

<https://doi.org/10.17816/ecogen17477-90>**THE POLYGENIC NATURE OF RHEUMATOID ARTHRITIS**

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☼ Current advances in the genetic basis of rheumatoid arthritis (RA) were summarized in the review. Influence of gene polymorphisms involved in different cellular processes including cytokine-mediated signal transduction, immune and inflammatory responses to exogenous stimuli was discussed. The principal role of the major histocompatibility complex (MHC) and a shared epitope (SE), as well as contribution of non-*HLA* genes to susceptibility to RA was considered in terms of patients' ethnicity and the serological status for the disease. The GWAS results for revealing candidate genes closely associated with RA risk were systematized as well as some aspects of epigenetics were mentioned. The findings indicated the polygenic nature of this complex disease. This problem was considered taking into account the recent results of mapping traits (eQTLs) with global gene expression. The novel "omnigenic" conception of heritability of complex traits/diseases was reported.

☼ **Keywords:** rheumatoid arthritis; immune and inflammatory responses; gene polymorphism; gene expression.

ПОЛИГЕННАЯ ПРИРОДА РЕВМАТОИДНОГО АРТРИТА

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☼ В обзоре обобщены современные достижения в изучении генетических основ ревматоидного артрита. Обсуждается влияние на предрасположенность к заболеванию аллельных вариантов генов, участвующих в различных клеточных процессах, включая опосредованную цитокинами сигнальную трансдукцию, воспалительный и иммунный ответ на экзогенные стимулы. Основная роль главного комплекса гистосовместимости (MHC, Major Histocompatibility Complex) и общего эпитопа (SE, Shared Epitope), а также эффекты не относящихся к этому комплексу (non-*HLA*) генов проанализированы в зависимости от этнической принадлежности и серологического статуса пациентов. Систематизированы результаты полногеномных ассоциативных исследований (GWAS, Genome Wide Association Studies) для выявления генов-кандидатов, тесно связанных с риском развития заболевания, а также затронуты некоторые аспекты эпигенетики ревматоидного артрита. Представленные в обзоре данные указывают на полигенный характер предрасположенности к данному многофакторному заболеванию. Эта проблема рассмотрена с учетом новейших результатов картирования и оценки вклада локусов количественных признаков (eQTLs, expression Quantitative Trait Loci), модулирующих уровень экспрессии одного или более генов. Изложена новая «омнигенная» концепция наследуемости комплексных признаков/болезней.

☼ **Ключевые слова:** ревматоидный артрит; иммунный и воспалительный ответы; генетический полиморфизм; экспрессия генов.

INTRODUCTION

Rheumatoid arthritis (RA) is a classic multifactorial autoimmune disease [1] primarily affecting small joints and proceeding as an erosive destructive polyarthritis. RA prevalence among the world's population is 0.5%–1%. The disease develops in middle age and later years mainly in women. It is characterized by pain and inflammatory syndrome and has a progressive course. Its social significance is unquestionable, since the disease leads quickly to loss of labor capacity and disability due to joint deformity and ankylosis, which greatly affects

the quality of life of patients. Currently, treatments for RA can only ease the symptoms and are not a cure. Therefore, an intensive search is ongoing across the world for the causes of RA and factors (exogenous and endogenous) contributing to its development, as well as the biological markers of early diagnostics, prognosis of the clinical course, and individual sensitivity to treatment.

The origin, distribution, some aspects of etiology and pathogenesis, and the clinical characteristics of RA have been discussed in previous reviews [2–4]. This study fo-

cuses on the genetics and epigenetics of RA. To date, hundreds of genes that contribute significantly to the development of RA are known, along with their polymorphisms, yet in the words of Perricone et al., their discovery is “a never-ending story” [5]. Over the past 10 years, it has become clear that, in addition to genetic polymorphism, the development and phenotypic manifestation of the disease are significantly affected by the expression of certain genes and their products. A quantitative assessment of the expression levels of genes associated with autoimmune and inflammatory responses, together with data from genome-wide association studies (GWAS) and epigenetic studies, represents the contemporary scientific basis for a comprehensive investigation into RA pathogenesis. This may allow an individual approach to diagnostics and treatment of the disease, thereby increasing the chances of successful therapy for each patient.

INFLAMMATION AND AUTOIMMUNITY IN THE PATHOGENESIS OF RA

Joint damage in RA occurs as a result of the chronic inflammation of the synovial fluid due to the interaction of resident cells, such as fibroblast-like synoviocytes, with cells of innate (macrophages, dendritic cells, mast cells, and neutrophils) and adaptive (B- and T-lymphocytes) immunity [3, 5, 6]. Synoviocytes acquire the traits of macrophages, secrete pro-inflammatory cytokines, become antigen-presenting cells (APCs), and cause the activation of type 1 T-helper cells. As a result, an autoimmune response occurs, which ultimately leads to the activation of osteoclasts, which gradually destroy the cartilage and bone tissue.

