Получена: 04 сентября 2021 / Принята: 18 февраля 2022 / Опубликована online: 28 февраля 2022

DOI 10.34689/SH.2022.24.1.016

УДК 616.72-002.77:575.1

GENETIC ASSOCIATIONS WITH RHEUMATOID ARTHRITIS SUSCEPTIBILITY. REVIEW.

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Abstract

Introduction: Rheumatoid arthritis (RA) is characterized by autoimmune inflammation affecting the joints and the entire body. The prevalence of RA in the world is 0.5-1%, but this indicator varies depending on geographical regions. The etiology of RA is still unknown. The relationship between endogenous and exogenous factors is confirmed by a number of studies. One of the culprits of the development of rheumatoid arthritis and the leading endogenous factors is genetic predisposition, which is a broad subject of study today.

Aim: To demonstrate the relevance of the subject of studying genetic associations with a predisposition to rheumatoid arthritis to the scientific and practical medical community of Kazakhstan**.**

Search strategy: The presented review article was written as part of a study on the AP08052703 project "Determination of microbiomic and genomic biomarkers of rheumatoid arthritis in the Kazakhstan population". Information search was carried out in the PubMed, Trip Database, EMBASE, Medline, Elsiever, GoogleScholar databases. A total of 206 literary sources were found, 100 of which met the selection criteria and were included in this review. *The inclusion criteria*: full-text articles published in English and Russian mainly during the last 5 years. However, for a detailed description of the basic knowledge and mechanisms, earlier sources were also used. *Exclusion criteria:* inappropriate sources, incomplete articles, duplicates, abstracts.

Results and conclusion: Currently, more than 100 loci of HLA and non-HLA genes of RA have been studied. In this article, we tried to focus on the most widely studied or pathogenetically leading genes associated with a high risk of developing RA. The study of genetic predisposition to RA, certainly, requires further extensive research. For our part, we hope that our work will complement the data on the pathogenesis of RA and the role of genetic markers in the development of this pathology.

Key words: *Rheumatoid arthritis, Single nucleotide polymorphism (SNP), Genetic predisposition, Human Leucocyte Antigen (HLA) genes, non-HLA genes, genome-wide association studies (GWAS).*

Резюме

ГЕНЕТИЧЕСКИЕ АССОЦИАЦИИ С ПРЕДРАСПОЛОЖЕННОСТЬЮ К РЕВМАТОИДНОМУ АРТРИТУ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение: Ревматоидный артрит (РА) характеризуется аутоиммунным воспалением, поражающим суставы и весь организм. Распространенность РА в мире составляет 0,5-1%, однако этот показатель варьируется в зависимости от географических регионов. Этиология РА до сих пор неизвестна. Взаимосвязь между эндогенными и экзогенными факторами подтверждается рядом исследований. Одним из виновников развития ревматоидного артрита и ведущих эндогенных факторов является генетическая предрасположенность, которая является широким предметом изучения на сегодняшний день.

Цель: продемонстрировать актуальность темы изучения генетических ассоциаций с предрасположенностью к ревматоидному артриту научно-практическому медицинскому сообществу Казахстана.

Стратегия поиска: Представленная обзорная статья написана в рамках исследования по проекту AP08052703 «Определение микробиомных и геномных биомаркеров ревматоидного артрита в Казахстанской популяции».

Информационный поиск осуществлялся в базах данных PubMed, Trip Database, EMBASE, Medline, Elsiever, GoogleScholar. В общей сложности было найдено 206 литературных источников, 100 из которых соответствовали критериям отбора и были включены в этот обзор. *Критерии включения*: полнотекстовые статьи, опубликованные на английском и русском языках в основном за последние 5 лет. Однако для подробного описания базовых знаний и механизмов также использовались более ранние источники. *Критерии исключения:* неподходящие источники, неполные статьи, дубликаты, рефераты.

Результаты и выводы: на сегодняшний день изучены более 100 локусов HLA и неHLA генов РА. В этой статье мы попытались сосредоточиться на наиболее широко изученных или патогенетически ведущих генах, связанных с высоким риском развития РА. Изучение генетической предрасположенности к РА, безусловно, требует дальнейших обширных исследований. Со своей стороны, мы надеемся, что наша работа дополнит данные о патогенезе РА и роли генетических маркеров в развитии этой патологии.

