Review Article

The Role of Genetic Variants in Rheumatoid Arthritis Pathophysiology and their Impact on Disease Mechanisms

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Abstract:

Rheumatoid arthritis (RA) is a chronic inflammatory condition caused by genetic and environmental factors. By identifying genomic regions associated with an increased risk of RA, Genome-wide association study (GWAS) has provided insight into the genetic component of the condition. A better understanding of these characteristics is necessary to improve RA therapy. The objective is to identify gene variants associated with RA susceptibility, severity, and progression. A search of PubMed, Embase, Scopus, Science Direct, and MEDLINE databases revealed articles concerning rheumatoid arthritis, genetics, genetic aspects, and autoimmune disorders. The research studies considered were reviews, meta-analyses, randomized controlled trials, and systematic reviews. The data was sought from May 2016 and May 2023. Genetic factors are thought to play a significant role in the production of cytokines, the activity of immune cells, and abnormal immune responses in RA. By combining molecular genetics with clinical characteristics, it is possible to enhance RA medications and provide tailored care to each individual. Recent studies have identified several susceptibility loci and key genes associated with the development of RA, providing insight into the mechanism underlying the disease. These genetic associations can be used to develop targeted medicines and personalized care strategies for people whom have rheumatoid arthritis. The purpose of this review is to enhance the quality of life by finding the gene mechanism of patients suffering from RAI; however, more research is still required to understand genetic and environmental influences fully.

Keywords: genetic variants, pathogenesis, pathways, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a severe autoimmune condition which often destroys the synovial joint lining and is associated with socioeconomic difficulties, early death, and growing disability[1]. The incidence of RA across the globe was 460 cases per 100,000 individuals between 1980 and 2019, with variations depending on the method of investigation and geographic location[2]. RA manifests in two primary forms: seropositive and seronegative. Seropositive RA has been found in 60-80% of RA cases, and involves the presence of antibodies, specifically anti-citrullinated protein antibodies (ACPAs), in the blood, leading to joint inflammation. In contrast, seronegative RA, though less common, lacks these antibodies, making diagnosis challenging. Notably, juvenile RA is a disease variant affecting pediatric age group. Although arthritis cannot immediately result in death, it has a substantial impact on patient's daily lives, and along with uncomfortable symptoms, it can result in severe joint damage, numerous long-term side effects, and a shortened life expectancy[4]. RA often leads to a 3 to 10-year decrease in life expectancy due to its widespread nature and potential complications[5].

While a substantial, inherited connection exists to the risk of developing RA, environmental triggers and genetic factors contribute to the disease's onset[6]. Genome-wide association studies (GWAS) have found around 150 susceptibility loci associated with RA risk during the past ten years[13]. These loci are most likely related to genetic differences that impact a person's propensity to develop rheumatoid arthritis[7]. Giving a functional interpretation from only statistical data is one of the most challenging tasks faced by genetic epidemiology researchers. Genetic research has identified physical single nucleotide polymorphisms (SNPs) that align with one or more genes of a particular family. With the growth of our understanding of the structure of the human genome, this kind of accuracy

of signal annotation has frequently been demonstrated to be occasionally deceptive[8,9]. A recent meta-analysis, with considerable overlap between these three studies, was conducted for 73,758 controls and 29,880 RA patients[10]. This study involved 288,664 controls and 22,628 patients with RA[11] and, more recently, 254,149 controls and 35,871 patients with RA[12]. However, they all identified genetic loci associated with RA, suggesting a complex, multigenetic architecture for RA. Due to further investigation in various communities during the ensuing years, numerous candidate genes have been discovered. Genetic connections of Human Leukocyte Antigen (HLA) variations to multiple subclasses of RA found in distinct people were the most crucial contributions to the disease's hereditary risk. More research into non-HLA genetic links to RA development is needed[13].

