is a marker of stimulatory activation that plays a role in driving pathogenic processes through the CD40/CD40L pathway, contributing to the persistence of chronic inflammation in RA.	[29]
5	PADI4	Peptidyl Arginine Deiminase 4	The process of citrullination is facilitated by the enzyme peptidyl arginine deiminase 4 (PAD4), which is encoded by the PADI4 gene. Elevated PAD4 activity contributes to RA development and progression.	[44]
6	HLA-DR15 (DRB1 / DRB5)	Major Histocompatibility Complex, Class II, DR Beta 1/ Major Histocompatibility Complex, Class II, DR Beta 5	The HLA-DR15 haplotype (DRB1/DRB5) is associated with a higher likelihood of developing active disease in ACPA-positive RA patients in a large sample of untreated individuals.	[63]
7	STAT1	Signal Transducer and Activator of Transcription 1	They control the inflammatory process in the synovial membrane mainly by acting on cytokines.	[9]
8	miR-146	MicroRNA 146	In the blood of patients with RA, the levels of miR-146, miR-155, and miR-16 are elevated, particularly during active disease periods.	[7]
9	miR-155	MicroRNA 155		[7]
10	miR-16	MicroRNA 16		[7]
11	miR-346	MicroRNA 346	miR-346 inhibits the IL-18 response in RA fibroblasts.	[7]
12	CTLA4	Cytotoxic T-lymphocyte-associated Protein 4	The CTLA4 gene contributes to the progression of RA in patients with ACPA compared to those without ACPA.	[13]

Discussion

The results underscore the intricate and multifaceted nature of RA, emphasizing the interdependent roles of genetic susceptibility, autoantibody production, and cytokine-driven inflammation. Autoantibodies such as RF and ACPA, have emerged as crucial serological markers for RA [28]. Their presence, often detectable years before the onset of clinical symptoms, emphasizes their significance in early diagnosis and assessment of disease risk. They are important early markers of rheumatoid arthritis in the pre-RA stage. The production of anti-CarP and anti-PAD4 autoantibodies provides additional diagnostic and prognostic value, as well as sheds light on the molecular mechanisms driving the transition from asymptomatic autoimmunity to clinically manifest RA [5, 30, 31, 57]. These findings support the idea that immune dysregulation precedes the development of symptomatic RA, opening a window for early intervention therapy.

The synovial tissue and immune cells in the bloodstream of individuals with RA produce pro-inflammatory cytokines, which contribute to the development of systemic inflammation. The study supports the importance of cytokines, such as TNF-α, IL-6, and IL-17, in maintaining joint inflammation and causing systemic complications [1, 22, 27, 38, 54]. It confirms their involvement in both synovial inflammation and systemic manifestations, such as interstitial lung disease and atherosclerosis [22, 54]. A higher level of IL-4 has been found in the synovial fluid of early-stage RA

compared to established RA. This suggests that IL-4 could be a useful diagnostic biomarker for early RA patients [24]. This finding emphasizes the dual role of cytokines as potential targets for controlling disease and preventing comorbidities. Development of cytokine-blocking therapies leads to more personalized approaches for managing the various clinical manifestations of rheumatoid arthritis.

The analysis of genetic data has revealed significant correlations between certain HLA and non-HLA genes and susceptibility to rheumatoid arthritis. Variations in the HLA-DRB1 gene, particularly those encoding the shared epitope sequence, are strongly associated with an increased risk and severity of the disease [63]. In addition to HLA, other genes such as STAT4, PADI4, and TRAF6 have been linked to immune dysfunction, inflammation, and joint damage [18, 21, 44].

There is a lot of evidence in scientific papers that autoantibodies, genetic changes, and cytokines play a vital role in the development of RA. The incorporation of immunological indicators into diagnostic and prognostic frameworks offers great potential for enhancing early identification, and prevention of RA. This study highlights the potential of these molecular and immunological markers as valuable diagnostic tools and reliable predictors of disease severity and outcome. By elucidating these interconnected pathways, this research opens up opportunities for more accurate diagnostic approaches and personalized treatment plans, ultimately improving the management of RA. These findings highlight the importance of incorporating genetic profiling into the diagnosis and prognosis of RA, thereby paving the way for identifying vital selections of autoantibodies and immune biomarkers that can be used in an immunogenic panel for RA, representing a promising approach to early diagnosis and personalized treatment strategies. Ongoing research continues to validate and expand these panels through multi-omics approaches and cohort studies.

Conclusion

Genetic factors, cytokines, and autoantibodies play a vital role in the development of rheumatoid arthritis. Studies have shown that specific genetic variations can disrupt the regulation of the immune system, leading to the formation of various autoantibodies, which serve as important biomarkers for the disease. Increased cytokines involved in inflammatory processes indicate the activity of the immune response. A deeper understanding of these interactions offers new perspectives for personalized early detection and timely management of RA, helping to prevent the progression of this chronic condition, which can result in significant disability.

Prospects for further research

The future endeavors should thoroughly examine the complex interplay between genetic mutations, cytokine-mediated processes, and the formation of autoantibodies in the development of RA, encompassing the exploration of distinctive genetic and immunological characteristics of autoimmune diseases in the local Kazakh population. Ongoing research will verify the effectiveness of the immunogenic panel in a clinical context and evaluate its usefulness for patient classification, prognostic assessment, and as a means of uncovering genetic profiles for autoimmune diseases.

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