Ключевые слова: *Ревматоидный артрит, Однонуклеотидный полиморфизм (SNP), Генетическая предрасположенность, гены лейкоцитарного антигена человека (HLA), гены, не относящиеся к HLA, исследования обще геномных ассоциаций (GWAS).*

Түйіндеме

РЕВМАТОИДТЫ АРТРИТКЕ БЕЙІМДІЛІГІ БАР ГЕНЕТИКАЛЫҚ АССОЦИАЦИЯЛАР. ӘДЕБИЕТТІК ШОЛУ.

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Кіріспе: Ревматоидты артрит (РА) буындарға және бүкіл денеге әсер ететін аутоиммунды қабынумен сипатталады. Әлемде РА таралуы 0,5-1% құрайды, бірақ бұл көрсеткіш географиялық аймақтарға байланысты өзгеріп отырады. РА этиологиясы әлі белгісіз. Эндогендік және экзогендік факторлардың өзара байланысы бірқатар зерттеулермен расталады. Ревматоидты артриттің дамуына және жетекші эндогендік факторлардың бірі-генетикалық бейімділік болып табылады, және де ол бүгінгі күнге дейін ғылым аясында кең зерттеу пәні болып табылады.

Мақсаты: Қазақстанның ғылыми-практикалық медициналық қоғамдастығына ревматоидты артритке генетикалық бейімділігі тақырыбының өзектілігін көрсету.

Іздеу стратегиясы: Ұсынылған шолу мақаласы AP08052703 "Қазақстандық популяциядағы ревматоидты артриттің микробиомалық және геномдық биомаркерлерін анықтау" жобасы бойынша зерттеу шеңберінде жазылған. Ақпараттық іздеу PubMed, Trip Database, EMBASE, Medline, Elsiever, GoogleScholar дерекқорларында жүргізілді. Барлығы 206 әдеби дереккөз табылды, олардың 100-і іріктеу критерийлеріне сәйкес келді және осы шолуға енгізілді. *Қосу критерийлері:* ағылшын және орыс тілдерінде негізінен соңғы 5 жылда жарияланған толық мәтінді мақалалар. Алайда, негізгі білім және механизмдерді сипаттау үшін бұрынғы дереккөздер де қолданылды. *Ерекшелік критерийлері:* жарамсыз дереккөздер, толық емес мақалалар, көшірмелер, рефераттар.

Нәтижелер мен қорытынды: Бүгінгі таңда РА гендерінің 100-ден астам HLA және HLAтыс локустары зерттелді. Бұл мақалада біз РА-ның жоғары қаупімен байланысты ең көп зерттелген немесе патогенетикалық жетекші гендерге назар аударуға тырыстық. РА - ке генетикалық бейімділікті зерттеу, әрине, қосымша зерттеулерді қажет етеді. Өз тарапымыздан, біздің жұмысымыз РА патогенезі және осы патологияның дамуындағы генетикалық маркерлердің рөлі туралы мәліметтерді толықтырады деп үміттенеміз.

Түйінді сөздер: *Ревматоидты артрит, Бір нуклеотидті полиморфизм (SNP), Генетикалық бейімділік, Адамның лейкоциттік антигенінің гендері (HLA), HLA-ға жатпайтын гендер, Жалпы геномдық қауымдастықтарды зерттеу (GWAS).*

Библиографическая ссылка:

Issilbayeva A.A., Ainabekova B.A. Genetic associations with rheumatoid arthritis susceptibility. Review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2022, (Vol.24) 1, pp. 139-146. *doi:10.34689/SH.2022.24.1.016*

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Introduction

Rheumatoid arthritis (RA) is characterized by the autoimmune inflammation affecting joints and the whole organism. The global prevalence of RA is accounted for 0,5 -1%, however, this indicator varies by geographical regions [72, 57, 21]. Females are usually more affected by this disease compared to male; the ratio is 3:1 [57]. The etiology of this disease is still unknown. The relationship between endogenic and exogenic factors is proved by the number of studies [16, 44, 79, 83]. One of the culprits of the RA development and the leading endogenic factors is genetic predisposition, which is a broad subject of study today. There are several genome-wide association studies (GWAS) that have identified several HLA and non-HLA genes that lead to a predisposition to rheumatoid arthritis [12, 22, 35, 38, 41, 54, 56, 58, 76, 79]. A large-scale study was conducted by Okada et al. to identify 100 non-HLA RA gene loci, confirming their key role in the development of RA [63]. Genetic predisposition to RA varies in different populations. In this review article, we will look at the main and widely studied representatives of these genes.