Many disorders, including lupus nephritis, rheumatoid arthritis, systemic sclerosis, psoriasis, and other autoimmune diseases, have been linked to SNPs in the *CCR6* (C-C chemokine receptor type 6) gene. As a result, identifying morphologically and operatively significant polymorphisms in *CCR6* is critical for studying possible malfunctions and developing therapeutic targets[14]: *IL-1β* is thought to be associated with the etiology of RA[15]. Additionally, the correlation between genetic variations in *TRAF1* and RA has received much attention. *TRAF1* blood concentrations were more significant in RA patients than in healthy controls, and it has been related to autoantibodies and RA disease activity[16]. According to the 2020 meta-analysis, *PTPN22* raises the risk of RA in Europeans and Africans[17]. Because RA is a T-cells-mediated autoimmune disease and *CTLA-4* is crucial in regulating T-cells function, *CTLA-4* expression or function is likely involved in the pathogenesis of RA[18]. Only a few new genetic variants associated with RA have been described earlier. In this review, we have focused on many crucial genes linked with RA; still, more

genetic variants are predicted to be identified as research progresses. This information may help improve the accuracy of RA diagnosis and therapies. The early identification of these distinct variations in genes brings a fresh perspective on the causes of RA and could open the path for developing innovative treatment methods.

Material and Methods

To find relevant papers for our literature review, we conducted a thorough search of several electronic databases; including PubMed, MEDLINE, Scopus, EMBASE, and ScienceDirect, from January 2016 to May 2023. We used the following text words as search terms: "Rheumatoid arthritis," "Autoimmune disorders," "Genes," and "Genetic aspects." We only considered papers written in English and did not apply any geographic restrictions. Additionally, we examined the reference lists of all identified articles to find studies not captured by electronic searches. Two authors (JM and RV) independently assessed the electronic search and the eligibility of the studies. The final inclusion of the studies was decided after a detailed examination, and we included all randomized clinical trials, retrospective studies, literature reviews, case reports, and series that dealt with patients having evidence of Rheumatoid arthritis. Any differences were discussed, and a consensus was reached.

Pathogenesis

B-cells are crucial to the immune system's dysfunction in RA, leading to joint inflammation. Drugs; such as rituximab, targeting B cells have shown promise in improving RA symptoms. Tertiary lymphoid tissues (TLTs) in RA patients are linked to continuous inflammation. The primary features of RA include abnormal increases in autoantibodies, inflammatory cytokines, pathogenic B-cells, Chemokines, M1 macrophages, and autoreactive CD4 T-cells. However, distinguishing between pathogenic and protective B cells remains challenging. Macrophages release cytokines that stimulate osteoclasts, causing bone erosion, while T-cells, especially those producing Interleukin-17, contribute to inflammation. Immune complexes and angiogenesis further exacerbate RA[19]. Figure 1 represents the overall mechanism of RA.
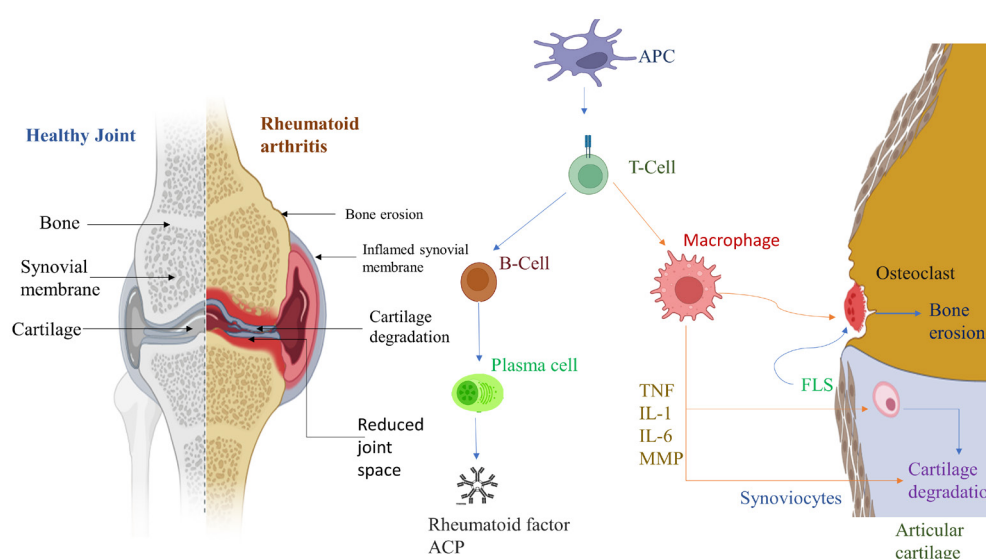

