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Mapping Risk And Response In Rheumatoid Arthritis: A Genomic And Environmental Perspective

Ayman Malek[1], Kavya Ahuja[2], Rupa Singh[3]

B.Pharm Student[1], B.Pharm Student[2], Assistant Professor[3]

Department of Pharmacy

Krishna School of Pharmacy and Research

ABSTRACT: Rheumatoid arthritis (RA) is a complex multigenic autoimmune disease. In this paper, the genetic basis of RA is explored, with a particular focus on HLA class II genes, and in particular HLA-DRB1 alleles, which account for a large proportion of the inflammatory disease susceptibility and severity in RA across different ethnic groups. Genome-wide association and meta-analysis studies have identified additional RA risk loci apart from the HLA region, including PTPN22, STAT4 and PADI4, indicating polygenic nature of RA. Shared epitope hypothesis relates how certain HLA-DRB1 alleles are responsible for predisposing individuals to RA by presenting autoantigens to T cells, which then initiate autoimmune response. Further ethnic specific variations emphasize the need for population based studies for an accurate risk assessment. Moreover, the field of pharmacogenomics has emerged as a strategy for personalizing RA treatment. Genes such as ATIC, TPMT, and NAT2 affect patient response to methotrexate, sulfasalazine and biologics. While more work remains in identifying causative variants and translating discoveries into clinical practice, gains in fine-mapping and functional genomics are closing the gap. Early diagnosis, risk prediction and the development of more tailored therapeutic strategies are all based on a good understanding of the genetic landscape of RA and this should ultimately improve patient outcomes and reduce the burden on healthcare.

I.INTRODUCTION

RA indicates a phase of systemic autoimmunity (RF/ACPA positivity) prior to the onset of clinically-evident joint inflammation [63].

- Seronegative RA: Patients lack detectable RF and ACPA. This seronegative form accounts for roughly 20–30% of RA cases [64]. By definition, these patients have no RF or anti-CCP antibodies, yet they fulfil clinical criteria for RA [64].

Women are several times more likely than men to develop RA (1,7). In population studies, the female: male ratio is about 3:1 [66] (2–4:1 by other estimates) [60]. Sex hormones play a key role in this disparity. For example, RA incidence and activity tend to decrease during pregnancy (when estrogen and progesterone levels are high) and increase postpartum or at menopause (when these hormones fall) [65]. Androgens (testosterone and DHEA/DHEAS) have anti-inflammatory effects: RA patients generally have lower serum testosterone and DHEAS than healthy controls [66], and these low androgen levels correlate with higher disease activity [67]. In particular, studies report an inverse relationship between serum testosterone or DHEAS and RA severity, consistent with a protective role for these hormones [67].

Genetic and environmental factors both contribute substantially to RA risk. Twin and family studies estimate RA heritability at roughly 40–65% [36]. This implies that genetic factors account for on the order of half of RA susceptibility, with the remainder (~35–60%) attributable to non-genetic influences (smoking, infections, hormones, etc.). In other words, approximately 40–60% of RA risk appears genetic [36], and about 40–60% environmental.

The observation that RA patients often have hypoandrogenism underlines the hormonal link to disease activity. For instance, patients with active RA frequently exhibit abnormally low serum testosterone and DHEAS [66]. These low androgen levels are found to be inversely associated with inflammatory markers and clinical disease scores [67], indicating that reduced androgen signalling is linked to more severe RA. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease marked by persistent synovial (joint) inflammation [60]. Patients typically present with joint pain, swelling and stiffness [60]. RA affects roughly 0.5–1% of adults worldwide [61].