In recent years, the ability of neutrophils to form an extracellular structure has been discovered, that is, a “trap” for pathogens (neutrophil extracellular trap (NET)). NETosis is the primary defense mechanism in the early stages of the inflammatory cascade [2]. In RA, neutrophils in the synovial fluid and peripheral blood show increased NETosis after stimulation with serum antibodies or pro-inflammatory cytokines, and spontaneous formation of a NET is induced by reactive oxygen species. Its components include cytoplasmic and extracellular citrulline antigens, which serve as targets for autoantibodies and act as inducers of the subsequent formation of such traps in rheumatoid and juvenile idiopathic arthritis [7].

Impaired regulation of the adaptive immune system also significantly affects the development of RA, since many types of T-lymphocyte are active players in the field of the pathological process, supporting inflammation

through the production of a number of signaling molecules, including cytokines and chemokines [2, 6].

Thus, RA pathogenesis involves various processes and components of innate and adaptive immunity, which begin to perceive the body's own tissues as foreign. Immune cells, soluble mediators, adhesive molecules, and autoantibodies contribute to the development of inflammation, leading to destructive changes in the joints and internal organs. Understanding the molecular mechanisms underlying the pathogenesis of RA contributes to the development of new, more effective ways, and means of treating the disease.

GENETIC BASIS OF RA

The basis of RA pathogenesis is presented by a triad of genetic predisposition, environmental influences, and autoimmunity, sometimes known as the Bermuda Triangle [8]. In this triad, a significant proportion is heredity, as evidenced by studies in twins and monitoring of incidence in families [9, 10].

Among the possible genetic factors contributing to the disease development, the genes of the main histocompatibility complex, or human leukocyte antigen (HLA), play a fundamental role. The HLA locus occupies a 7.6 Mb site on chromosome 6 (6p21) and contains 250 highly polymorphic genes responsible for the production of glycoproteins in cell membranes [11]. HLA proteins (antigens) ensure the presentation of endogenous and exogenous peptides processed in APCs to T-lymphocytes. They also regulate the immune response to foreign and own antigens in the context of own HLA determinants [12, 13]. HLA antigens are divided into classes I and II. Class I antigens are necessary for the recognition of transformed cells by cytotoxic T-lymphocytes, whereas class II antigens provide the interaction between APCs and T-lymphocytes during the immune response.

QKRAA, QRRAA, and RRRRAA amino acid motifs in residues 70–74 of the hypervariable region of the disease resistance β (DR β) chain, known as a shared epitope (SE) and encoded by some members of the allelic group (*HLA-DRB1*)*04 or *HLA-DRB1**01, as well as the alleles *HLA-DRB1**14:02 and *HLA-DRB1**10:01 [12], not only increase the risk of RA, but they are also associated with more serious erosive changes in the bone and titers of cyclic citrullinated peptide antibodies (CCPAs) [14, 15]. By contrast, the 70-DEAAA-74 motif is associated with a protective effect [13]. It has been revealed that alleles encoding this motif, particularly *HLA-DRB1**13, reduce the likelihood not only of RA but also of other autoimmune diseases [16].

The important diagnostic markers of RA are serological parameters such as rheumatoid factor (RF) and CCPA. Depending on the presence or level of these antibodies, RA is attributed to either seropositive or seronegative arthritis; in percentage terms, they constitute 75%–85% and 15%–25%, respectively [17, 18]. Owing to the increased affinity of a protein containing an SE to citrulline antigens, the likelihood of seropositive arthritis increases. Indeed, it has been demonstrated in Swedish and North American populations that the *HLA-DRB1* alleles represent a significant risk factor for the development of CCPA-positive, but not CCPA-negative, arthritis [19, 20]. However, a number of works, including those conducted in European countries, indicate the relationship of SE with seronegative RA [21, 22]. The contribution of the disease resistance (DR) 3 allotype to the formation of a predisposition to seronegative RA in Europeans has been established [23], and DR14 and DR8 have been shown to contribute to that in the Japanese population [24]. Evaluations of heritability at both serological statuses also showed that the contribution of the alleles of the SE of the *HLA-DRB1* locus was markedly different, accounting for 18% of heritability of RA in patients who were CCPA-positive and only 2.4% in patients who were CCPA-negative [25]. These data, along with some others, enabled us to consider seropositive and seronegative RA as genetically independent diseases [13].