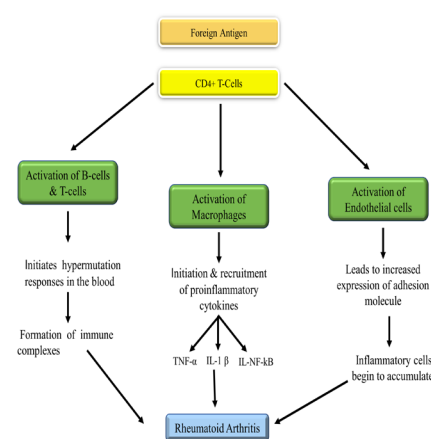**Figure 1** Mechanism of rheumatoid arthritis

Role of B-cells

Research has revealed that B-cells play a crucial part in the etiology of RA, as noticed by the improvement of symptoms in RA patients that received B-cell-reducing medications such as rituximab an anti CD20 antibody[20]. The synovial tissue in individuals with RA can be categorized as TLTs or ectopic lymphoid structures. Akin to secondary lymphoid tissue, it has sites for B-cells and T-cells development. TLTs have been associated with ongoing inflammation in RA, as they are allied with autoantibody titters, inflammatory cytokine intensities, and disease difficulty in patients with RA[21]. The primary characteristic of RA is immune system dysfunction, which results in unusually high levels of autoantibodies, autoreactive CD4 T-cells, pathogenic B-cells, chemokines, M1 macrophages, and inflammatory cytokines in the bodies of RA patients. The importance of B-cells in the pathophysiology of RA has been well demonstrated by B-cell depletion therapy, and increasing focus is being made on treating RA by targeting B-cells. Despite significant improvements in inflammatory markers, the risk of infection and malignancy has risen in RA patients undergoing B-cells reduction therapy. Thus, it appears that pathogenic B-cells should be targeted for depletion rather than all B-cells. However, at this time, we cannot differentiate between pathogenic and defensive B-cells in RA patients[22]. In the beginning, macrophages release cytokines such as TNF, IL-1, and IL-6. These cytokines stimulate osteoclasts, which causes bone erosion and leads to RA. At the same time, fibroblast-like synoviocytes (FLS) become active and multiply, resulting in RANKL expression and activation of osteoclasts. These FLS can produce the enzyme protease, which breaks down cartilage and can spread from one joint to another, causing symmetrical arthritis[23].

Role of T-cells

In RA, T-cells are essential as they constitute more than 50% of immune cells in the synovium. These T-cells produce Interleukin-17, which causes inflammation by activating macrophages and stimulating FLS. Moreover,

T-cells also contribute to the development of Rank-L, leading to bone degradation[24]. Inflammation in the synovium is also caused by cytokines and antibodies produced by only 5-7% of plasma cells. Neutrophils in the synovial fluid generate protease and reactive oxygen species (ROS), which can further induce inflammation[25]. Immune complexes (Antibody-Antibody interaction) are also responsible for causing inflammation and inflamed joints in RA[26]. Figure 2 represents the Role of T-cells in RA.

Figure 2 Role of T-cells in Rheumatoid arthritis

Angiogenesis and pre-RA

The cytokines present in these cells aid in promoting vascular permeability and the development of adhesion molecules in the vascular system, which allows immune cells to travel to the joints. Citrullination occurs when genetic, environmental, and other biological factors modify autoantigens as foreign antigens, causing the stimulation of APCs. These APCs then move towards lymph nodes containing B-cells in their germinal centers and activate T-cells; specifically CD4-T-cells. The stimulated B-cells grow, change classes, and become plasma cells, producing autoantibodies. There are two pathways for antibodies in this immune response: ACPA and the IgM antibody pathway. ACPA targets only citrullinated proteins, while the IgM antibody targets the Fc region of IgG and forms an immune complex. The extra-articular environment

produces cytokines such as *IL–6* and *IL–1*, within joints and surrounding areas. These cytokines and the inflammatory cytokines in the blood circulate to other organs like the liver, heart, and kidney, leading to various disorders. Figure 3 illustrates the angiogenesis involved in RA[27].
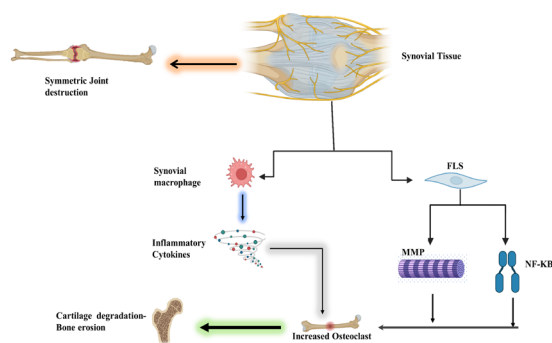