Aim: to demonstrate the relevance of the subject of studying genetic associations with a predisposition to rheumatoid arthritis to the scientific and practical medical community of Kazakhstan.

Search strategy: The presented review article was written as part of a study on the AP08052703 project "Determination of microbiomic and genomic biomarkers of rheumatoid arthritis in the Kazakhstan population" of the Ministry of Education and Science of the Republic of Kazakhstan. Information search was carried out in the PubMed, Trip Database, EMBASE, Medline, Elsiever, GoogleScholar databases. A total of 206 literary sources were found, 100 of which met the selection criteria and were included in this review. *The inclusion criteria:* full-text articles published in English and Russian mainly during the last 5 years. However, for a detailed description of the basic knowledge and mechanisms, earlier sources were also used. *Exclusion criteria:* inappropriate sources, incomplete articles, duplicates, abstracts.

Results:

HLA-genetic predisposition. According to several studies class II major histocompatibility complex genes, particularly, human leukocyte antigens (HLA)- DR demonstrated the great input to the RA development [12, 35] accounting for 30% of heritability to RA [38]. The HLA-DRB1 and its shared epitope (SE) were recognized to play a crucial role in RA susceptibility, the presence of these genes is strongly associated with disease severity [76]. The relationship with these genes and the development of extra-articular manifestations in patients with RA was proved by several studies [41, 54, 76]. The concordance between RA susceptibility and these genes presence has been proven in studies of RA among twins [22]. Traylor at el. conducted the Meta-analysis of seven GWAS articles and confirmed the association between the HLA-DRB1 shared epitope and RA radiological damage [79]. The genes of the HLA system, of course, occupy a huge niche in the research on the etiopathogenesis of RA and requires special attention and further study.

Non-HLA-genetic predisposition.

PTPN22. Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) provides negative regulation of T-cell receptor (TCR) signaling pathways by the induction of dephosphorylation process [55]. Nabi et al. showed high relationship of PTPN22 (C/T) polymorphism with RA susceptibility in Caucasians, however there was not any association of this SNP with RA in Asians [58]. The systematic review that included 52 case–control studies, revealed significant correlation of PTPN22 gene rs2476601 with RA according to all hereditary models. This SNP is predominated in Caucasian and African populations [1]. According to Newman et.al PTPN22 associated with the high risk of autoimmune thyroid disease formation in the RA patients, which in turn worsens the disease prognosis [60]. This gene also was identified in patients with juvenile idiopathic arthritis, which further may transform to RA [77].

PADI. Citrullination process that plays an essential role in RA manifestation is catalyzed by a group of peptidylarginine deiminases (PADs) including PADI 1, 2, 3, 4 and 6 [8]. Thus, PADI4 (Peptidyl Arginine Deiminase) leads to RA formation via arginine`s citrullination, playing a crucial role in regulation of stem cell function [4, 86]. PADI4 has shown significance in RA development among Asian ancestry [49]. Plenge et al. and Cheng et al. identified high association of PADI4 with RA in North American and Chinese population, respectively [11, 65]. However, Chen et al. in other work demonstrated contradictory results, there was not any proof of association of PADI4 and Han Chinese population in this work [10]. Mergaert et al. had also showed strong correlation of PADI4 with RA in North American cohort [53]. According to the largest study of Burr et al. the PADI4 genotype was not associated with RA in Caucasian population [7]. Swedish, French, British and Spanish data also confirm the absence of relationship of this SNP with RA susceptibility [52, 65, 66]. There are some studies that have aimed to study the PADI2 relationship with RA susceptibility and confirmed it [8]. Guzma et al. in recent study showed the strong correlation of this gene with RA in Mexican population [26].

CTL4. RA pathogenesis` major mechanism includes various T-cell activation pathways. CTLA-4, CD28 and CD40 are genes that own the essential position in T cells` stimulation and inhibition processes. Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4), the member of immunoglobulin superfamily, encodes the protein which sends the inhibitory signal to T cells and provides it`s regulation [13]. It is also responsible for inhibition of the differentiation of monocytes into osteoclasts [69] and regulates peripheral tolerance [25]. Walker et al. presented the study affirming the association of this gene in Canadian patients with RA [85], while the Aslam et al. revealed the genetic association of CTLA4 with the risk of RA in the Pakistani population [3]. The several meta-analyses determined whether CTLA4 is supports predisposition to RA manifestation [23, 29, 42]. Recently, Zhou et al. conducted meta-analysis confirming the association of this gene polymorphisms with the risk of RA in both Asian and European population [89].