When studying the ethnic specificity of the association of individual HLA genotypes/alleles with RA, it was revealed that in Europeans with seropositive RA, the SE is predominantly encoded by the *HLA-DRB1**04:01, *04:04, 01:01, and 10:01 alleles, whereas in East Asians, the most common is the SE-coding *DRB1**04:05 allele [26]. In North American indigenous populations and natives of Alaska, the *DRB1**14:02 allele manifests itself as a risk factor for the severe course of the disease [27]. In African Americans, the frequency of SE-coding alleles is approximately one-third compared with people of European descent, while remaining the risk factor for RA [28]. Recently, the absence of fundamental differences between subpopulations of African and European descent in the UK has been established [29]. In Latin America, association of RA with the HLA region of class II and some other genes, which are also characteristic of the European and Asian populations, were found [30]. Asian ethnic groups, including those inhabiting Malaysia, also showed an analogy with Europeans, since they lacked the connection of a number of alleles of the SE with seronegative arthritis [31].

Thus, the HLA locus polymorphism plays a key role in the development of RA in various populations, demonstrating a certain ethno-specificity with respect to the disease risk alleles. The associations of alleles of a given locus with RA depend on the patient's seropositive or seronegative status. Further study of this problem would be relevant from the point of view of fundamental science and practical medicine.

In addition to the *HLA-DRB1* alleles, the role of the so-called non-HLA genes that are not related to the major histocompatibility complex has been identified [8, 32]. These include *PTPN22*, *IL23R*, *PADI4*, *TRAF1*, *CTLA4*, *IRF5*, *STAT4*, *FCGR3A*, *IL6ST*, *IL2RA*, *IL2RB*, *CCL21*, *CCR6*, *CD40*, and other genes involved in signal transduction and regulation of the activity of interferons, cytokines, chemokines, and their receptors that initiate and support inflammation.

In some cases, non-HLA gene variants increase the risk of RA in different populations, and others, conversely, show ethnic specificity. For example, an association of the T allele of the *STAT4* locus (rs7574865) with RA has been found in both European and Asian populations (odds ratio (OR) [95% confidence interval (CI)] = 1.3 [1.195–1.414], $p < 0.001$; OR [95% CI] = 1.216 [1.135–1.303], $p < 0.001$, respectively) [33]. The stratification of patients by ethnicity in Elshazli's and Settin's work [34] showed that the T allele, CT, and TT genotypes of the *PTPN22* locus (rs2476601) and the T allele, GT, and TT genotypes of the *STAT4* locus (rs7574865) are significantly associated with RA in individuals of European, Asian, and African descent, whereas the TT genotype of the *PTPN22* locus is associated with RA in Europeans, but not in Asians and Africans, and the TT genotype of the *STAT4* locus is associated with RA in Europeans and Asians, but not in Africans. No evidence was found on the associations of single nucleotide polymorphisms (SNPs) in the *TRAF1/C5*, *CD40*, and *CCL2* genes with RA in the Korean population [35]. The connection between the *PTPN22* gene polymorphism and RA for European populations, and the *PADI4* gene for populations of Asian origin was established [36]. As for the fragment crystallizable (FC)-gamma receptor (FCGR) loci, although the *FCGR3B* polymorphism was not shown to modify sensitivity to RA, *FCGR2A*, and *FCGR3A* were associated with the disease in Europeans, while remaining neutral in Asians [37]. A meta-analysis of 32 studies involving samples from 25,059 patients with RA and 25,466 control individuals revealed the effect of 1858C/T polymorphism at the *PTPN22* locus (rs2476601) on RA susceptibility in Caucasians (OR = 1.612, 95% CI:

1.544–1.683, $p < 0.001$), whereas in Asians, the frequency of the minor allele of this gene was extremely low [38, 39]. It is a characteristic that this polymorphic variant is associated with a seropositive subtype of the disease and is less common in the RF- or CCPA-negative patients. In the Egyptian population, variant 1858C/T (rs2476601) was identified in a heterozygous form in only two (out of 100) patients with RA and was not detected at all in the control group [40]. By contrast, the association of the polymorphic variant of the *STAT4* gene (rs7574865) with RA was established, and it prevailed RF- or CCPA-positive patients.

The results of the studies of the polymorphism of the *HLA-DRB1* locus and polymorphic variants of 11 genes (*PTPN22*, *STAT4*, *CTLA4*, *TRAF1/C5*, *IRF5*, *TNFAIP3*, *AFF3*, *PADI4*, *CD28*, *CSK*, and *FCGR3A*) in CCPA-positive RA in the population of Slovakia are the most interesting for us [41]. The authors showed a close relationship between SE-coding alleles and the development of seropositive RA, and among the non-HLA gene variants, risk alleles, and genotypes were identified in the *PTPN22*, *STAT4*, *IRF5*, and *PADI4* loci. By their significance, the genotypes were arranged in the following order: SE0 > *IRF5* TT > SE1 + SE2 > *STAT4* GG > *PADI4* CC + *PADI4* TT > *PTPN22* CC.

Therefore, in contrast with the fundamentally similar effects of polymorphic variants of HLA genes in ethnically diverse populations, many meta-analyses show differences between Europeans and Asians, as well as other ethnic groups, in the effect of non-HLA genes on population sensitivity to RA. It should be emphasized that the data presented in most cases indicate the association of genetic markers with seropositive (CCPA⁺, RF⁺) arthritis, which may be due to the dominance of the disease seropositive subtype in adults, and a larger sample size of these patients, which enables us to draw statistically valid conclusions.