Figure 3 Role of angiogenesis in cartilage degradation

Genes associated with RA

RA is a condition that is caused by our immune system, and it has a vital genetic component. This can make studying it challenging because the disease is complicated, and various hereditary factors influence its development.

One approach researchers use to learn more about RA is the candidate gene strategy. Through this method selecting genes thought to be involved in the condition's development can be accomplished[28]. The genes identified in the last eight years include those with specific expression of 548 patterns and genetic variants; including mutations in both exonic and intronic regions and single nucleotide polymorphisms. This strategy relies heavily on prior knowledge of disease causes to recognize the genes involved accurately[29] Figure 4 represents the genetic polymorphism in RA.

Protein tyrosine phosphatase, non–receptor type 22 *(PTPN22)*

The *PTPN22* gene, found on chromosome 1 and comprising of 18 exons, is connected to Systemic Lupus Erythematosus and RA. It encodes a protein known as lymhoid protein tyrosine phosphatase (LYP), which consists of roughly 663 amino acids and plays a vital role in regulating the immune system. This gene is associated with TCR signaling in the REACTOME pathway and is involved in the phosphorylation of CD3 and TCR zeta chains. This gene is responsible for producing LYP, a crucial factor in suppressing T–cells responses. According to gene
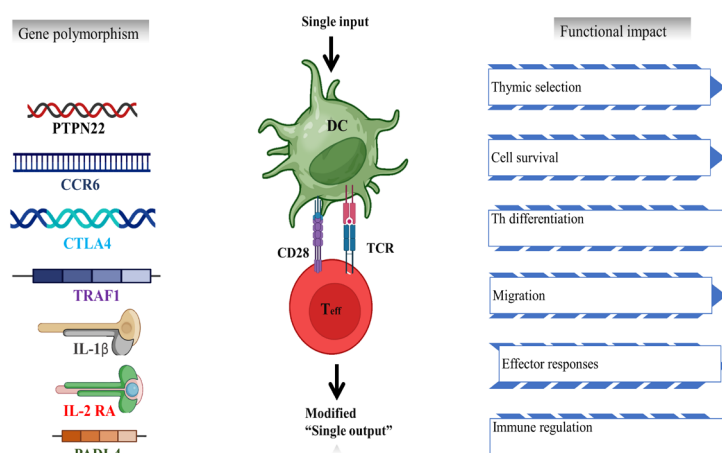

Figure 4 Potential roles of genetic polymorphisms in the pathogenesis of rheumatoid arthritis

ontology (GO), this gene is engaged in phosphatase and protein tyrosine phosphatase activity: *PTPN12* is a related gene. Research has shown that even minor changes in T-cells function can affect B-cell differentiation, impacting the body's ability to form auto-antibodies and develop autoimmunity. The *PTPN22* risk allele has been linked to autoimmune diseases where autoantibodies are present; indicating it may contribute to their development[30,49].

The T-cell receptor-mediated signaling pathway (TCR) plays a significant function in controlling T-cells initiation and is negatively regulated by LYP. The *PTPN22* gene encodes LYP, inhibiting T-cells' spontaneous activation. However, a non-synonymous substitution in the PTPN22 gene alters the physical binding to Csk tyrosine kinase during T-cells activation, which switches arginine (R) to tryptophan (W) at position 620. Several studies have linked the *PTPN22* polymorphism to the emergence of RA, and the relationship between the T allele and the development of RA has been demonstrated in patient samples from Hungary and the United Kingdom as well as in Europeans and representatives of other races. According to a meta-analysis, *PTPN22* is a significant threat to RA in people of European and African descent[31].