CD28. This gene encodes the protein that regulates the T-cell proliferation, cytokine production, and T-helper formation [46]. Luterek-Puszyńska et al. recent study didn`t show any significant correlation between CD28 and CTLA-4 gene polymorphisms and RA patients in Poland, however there was weak association between CTLA-4 gene polymorphism and RA activity in this cohort [50].

CD40. This gene is one of the TNF-receptor superfamily. It encodes the protein which plays the role of receptor on antigen-presenting cells and owns substantial role in various immunological responses, such as T cell regulation and B cell formation [19, 34]. All these processes lead to an inflammatory process, damage all components of the joints and formation of extra-articular manifestations. This gene also regulates the costimulating signaling of T cells that enhances the inflammatory process during RA [72,87]. Fernández et al. studying the correlation of CD40 gene and clinical features of RA, identified alteration of this gene loci expression in female patients with RA [81]. Liao et al. also showed the association of CD40 with RA in female patients [43].

STAT4. Signal Transducer and Activator of Transcription 4 (STAT4) is a gene that encodes protein which is a member of the STAT family, which in turn undergo phosphorylation in response to proinflammatory cytokines and activates the transcription process and usually these factors are activated by interleukin-12. This protein also plays a crucial role in T helper cells` differentiation and proliferation processes [61]. Several authors aimed their study to identify the contribution of STAT4 to RA development and successfully proved it [28,78]. Elshazli et al. conducted meta-analysis confirming the relation of PTPN22 rs2476601 and STAT4 rs7574865 to RA susceptibility in major ethnic groups [20]. Jiang et al. presented the research outlining the STAT4 correlation with RA in Asian cohort [32].

TAGAP. T cell activation Rho GTPase activating protein (TAGAP) plays an important role in the regulation of T-cell activation by changing the cytoskeleton of these cells [5]. It was revealed in patients with RA of Caucasian and Asian population [74]. Chen et al. confirmed the contribution of this gene to RA development [11]. Chatzikyriakidou et al. suggests that single nucleotide polymorphism rs212389 better predicts the association of TAGAP with RA [8]. In study of Castro-Santos et al. TAGAP gen loci showed significant association with RA ($p=5 \times 10-3$) along with STAT4 loci in Latin America population [82]. While Perkins et al. found out that TAGAP rs1738074 and rs4709267 alleles associated with RA in healthy cohort of African American compared to main RA group [63].

COG6. Component of oligomeric Golgi complex 6 (COG6) gene which provides the normal functioning of the Golgi apparatus [37]. Márquez et al. revealed the strong association of this gene loci with RA susceptibility in RA and SLE patients [51]. This gene polymorphisms are also associated with psoriatic and juvenile idiopathic arthritis development [48,77].

TRAF1. Tumor necrosis factor (TNF) receptor-associated factor-1 (TRAF1) encodes the protein which is a member of the TNF receptor associated factor (TRAF) superfamily which regulates the anti-apoptotic process [17]. An interesting fact is that Epstein-Barr virus (EBV), which is the major trigger of RA, stimulates the expression of this gene [83]. Plenge et al. in their study showed the significant association of PTPN22 and TRAF1 with RA debut, with p value less than $5\times10-8$ [65]. The correlation of this gene and radiological progression of RA was identified in Egyptian and Iceland cohorts, moreover STAT4 loci also confirmed it`s position [35, 55].

SYNGR1. Synaptogyrin 1 (SYNGR1) is gene encoding the protein located in membrane of neuronal cells [34]. Although the function of this protein is still unknown to science, there were several studies conducted on mice, which demonstrated it`s effect on synapsis [6]. Despite the fact, that earlier this gene was more often associated with schizophrenia [30], today there are number of works confirming the role of this polymorphism in the development of RA. Thus, Liu et al. identified strong correlation with RA risk and this gene presence in European and Korean populations [47].

RASGRP1. RAS guanyl releasing protein 1 (RASGRP1) activates certain kinase secretion and regulates T-cells and B-cells development and differentiation [73]. Ruiz-Larrañaga et al. obtained the data confirming the RASGRP1 contribution to RA formation in European population [70]. The study of Golinski et al. which included the TNF-inhibitor treated RA patients identified RASGRP1 dysregulation in RA patients [24].