In the pathogenesis of any autoimmune disease with a pronounced inflammatory component, an important role is played by cytokines, among which the tumor necrosis factor (TNF- α) and interleukins (ILs), which stimulate inflammation, and degradation of bone and cartilage, stand out. Therefore, their level in the blood plasma of patients with RA enables us to determine the phase of the disease. In addition, it was found that the pre-disease stage, which lasts from several months to several years, is characterized by the presence of circulating autoantibodies in the blood, an increased concentration and range of inflammatory cytokines and chemokines, and altered metabolism [3], which can serve

as the disease biomarkers at an early pre-symptomatic stage.

TNF- α exhibits its biological activity upon binding to specific membrane receptors. Soluble tumor necrosis factor receptor I (STNF-R1), also known as CD120a, predominates, and is expressed by cells of most types of tissues. It is involved in apoptosis and has antiviral activity [42]. By contrast, the tumor necrosis factor receptor II (TNF-RII or CD120b) promotes cell proliferation [43]. The combination of clinical and experimental data shows that the presence of soluble forms of TNF- α receptors in blood and other biological fluids is an important diagnostic and prognostic marker of the disease [44].

The *TNFA* gene is located on the sixth chromosome (6p21.3) at the major histocompatibility complex (MHC) locus [45]. More than 30 polymorphic variants of the gene are known, but approximately half of them affect the protein expression *in vitro*. The most significant for humans are single nucleotide substitutions at positions -308G/A (rs1800629) and -238G/A (rs361525), which can change the transcription rate and the level of TNF- α production [46, 47]. However, studies of the associations of these variants with RA did not produce the expected results: *TNFA*-308G/A polymorphism (rs1800629) was found to be associated with the development of the disease in Latin America, but not in other populations [48, 49]. The gene promoters, -609G/T and -238G/A, were also not associated with RA [50]. Contradictory data were obtained regarding the effects of *TNFA* gene polymorphism on the course of the disease. Patients with AA and AG genotypes at position -308 showed accelerated disease progression, with the development of erosive arthritis in one study [51], whereas in another, the authors did not consider this variant as a predictor of destructive joint damage [52]. Although it is established that an elevated TNF- α content in a patient's biological fluids indicates the active phase of the disease, the data on the effect of the above genetic variants on RA susceptibility are contradictory and mostly negative. This may be due to the small frequencies of minor alleles at the studied loci. For example, the frequency of the A allele of the *TNFA* -308G/A variant (rs1800629) in the Belarusian population varies within 11.4%–12.8%, and no homozygous carriers of this allele were found in the studied population samples [53–55].

Interleukins represent a large group of cytokines synthesized by leukocytes, mononuclear phagocytes, and other immune cells and, in turn, affect the production, and differentiation of T- and B-lymphocytes and hemato-

poietic cells. Variants of genes encoding cytokines have been studied in connection with erosive joint damage. Among them, 511A/G (rs16944) in the *Interleukin 1 beta* (*IL-1B*) gene promoter is positively associated with RA, and the +3954T allele of this gene contributes to more severe structural damage to joints [5, 32]. A meta-analysis of a number of studies revealed that, depending on the ethnicity of patients, statistically significant associations exist between RA and the *IL-6* -174G/C polymorphism in European and Asian populations, and the -572G/C polymorphic variant of this gene showed an association with RA in Asians, but not in Arabian populations [56]. More recently, an association has been identified of the *IL6* 174G/C variant (rs1800795) with RA in Belarus [57]. Analysis of the frequency distribution of the genotypes for the locus under study revealed a tendency to change in the group of patients with RA compared with the control group ($p = 0.08$) because of an increase in the frequency of CC genotype (OR [95% CI] = 1.75 [1.02–3.02], $p < 0.05$). Statistically significant differences were also found in the distribution of allele frequencies ($p = 0.02$).

The biological significance of the polymorphism of interleukin genes and their receptors in RA was reported in a review by Magyari et al. [58], who analyzed the functions of interleukins belonging to different classes, the dependence on serological variants of RA of the revealed associations, and the ethnicity of patients. It was found that polymorphic variants of these genes, to varying degrees modify the risk of developing the disease, manifesting, in some cases, ethnic specificity and the opposite effects. Thus, a meta-analysis of 10 European, 7 Asian, and 1 Latin American populations revealed an association of the +3953C>T polymorphism of the *IL-1B* gene with RA in the Asian cohort only. In the Chinese population, the probability of RA increased under the influence of the 592C>A (rs1800872) polymorphism of the *IL-10* gene [59].