C-C chemokine receptor 6 *(CCR6)*

The *CCR6* gene is responsible for coding a protein and is allied with specific diseases; such as limited sclerosis and autoimmune diseases of the musculoskeletal system. This gene is located on Chromosome 6 and consists of 5 exons, encoding 374 amino acids. It is linked to two pathways, G protein-coupled receptor (GPCR) downstream signaling and Class A/1 (Rhodopsin-like receptors). This gene's GO annotations encompass functions related to G protein-coupled receptor activity and chemokine receptor action. *CCR7* is a crucial paralog of *CCR6*[32], and studies indicate that *CCR6* plays a significant part in the etiology

of RA, showing a connection between the *CCR6* locus and RA. The *CCR6* protein is a surface marker for T helper 17 (Th17) cells and plays a significant role in transcription. It is expressed by various T-cells subtypes; such as Th17 and Treg, dendritic cells, and B-cells. Additionally, *CCR6* contributes to cell recruitment during inflammation. The exclusive ligand for *CCR6* is CCL20, which is produced within inflamed joints by various cells; including FLS, neutrophils and Th17 cells[50]. One of the genes with a potentially important function in the etiology of RA is this one. It helps differentiate Th17 cells from other CD4+ (cluster of differentiation 4) cells and is expressed on the cell surface. Moreover, this gene exhibits expression in immature dendritic cells and memory T-cells, exerting a substantial influence on the development and differentiation of B-cells. Consequently, it facilitates the conscription and movement of dendritic cells, while also contributing to the regulation of T-cells function during immune responses[33].

Cytotoxic T-lymphocyte associated protein 4 *(CTLA-4)*

The *CTLA4* gene produces a protein linked to several diseases; including Immune Dysregulation with Autoimmunity, Immunodeficiency, Lymphoproliferation and Celiac Disease. The *CTLA-4* gene is positioned on chromosome 2 and consists of four exons, encoding 223 amino acids. It is associated with gene expression (transcription) and CD28 co-stimulation: CD28 is a crucial component of this gene. The interaction between the inhibitory *CTLA-4* and the stimulatory signal transducer CD28 coupled with their ligands affects T-cells activation. Both receptors are activated by similar ligands; CD86 and CD80, which are present on antigen-presenting cells. CD28 ligation to CD80 and CD86 promotes T-cells activation, while CTLA-4 ligation results in T-cells repression[34]. In RA, the overactivation of CD4+ T-cells and their helper

subsets causes the synovium to produce inflammatory mediators. These mediators attract and activate pathogenic cells, leading to the progression of the disease. T–cells activation is regulated by the interactions between inhibitory *CTLA–4* and stimulatory signal transducer CD28 and their ligands. Both CD80 and CD86 are ligands expressed on antigen–presenting cells, activating both receptors. Inhibiting *CTLA–4* leads to the suppression of T–cells activation; whereas, the interaction between CD28 and the CD80 and CD86 molecules promotes T–cells activation. *CTLA–4* is an immunological checkpoint molecule found on T–cells, and it prevents the maturity of peripheral tolerance and T–cells activation. Research has demonstrated the substantial influence of *CTLA–4* on the modulation of self–tolerance and its association with the onset of autoimmune diseases; such as rheumatoid arthritis. Moreover, *CTLA–4Ig*, a molecule designed to replicate the inhibitory function of *CTLA–4*, has been observed to impede the differentiation of osteoclasts and modulate osteogenesis. This suggests a potential application in preventing bone destruction in RA. This dual impact of *CTLA–4*, involving its regulatory influence on T–cells activity and its potential role in averting bone destruction, underscores its significance in RA[35,36].

TNF receptor associated factor 1 *(TRAF1)*

A gene called *TRAF1* codes for protein. The *TRAF1* region is in Chromosome 9 and has about 10 exons. This gene encodes 416 amino acids. This gene is associated with diseases; such as anaplastic large–cell lymphoma and rheumatoid arthritis. The TNFR1 Pathway and TNF signaling are two pathways related to *TRAF1*. According to GO, *TRAF1* has annotations for ubiquitin protein ligase binding and thioesterase binding: *TRAF2* is a crucial paralog of *TRAF1*. TRAF1 belongs to the TRAF protein family, which can transmit signals by binding to various adapter proteins and protein kinases for several receptors of the TNF superfamily affiliates (TNFSF); comprising of TNF–α. It has been identified as a remedial target for rheumatic syndromes like RA[37]. Numerous genetic investigations have revealed a link between certain variations of the