ETS1. Proto-oncogene 1, transcription factor (ETS1) encodes a protein, which leads to activation or expression of large number of genes, as a result, playing an important role in the immune tolerance [16]. Zhang et al. determined the association between the ETS1 rs1128334 G/A genotype with the high risk of RA development in a Chinese population [88]. This gene was also associated with bone erosion formation in RA patient of Chinese population. The determined association of this gene with Sjogren 's syndrome was found, which in turn significantly aggravates the course and worsens the prognosis of rheumatoid arthritis [71].

FCRL3. Fc receptor like 3 (FCRL3.) encodes a protein that influence the activation and suppression of immunoreceptors [59]. Mutations in this gene have been associated not only with RA, but also with autoimmune thyroiditis and systemic lupus erythematosus [36]. Newman et al. conducted the study aiming the FCRL3 and PTPN22 genes assessment and got contradictory results, such as the negative correlation between PTPN22 and FCRL3 C allele in RA formation ($p = 0.0008$, $p = 0.001$, respectively), moreover FCRL3 presence decreased the risk of AITD in the RA patients [60]. Ramírez-Bello J. et al. reported that FCRL3 gene`s SNP showed the protective features in combined cases of juvenile RA and asthma in Mexican patients with RA of male sex [68]. The recent study of Lin et al. identified significant linkage of FCRL3 -169T/C variant with an increased ACPA positive RA formation risk in the Chinese Han population [45].

LBH. Llimb bud and heart development (LBH.) is a regulator of WNT (wingless-related integration site) signaling pathway [75]. This gene evolved in synovial pathology process in RA patients, being regulated by growth factors, it leads to hyperplasia of synovium [18]. Ekwall et al., continuing the study of this gene, concluded that it affects enhancer function and control cell lifetime

cycle [18]. This gene loci contribution to RA formation was noted in several studies [38, 62, 67]. Sun et al. in their study didn`t identified any association of LBH with RA in a Chinese population. However, the decreased levels of LBH`s mRNA in peripheral blood mononuclear cells was determined [75].

The association of the LINC01104(long intergenic non-protein coding RNA 1104) locus with the development of RA was also revealed in several GWAS [74, 77].

Recent genetic population studies.

Danilla et al. conducted the study aiming the evaluation the contribution of genes, early confirmed in other ethnicities, in African American population. According to their data HLA-DRB1 showed the strongest correlation with RA susceptibility, in turn CTLA4, TRAF1 and ETS1 gene loci were associated with radiographic severity and joint deformation in RA patients [14]. Allam et al. in their study of PTPN22 (rs2476601) and PADI4 (rs2240340) polymorphisms` distribution, couldn`t find out any prove of this SNPs presence in Algerian patients with RA, however, the correlation between seropositive RA form and PTPN22 (rs2476601) was identified [2]. Zhu et al. studying the genetic predisposition to RA among European and Asian populations, identified 221 novel RA-related genes and 20 of them were highly verified: TUBB, HSP90AB1, RPS18, BRD2, PHTF1, MAPK13, BAK1, HLA-F, IER3, RNASET2, HLA-G, ZKSCAN4, HFE etc. [90]. Laufer et al. presented the study of replication of 33 genetic variants previously associated with RA in persons of EUR/Asian ethnicity on African American population, moreover this study also checked the prevalence of 4 new RA associated polymorphisms, such as PADI2 rs761426, CSMD3 rs2203098, GPC5 rs9516053 and RBFOX1rs4602043, that showed the significance at least in one of the worldwide populations [39]. Recently, Leng et al. performed GWAS on 1027 RA cases and 2879 controls, identifying five new susceptibility loci (IL12RB2, BOLL-PLCL1, CCR2, TCF7 and IQGAP1) of RA in Chinese population [41]. According to GWAS conducted by Hayashi et al. GALNT12 rs2295926 and KCNN2 rs11958855 was strongly associated with rapid joint destruction in RA [27].

Conclusion

The study of the genetic predisposition of RA, certainly, requires further extensive research. In this paper, we tried to focus on the most widely studied or pathogenetically leading genes associated with a high risk of developing RA. For our part, we hope our work will supplement the data on the pathogenesis of RA and the role of genetic markers in the development of this pathology.

Author contribution: *All authors took equal participation in writing this review article.*

Conflict of interest: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

Funding: *Financial support for publication of this review article was given from the grant AP08052703 "Determination of microbiomic and genomic biomarkers of rheumatoid arthritis in Kazakhstan population" of the Ministry of Education and Science of the Republic of Kazakhstan.*

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