Along with the risk potential of allelic variants of interleukin genes, it was found that some reduce the population's sensitivity to the disease development. A 25% reduction in the risk of developing RA was shown in European carriers of the polymorphic variant -1082A/G (rs1800896) of the *IL-10* gene [58], and the variant -3575T>A (rs1800890) of *IL-10* among the Chinese had the same effect [60]. This protective effect was established in the G allele of -1464C>G variant (rs1143623) of the *IL-1B* gene, and aggressiveness of the disease was weakened because of the *IL-27*-mediated suppression of osteoclastogenesis [58].

Thus, at this stage, the search for candidate genes mainly focused on genes involved in the immune and inflammatory response, cytokine signaling pathways, and other pathogenetically important cellular processes. Some aspects of the implementation of the risk potential of polymorphic HLA loci and genes not related to this complex have been proved. The *HLA-DRB1* SE-coding alleles showed a more stable association with RA. However, risk alleles could vary depending on the ethnic origin of the patients, and these were more closely associated with seropositive arthritis. Data on the effect of non-HLA genes on the predisposition to RA were found to be ambiguous for several populations, making it necessary to study this problem under specific ethnogeographical conditions.

GWAS

In contrast with the methods of analysis of one or several specific genome regions, when the “candidate” approach is used in case–control studies, in GWAS the entire DNA, the entire DNA sequence is analyzed, which enables us to identify the relationship of certain SNPs with the disease or its traits [61].

To date, verified associations of 14 autoimmune diseases with more than 250 loci have been established using GWAS [62, 63], some of which have manifested in various diseases. A meta-analysis of a cohort of more than 100,000 individuals of European and Asian origin, genotyped for 10 million SNPs, revealed 98 candidate genes belonging to different pathogenetic pathways of RA [64]. Among 42 new loci associated with RA in the general sample, the majority (27) showed a similar relationship among Caucasians, and a smaller portion (6) among Asians. Most risk alleles were involved in the regulation of immunity and combined immunodeficiency and were related to the molecular pathways of B- and T-cell-mediated immunity and cytokine-mediated signal transduction. The role of several genes as targets for improved RA therapy has been confirmed.

A meta-analysis of 22 GWAS results (18 studies in European populations and 4 studies of Asian patients) identified 221 genes associated with RA [65]. This new list included 71 common genes for patients of European and Asian descent, 76 genes specific to Europeans, and 74 genes most common to Asians. In addition, it was found that genes peculiar to people of Asian origin form clusters within chromosome 6, whereas the European risk genes are characterized by a relatively uniform distribution across different chromosomes, which may be associated with a high genetic heterogeneity of RA in Europeans. More than half of the allelic variants identified

in Asians belonged to the family of histone (1H) genes, which constitute less than $1/10$ of all European genes. It is well known that histones are involved in the regulation of DNA repair, replication and transcription and maintain the stability of chromosomes, which, in combination with new data, gives insight into ethnic differences in the etiology and pathogenesis of RA.

The GWAS and meta-analysis of a number of such studies every year add to the list of genes with predisposition to RA in various ethnic groups. In Slavic populations, genes most closely associated with RA in Caucasians are of interest. Those previously established include the following: rs6910071 of the *HLA-DRB1* gene (OR = 2.88 [2.73–3.03]), which confirmed the association with RA at $p < 10^{-299}$; rs2476601 of the *PTPN22* gene (OR = 1.94 [1.81–2.08]), which proved an association with RA at $p = 9.1 \cdot 10^{-74}$; and rs6920220 and rs5029937 of the *TNFAIP3* gene (OR = 1.22 [1.16–1.29] $p = 8.9 \cdot 10^{-13}$ and OR = 1.40 [1.24–1.58] $p = 7.5 \cdot 10^{-8}$, respectively) [66, 67]. The risk significance of the rs2230926 and rs5029937 polymorphic variants of the *TNFAIP3* gene was convincingly confirmed by meta-analysis of 18,014 cases and 20,112 control samples [67]. A statistically significant association with RA, though at a slightly lower level, was found in rs3761847 of the *TRAF1/C5* gene (OR = 1.13 [1.08–1.88] $p = 2.1 \cdot 10^{-7}$). The listed SNPs increased the sensitivity to the disease, and rs3087243 of the *CTLA4* gene (OR = 0.87 [0.83–0.91] $p = 1.2 \cdot 10^{-8}$) and rs4810485 of the *CD40* gene (OR = 0.85 [0.80–0.90] $p = 2.8 \cdot 10^{-9}$) reduced the likelihood of RA. Among the newly detected allelic variants, the closest association with RA in Caucasians was shown for *HLA-F* (Online Mendelian Inheritance in Man database (OMIM) 143110) at $p = 1.03E-31$, *HLA-DMA* (OMIM 142855) at $p = 2.75E-133$, and *HLA-G* (OMIM 142871) at $p = 3.34E-34$. Risk factors also included genetic variants of *PHTF* (OMIM 604950) associated with RA at $p = 1.74E-147$, and *RPS18* (OMIM 180473) associated with RA at $p = 9.49E-37$ [65].