TRAF1 gene as well as a higher risk of developing RA. The *TRAF1–C5* gene cluster on chromosome 9 contains many variants; including one that is repeatedly linked to RA susceptibility: identified as rs10818488. People with RA are more likely to have this variation than those without. *TRAF1* is a signaling network that regulates the immune system and inflammation, wherein immune receptors and TNF receptors use it to relay their signals. Dysregulation of these pathways may lead to inflammation and ongoing inflammation, which is characteristic of RA. The activation of *TRAF1*–related pathways may also be responsible for the degradation of joint tissues seen in RA. *TRAF1* serves as a negative regulator of Toll–like receptor (TLR) signaling by sequestering the linear ubiquitin chain assembly complex (LUBAC), and disease–associated SNPs in *TRAF1* reduces its expression; leading to heightened proinflammatory cytokine production. In the RA synovium, elevated *TRAF1* levels contribute to synovial hyperplasia by suppressing apoptosis through activation of the JNK/ NF–κB pathway. Furthermore, *TRAF1* induces a shift in TNFR1–TNFR2 signaling, moving from apoptosis induction to proinflammatory *NF–κB* signaling[51]. Excessive inflammation and immune cell activation can cause inflamed joints to lose bone and cartilage. *TRAF1* might also interact with other genes linked to an increased risk of RA; such as the *PTPN22* gene and the HLA–DRB1 allele. Additionally, multiple genetic variations that act together may increase a person's susceptibility to RA[38,39].

Interleukin 1 beta *(IL1β)*

The gene known as IL1β encodes a protein belonging to the interleukin–1 cytokine family. This gene is located on Chromosome 2 and contains 8 exons, and is responsible for synthesizing a protein consisting of 269 amino acids.

IL–1β activation involves caspase–1–dependent and –independent processes; including neutrophil participation. *IL–1β* administration worsens RA and bone injury, increasing inflammatory factor expression in synovial fluid–derived FLS via *NF–κB*–mediated ERK–STAT1 signaling. In contrast, *IL–1β*–stimulated human umbilical cord mesenchymal

stem cells alleviate RA by inducing FLS apoptosis, showcasing the dual, context-dependent role of *IL-1β* in RA pathophysiology[52]. Activated macrophages produce this cytokine as a proprotein, which is subsequently transformed into its effective state by caspase 1 (CASP1/ICE). IL-1 plays a pivotal role in the inflammatory reaction and partakes in a range of cell functions, comprising of cell propagation, differentiation, and cell death. Furthermore, IL-1 is crucial for initiating and driving the pathological processes associated with RA and contributes to the body's natural response. GWAS has detected several SNPs that are related to susceptibility of RA. In RA, IL-1 serves a significant part in mediating joint inflammation and destruction[40]. A proinflammatory cytokine heavily influences the development of RA called interleukin-1 beta (IL-1). In RA, this cytokine causes and sustains joint inflammation and injury. When various stimuli trigger immune cells, they release IL-1, which directs the secretion of other inflammatory cytokines; namely: TNF-α and IL-6, that promote synovial inflammation. IL-1 activates matrix metalloproteinases that breaks down cartilage and increases osteoclast activity, promoting bone resorption; additionally, it directly causes joint damage. Furthermore, IL-1 participates in angiogenesis, leading to more blood vessels in the inflamed synovium; exacerbating inflammation. Biological drugs; such as anakinra, have been used to control RA by reducing these inflammatory processes; however, the effectiveness of the therapy may vary depending on individual responses, due to the complex nature of RA[41,42].

Interleukin 2 receptor subunit alpha *(IL2RA)*

IL2RA gene codes for a protein. Immunodeficiency 41, with Autoimmunity and Lymphoproliferation, are two diseases related to *IL2RA*. This gene, located on Chromosome 10, has 8 exons and codes for 272 amino acids. Apoptotic pathways in synovial fibroblasts and TGF-β pathways are two related pathways. The GO annotations associated with this gene encompass interactions; such as outdated drug binding and interleukin-2 binding. CD25, or IL2RA, the alpha chain of the IL-2 receptor, is responsible