However, these associations were established because of the combination of samples of various ethnic and population groups, the total number of which reached several tens of thousands, and research in specific populations faces the problem of small samples size, which are usually not sufficient to prove the statistical significance of the deviations registered in the distribution of genotype/allele frequencies. Another limitation related to multitude of genes that control RA pathogenesis pathways. With such a wide range of risk variants, the individual contribution of any specific gene to the

genetic component of the disease, with the exception of *HLA-DRB1*, is very small. For the most part, the OR does not exceed 1.5. Therefore, it is advisable to study the effect of combined genotypes, since by analogy with oncological diseases; a significant increase in the small effects of SNPs can be expected in assessing their joint effect [68]. This aspect on the example of studies conducted in Belarus will be covered separately.

ROLE OF EPIGENETIC MODIFICATIONS AND QUANTITATIVE TRAIT LOCI AS REGULATORS OF THE EXPRESSION OF GENES INVOLVED IN RA PATHOGENESIS

The level of gene expression can be associated not only with structural changes in DNA (for example, SNPs) but also with the influence of various mechanisms of gene activity regulation, particularly epigenetic modification (post-transcriptional modification of histones, methylation of cytosine DNA bases, and micro ribonucleic acid (microRNA or miRNA) effects) [69–72].

The effect of DNA methylation on gene expression in cell populations affected by the pathological process has been studied to great extent [72]. Among these works, a genome-wide study of the fibroblast-like synoviocyte methylome from patients with RA and osteoarthritis (OA) is notable [73, 74]. Variations in methylation of many loci associated with cell movement and adhesion have been established, and it has been shown that hypomethylated genes form clusters in key pathways related to these cellular processes. Analysis of the methylation pattern in the promoter of the *IFNG* gene encoding a soluble cytokine (class II interferon) revealed hypomethylation mainly in CD4 and CD28^{null} T-cells, which was accompanied by increased production of interferon gamma after the stimulation of the T-cell receptors [75]. One of the mechanisms of global hypomethylation in RA may be the excessive consumption of S-adenosylmethionine (SAM), which is a donor of methyl groups in the process of DNA methylation in synoviocytes [76].

Recent efforts have been focused on integrating the epigenetic and genetic components of predisposition to RA [71, 72]. Thus, a genome-wide study of methylation and SNPs in the leukocytes of patients with CCPA-positive RA led to the identification of nine clusters of abnormal methylation at the MHC locus and one outside it on the same chromosome, which, according to the authors, indicates the mediation of epigenetic changes in the implementation of increased sensitivity to the disease [77]. Okada et al. also showed that the loci of candidate genes associated with RA risk overlapped with the methylation peaks in regulatory T-lymphocytes [64].

The results of a comprehensive study of DNA methylation, miRNA profiles, and genetic variations in synoviocytes in patients with RA and OA [74], published in 2019, confirmed the previous findings on global hypomethylation in RA, since the degree of DNA methylation outside of the CpG islands did not exceed 0.1%. Global methylation patterns did not differ in these joint diseases, but at the same time, more than 500 RA-specific local methylation regions (LMRs) were found in immune or blood cells. LMRs were predominantly localized in 5'-regions and overlapped with binding motifs of transcription factors *GLI1*, *RUNX2*, and *TFAP2{A,C}*. Differentially methylated CpG islands were found to be included in regulatory networks that control the organization of collagen fibrils and correlated with the level of miRNA expression. The authors suggest that LMRs act as distal regulatory elements of the immune response, and the observed differences between LMRs in RA and OA reflect functional changes in synoviocytes in patients with RA. The data obtained can be an information resource for the search for new biomarkers that contribute to the differential diagnostics of RA [74].

According to Cribbs et al., the study of methylation as a therapeutic target is more important for clinical practice [78]. There are effective drugs against RA. However, not all patients respond positively to treatment, and some are resistant to it. Thus, methotrexate, used for basic therapy of RA, eliminates global hypomethylation, but the mechanism of this phenomenon is still unknown. It is possible that other drugs also eliminate the epigenetic disorders underlying disease chronization, so the preliminary identification of those who are not sensitive to treatment using methylation patterns for this purpose would be useful [78].

Since in RA, in fibroblast-like synoviocytes, the expression of matrix-destroying enzymes and the levels of adhesive molecules, chemokines, cytokines, and their receptors all increase, the approach of targeted therapy based on the suppression of the activated phenotype of synoviocytes by modulating DNA methylation is justified. It was shown that a change in methylation of the promoter of *PMF1* promotes the expression of *SAATI*, causing excessive consumption of SAM. Owing to inhibition under the influence of *SAATI* diminazine acetate involved in polyamine recycling, the adhesion ability of cells and their invasiveness decrease, which is proposed to be used in a new strategy to control bone destruction in RA [79].

Thus, epigenetic studies clarify why genetically predisposed individuals are affected by the disease in one case and are not affected in another. They also explain

the heterogeneity of the symptoms of RA registered in the clinic and their responses to treatment [78], and they stimulate the development of new approaches for the treatment of the disease [79]. We emphasize that the development of effective methods and means of treating RA based on individual molecular, genetic, and epigenetic characteristics is an innovative field that can improve the survival and quality of life of patients in the future. This aspect is of great practical importance, is attracting more attention, and should be studied in an independent review.

Protein-coding SNPs do not cover the entire hereditary component of complex diseases, giving rise to “missing heritability” [80]. In fact, more than 90% of the polymorphic risk variants of RA identified using GWAS are related to the non-coding regions of the genome [81, 82]. In parallel with the accumulation of information regarding the qualitative associations of the disease with many functionally significant SNPs, the analysis and mapping of quantitative trait loci (eQTLs) are performed. This approach provides a deeper understanding of the properties of genetic loci that perform regulatory functions [83, 84]. By definition, eQTLs are regions of the genome containing variants of DNA sequences that affect the expression level of one or more genes [85]. eQTLs mapped near the gene are denoted as cis-eQTLs, and if they are detected at a distance or even on another chromosome, they are trans-eQTLs. Cis-eQTLs are found in many types of tissue, whereas trans-eQTLs are tissue-specific. The details of mapping of eQTLs and the place of this procedure in a combination of methods for studying the contribution of genetic factors of predisposition to multifactorial diseases are discussed by Cookson et al. [86], who suggested that the availability of systematically generated information on eQTLs will help in identifying the gene network involved in disease pathogenesis.

Indeed, as a result of the analysis of eQTLs in different subpopulations of immune cells, cis- and trans-loci were revealed, indicating the role of the *PPARG* gene and its signaling pathway in the development of autoimmune pathology [87]. It was revealed that HLA alleles are associated with the expression of *AOAH* and *ARHGAP24* (RhoGTPase-activating protein, which is a family of cell signal G-proteins belonging to the Ras superfamily) in monocytes, but not in B-cells. Therefore, by mapping the loci that control gene expression, a transregulated genetic network specific for a certain type of immune cells has been identified, which is responsible for the formation of susceptibility to autoimmune diseases [87].

In a Danish population of approximately 5,000, the effect of the non-synonymous SNP rs2228145 in the *IL6R* gene on the level of the soluble interleukin 6 receptor (sIL6R), the most important mediator of inflammation, was studied. It was revealed that the protein product content and fluctuations of this parameter were caused not only by the functional nucleotide substitution of rs2228145 but also by other variants at this locus (particularly sequences at the 3'-end of the gene associated with rs60760897) that regulate *IL6R* gene expression [88]. It was later discovered that the RA-associated SNP rs13330176, located on the 16th chromosome (16q24.1), affects the long non-coding RNA (lncRNA) transcript *RP11-542M13.2* in the cis-position, which supposedly regulates the proliferation of B-lymphocytes. The same SNP is moderately associated with the expression level of more than 10 genes in the trans-position that also control the functioning of the B-cells [63].

More recently, on the basis of 39 genome-wide studies, an algorithm of high-quality genetic and epigenetic mapping has been developed to identify causal genetic variants associated with 21 autoimmune diseases [89]. According to the results obtained, more than 90% of such variants are located in non-coding regions of the genome, which coincides completely with previous estimates [81]. Approximately 60% are located at binding sites with transcription factors. However, it seems that only 10%–20% of them can directly regulate gene expression through binding sites with classical transcription factors, and 80%–90% function by modifying non-canonical regulatory sequences [89]. For better understanding of how the non-coding part of the genome affects the development of autoimmune diseases, Ricano-Ponce et al. proposed a model according to which critical genes are regulated by a network of interacting non-coding chromatin loci [63].

In this context, the work of Ishigaki et al., who evaluated the “polygenic burdens” in five cell subpopulations (CD4⁺T-, CD8⁺T-, and B-cells, natural killer cells, and monocytes) in RA [90], is of great interest. By studying the expression of genes and exons by RNA sequencing, as well as by analyzing the associations between the level of expression and the neighboring common genetic variants in each cell type, the authors identified 8,204 expressed genes and 43,200 exons. The regularities were established, namely, opposite effects of alleles in different cell lines, high concordance of data under comparable conditions when comparing Japanese and European variants, and the accumulation of eQTLs within binding sites with transcription factors characteristic of a certain type of cells. Activation of the TNF-cytokine pathway in

T-lymphocytes was detected, regardless of the origin of cell populations. The data obtained are consistent with the fact that dysregulation of the cytokine network is a fundamental mechanism of RA [91] and indicate that the burden of polygenic disorders in immune cells can stimulate inflammatory processes, predisposing to the development of RA [90].