for immune system regulation. *IL2RA* is responsible for encoding the alpha chain of the high-affinity IL-2 receptor, expressed on activated T-cells, and pivotal in T-cells activation and proliferation. Variants in *IL2RA* are recognized for their protective role against multiple sclerosis, diabetes mellitus and RA. This protein is pivotal in activating and propagating T-cells, essential to the body's immune defense. Scientific investigations have demonstrated that genetic variations within the *IL2RA* gene can contribute to autoimmune conditions; including RA[43]. IL-2, a vital cytokine secreted by stimulated T-cells, is crucial in governing immune responses; including activating and multiplying T-cells. The IL-2 receptor is made up of three subunits, with IL-2Rα (CD25) being the subunit that binds IL-2 the most effectively. T-cells activate and produce cytokines, including IL-2, when they encounter antigens. The *IL2RA* gene encodes IL-2RA, which controls T-cells sensitivity to IL-2, fine-tuning immune responses. When IL-2 binds to the receptor complex, it initiates intracellular signalling. This promotes T-cells activation and proliferation. Genetic variations in IL2RA can affect receptor function, potentially increasing the susceptibility to autoimmune diseases like RA. In RA, these variations can lead to immune dysregulation, causing hyperactive T-cells and chronic inflammation, contributing to the autoimmune features of the disease. Understanding these mechanisms provides valuable insights into potential therapeutic strategies for treating RA[44,45].

Peptidyl arginine deiminase 4 *(PADI4)*

The *PADI4* gene, which has 18 exons, is in Chromosome 1 and codes for 663 amino acids. The *PADI4* gene is responsible for producing a protein and has been linked to Arthritis and RA. Two pathways related to this gene are chromatin organization and genes allied with the maturity of RA. According to GO annotations, the *PADI4* gene is involved in calcium ion binding and arginine deiminase activity. *PADI1* is an essential paralog of this gene. Studies have shown that certain genetic variations and higher expression levels of *PADI4* are

interrelated with an augmented chance of developing RA in specific populations. Moreover, RA patients have higher levels of *PADI4* expression in their synovial tissue, which lines the joints; suggesting a potential role in the disease process[46]. The *PADI4* gene encodes the PAD4 enzyme responsible for protein citrullination by converting arginine to citrulline. In RA, the overactivity of PAD4 leads to an increase in the citrullination process within joint tissues. This process generates autoantigens, which the immune system mistakenly identifies as foreign and then targets them, causing joint inflammation. In RA, B-cells manufacture ACPA, which play a role in inflammation and the resulting joint damage. Specific gene variants of *PADI4* are associated with RA risk and affect PAD4 activity. Researchers are studying therapies targeting PAD4 or ACPA to mitigate autoimmune responses and inflammation in RA. However, RA involves many genetic and environmental factors, and *PADI4* is only one piece of this complex puzzle[47,48]. As previously mentioned, rheumatoid arthritis has been associated with multiple genes. A combination of environmental and genetic factors determines the complex etiology of the disease. The finding of selected and additional genes linked to RA sheds further light on the disease's pathogenesis.

The environmental aspects of RA

Exploring the environmental aspecst of RA is essential, because the development of the disease is markedly shaped by environmental factors. Research has demonstrated that diverse environmental influences can modify susceptibility to RA. These factors encompass: smoking, alcohol consumption, birth weight, breastfeeding, socioeconomic status, region of birth, early growth, feeding practices, exposure to infections, and contact with pollutants; such as dioxin and silica dust[53]. RA is significantly impacted by smoking, serving as a key environmental risk factor; especially in individuals testing positive for ACPA. Additionally, exposure to other environmental pollutants; such as dioxin, has been associated with heightened risks and severity of RA. Living in urban areas or in proximity to highways has also been linked to the disease: irrespective of cigarette consumption[54]. Vitamin D functions as a hormone crucial for maintaining bone and mineral balance; additionally, it plays a role in regulating cells within the innate and adaptive immune system by interacting with the vitamin D receptor (VDR), acting as a suppressor of pro-inflammatory responses[55]. The interaction between genetic and environmental factors in the development of RA is intricate, and current research is dedicated to unraveling the complexities of their contribution. Emphasizing the importance of incorporating these environmental factors into future studies is crucial for obtaining a holistic understanding of the disease and its associated risk factors[56].

Future perspectives

RA presents itself as a complex autoimmune illness, with diverse impacts, urging us to delve deeper into genetic information and explore innovative treatment approaches. Successfully navigating this condition involves a blend of pharmaceutical and non-pharmaceutical treatments, reflecting the intricate nature of managing its various aspects. Several polymorphism studies have revealed novel genetic variants linked to the risk of RA. Building on prior research, genes; such as *PTPN22, CCR6, CTLA4, TRAF1, IL-1β, IL2RA and PADI4*, have emerged as robustly being associated with the pathogenesis of RA. Our study suggests that these genes could serve as both therapeutic and prognostic markers. Therefore, further research is warranted to pinpoint the specific SNPs responsible for disease progression. Additionally, exploring gene therapy applications holds promise for proposing novel treatments for RA. It's noteworthy that many of these genes have

been previously identified as therapeutic targets in past reports. Genetic therapies for RA provide an opportunity to deliver therapeutic gene products directly to the affected site. This approach aims to circumvent potential side effects associated with systemic injections or infusion. By doing so, it not only enhances treatment efficacy but also enables sustained local expression, ensuring the endogenous production of therapeutic agents at high concentrations over the long term. A promising avenue lies in a gene therapy approach, given that various forms of RA involve joint inflammation, sharing common inflammatory processes. In treating RA, the primary objective extends beyond pain relief; as it includes achieving remission or, at the very least, low disease activity for all patients, while preventing

Table 1 Gene associated with Rheumatoid arthritis

Gene symbol	Gene name	Location	Number of Exon	Amino acid	Role	Reference
PTPN22	Protein tyrosine phosphatase, non–receptor type 22	1p13.2	23	807	Acts as a negative regulator of TCR	[30]
CCR6	C–C motif chemokine receptor 6	6q27	5	374	The receptor is responsible for binding to the C–C type chemokine CCL20	[33]
CTLA4	Cytotoxic T–Lymphocyte Associated protein 4	2q33.2	4	223	A significant negative controller of T–cell reactions is the inhibitory receptor	[35]
TRAF1	TNF receptor–associated factor–1	9q33.2	10	416	Cell survival and apoptosis are regulated by it	[38]
IL1β	Interleukin–1 beta	2q 14.2	8	269	It participates in angiogenesis by collaboratively stimulating the production of VEGF with TNF and IL6	[41]
IL2RA	Interleukin–2 Receptor subunit alpha	10p 15.1	8	272	Receptor for interleukin–2	[44]
PADI4	Peptidyl arginine deiminase 4	1p 36.13	18	663	Catalyzes the citrullination/deimination of arginine residues of proteins such as histones	[47]

PTPN22=Protein tyrosine phosphatase, non receptor type 22, CCR6=C-C motif chemokine receptor 6, CTLA4=cytotoxic T-Lymphocyte Associated protein 4, TRAF1=TNF receptor associated factor–1, IL1β=Interleukin–1 beta, IL2RA=Interleukin-2 Receptor subunit alpha, PADI4= Peptidyl arginine deiminase 4

irreversible damage to affected joints. This approach seeks to either inhibit proinflammatory cytokines or enhance the expression of anti-inflammatory cytokines, addressing the underlying inflammatory mechanisms.

Conclusion

An extensive number of hereditary and environmental factors influence the pathophysiology of RA. The role of genetic variants in specific genes in the development and progression of this disorder has been studied in many research papers. *TNF-, IL-6, CCR6, STAT4, HLA-DRB1*, and *PTPN22* are specific genes that are highly significant in the etiology of rheumatoid arthritis. To understand how rheumatoid arthritis develops, we must examine the complex networks and critical genes that are associated with it. Genetic variations may affect cytokine production, T-cell activation, and the immune system, offering insight into the mechanisms causing sickness and potential therapeutic approaches. A genetic variant's impact on RA pathophysiology gives crucial insights into disease processes, and allows personalized treatment approaches to be developed. These distinctions result in immune system dysregulation; resulting in inflammation and joint damage. By tailoring therapeutic programs to RA patients' specific genetic profiles, we may be able to treat these patients more effectively. Further study is required to understand the many roles, relationships with the environment, and responsibilities that exist among different groups.

Conflict of interest

The authors confirm that there are no potential conflicts of interest to declare.

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