The publications discussed demonstrate the polygenic nature of predisposition to RA. Hundreds of genetic variants associated with multifactorial (complex) diseases and their symptoms have been revealed. More than 220 genes are known for RA, the polymorphisms of which affect the sensitivity to this joint pathology. However, the implementation of the genetic potential depends largely on the expression of genes involved in disease pathogenesis. The expression of genes is regulated by epigenetic modifications. In particular, global DNA hypomethylation and the presence of specific local LMRs in immune cells are characteristics of RA. In addition, many eQTLs have been mapped in cis- and trans-positions relative to regulated genes. Identification of these loci serves as a key to the “missing heritability” and confirms the prevailing contribution to the genetic component of autoimmune diseases of non-coding regions of the genome that perform regulatory functions.

FROM POLYGENIC TO OMNIGENIC

Such a subtitle has been given in an article [92] published in the journal *Cell* in 2017 and resonated powerfully. Stanford University professor J. Pritchard and colleagues Y. Li and E. Boyle put forward an omnigenic model of the genetic risk of multifactorial (complex) diseases. Since individual genes function as a part of branched and mutually overlapping gene networks, this concept assumes that “every gene affects everything,” and complex traits, like diseases, are influenced by all of the genes activated in certain tissues.

According to Boyle et al., despite the successes of modern molecular genetics, existing conceptual models of complex diseases remain incomplete. On the basis of the data on schizophrenia, Crohn's disease, and RA, the authors focused on enrichment of the genetic signals in transcriptionally active chromatin regions occurring in pathogenetically significant tissues and cells. According to the omnigenic model that they formulated, complex traits are determined by a limited number of so-called core genes unique for a given trait or disease. However, any gene expressed in cells affected by the pathological process can affect the regulation and functioning of the core genes. Peripheral genes are quantitatively superior to the core ones and, without being directly responsible

for the etiology and pathogenesis of the disease, provide most of the hereditary component. Their individual effects are small, but their collective action significantly increases the risk of the disease.

From this point of view, the aforementioned results can be explained. The omnigenic model also obtained support in reconstructing the genetic architecture of systemic lupus erythematosus (SLE), which enabled the identification of three new candidates for the main functional genes (*DNMT3A*, *PRKCD*, and *CIQTNF4*) by identifying a network (set) of rare variants associated with the risk or severity of the prognosis and various clinical phenotypes of SLE [93].

However, the limited nature of the omnigenic model, with respect to schizophrenia, was noted [94]. Given the variety of causes leading to this mental disorder, including maternal effects, impaired fetal development, and social and psycho-emotional factors, Curtis [94] believes that many genes, in addition to the core ones, influence the development of schizophrenia, and the situation is more complicated than the model implies. Recently, Wray et al. also suggested that multifactorial diseases are more complex than the omnigenic model can explain [95]. They believe that the term omnigenic describes the same genetic architecture as the infinitesimal model [96], whereas the term polygenic characterizes any genetic architecture that combines several or all contributing variants, thus covering many structures and relationships, both between and within the disease classifications [95].

Without defending the position of supporters or critics of the omnigenic model, we only point out that it does not deny the polygenic nature of multifactorial diseases, but it postulates that the expression of the core genes characteristic of this disease, with a clear biological function, is regulated through gene networks by numerous peripheral genes activated in tissues and cells that are involved in the pathological process. The total contribution of variants affecting gene expression is significantly dominant, although their individual effects may be minimal. It remains to be seen how justified this model is and whether the concept of the omnigenic model will become generally accepted.

CONCLUSION

RA is a common and socially significant multifactorial disease with an unclear etiology but a proven role of hereditary factors. The relationship between the risk of developing RA and the genes of the major histocompatibility complex is most pronounced, but genes associated with RA have also been found outside this complex.

Patients do not have key mutations that completely determine the risk of the onset and course of the disease. Therefore, the search for associations relates to SNPs and may be performed in two ways: the risk significance of the individual genes that control the inflammatory and immune responses is established, and GWAS is performed. Through GWAS, hundreds of RA associations with genes that control B- and T-cell immunity and cytokine production have been detected and verified in independent studies. However, most (by some estimates, more than 90%) polymorphic variants associated with multifactorial diseases belong to non-coding regions of the genome and manifest their effects by regulating gene expression. In RA, this mechanism is confirmed by epigenetic studies, as well as the results of analysis and mapping of DNA sequence variants (eQTLs) that affect the level of gene expression. It was demonstrated that because of this approach, the “polygenic burden” differs in different types of immune cells and stimulates the inflammatory response, which is mediated, for example, by the TNF- α cytokine, mainly in T-lymphocytes, predisposing carriers of such variants to the development of RA. The data of recent years presented in the review confirm and specify the polygenic nature of the disease. According to the new omnigenic model of complex traits/diseases, including RA, an increase in sensitivity to the development of the disease is due to the interaction of the core (and many peripheral) genes activated in cells and tissues involved in the pathological process.

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