RA is clinically categorized into two subtypes [36]:

- Seropositive RA: Patients have detectable autoantibodies – rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs, e.g. anti-CCP) [36]. Approximately 70–80% of RA patients fall into this seropositive category [62]. In seropositive RA, these antibodies often appear years before symptoms; this asymptomatic interval is known as “preclinical RA” (3,5). Preclinical

II. HLA Region: Shared Epitope and Amino Acid Residue Contributions.

The HLA-DRB1 gene encodes the β-chain of major histocompatibility complex (MHC) class II molecules, which are essential for antigen presentation to $CD4^+$ T helper cells. It is recognized as one of the most polymorphic genes in the human genome. A strong genetic association has been consistently demonstrated between rheumatoid arthritis (RA) and specific HLA-DRB1 alleles, particularly DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408, DRB1*0101, DRB1*0102, DRB1*1001, and DRB1*1401, across diverse populations.[1]However, RA risk varies depending on specific HLA-DRB1 alleles and ancestry—being higher for HLA-DRB1*0101, 0401, and 0404 in Caucasians; 0405 and 0901 in Asians; and 1402 in Native American populations[2,3]. A major breakthrough in understanding this association was the identification of a conserved five–amino acid sequence (QKRAA, QRRAA, or RRRAA) spanning residues 70–74 in the third hypervariable region of the DRβ1 chain, encoded by the HLA-DRB1 gene. This sequence, found in many RA-associated alleles, was termed the Shared Epitope (SE)[2,4].

The SE hypothesis proposes that this sequence enables the binding of specific self or modified peptides to MHC class II molecules on antigen-presenting cells (APCs), leading to their recognition by $CD4^+$ T cells and initiating an autoimmune response. While the exact antigen responsible has not been conclusively identified, and the relevance of SE-containing alleles appears to vary among populations[2], the

hypothesis has provided a mechanistic framework to support previously observed epidemiological associations.

Nonetheless, the SE hypothesis does not fully account for the differential risk levels conferred by different SE alleles (e.g., higher risk with 0401 and 0405 vs. 0101 and 0404), implying the involvement of additional genetic or environmental factors[5,6]. Furthermore, the presence of the SE is more strongly associated with ACPA-positive RA than ACPA-negative forms[6,7], and has been linked to increased disease severity, extra-articular manifestations[6,8,9], and greater radiographic joint damage.

Subsequent studies have extended the Shared Epitope (SE) hypothesis, revealing that the majority of RA risk attributed to the MHC region can be explained by six key amino acid residues across four HLA molecules: HLA-DRB1 (positions 11/13, 71, and 74), HLA-B (position 9), HLA-DPB1 (position 9), and HLA-A (position 77) [10,11,12]. Notably, although many of these residues lie outside the classical SE region, all are located within the peptide-binding grooves of their respective HLA molecules. This underscores the critical role of antigen presentation to T cells, both $CD4^+$ and $CD8^+$, in the pathogenesis of RA.

Importantly, recent studies have confirmed that HLA gene associations, including those involving SE alleles of HLA-DRB1, are also present in seronegative RA, albeit with smaller effect sizes and distinct patterns compared to ACPA-positive disease [10,13,14]. In light of these findings, a more refined classification has been proposed—replacing the binary SE-positive/negative model with a 16-category hierarchy based on specific combinations of amino acid residues at positions 11/13, 71, and 74 of HLA-DRB1 alleles [12]. This expanded model has also demonstrated predictive value for radiographic progression and RA-related mortality [15,16].

III. Non-HLA Genetic Risk Loci

In addition to HLA-DR alleles, numerous association studies have established the involvement of several non-HLA genes in conferring susceptibility to rheumatoid arthritis (RA). Among the 31 confirmed non-HLA loci associated with increased RA risk, the PTPN22 and IL23R genes demonstrate some of the strongest associations [17, 20, 22–25]. These associations have also been validated in Hungarian RA patient cohorts [23,24]. The PADI4 gene, which encodes the peptidylarginine deiminase 4 (PADI4) enzyme, plays a critical role in the citrullination of proteins—a central mechanism in RA pathogenesis. While a significant association between PADI4 haplotypes and RA has been observed in Asian populations, this finding has not been consistently replicated in Caucasian cohorts, including Hungarian populations [26–28]. As further discussed in the context of genome-wide association studies (GWAS), additional confirmed susceptibility loci include TRAF1, CTLA4, IRF5, STAT4, FCGR3A, IL6ST, IL2RA, IL2RB, CCL21, CCR6, CD40, among others [17, 18,20, 7, 28,33].

The PTPN22 gene, which encodes the intracellular phosphatase protein tyrosine phosphatase non-receptor type 22, exhibits the second strongest genetic association with rheumatoid arthritis (RA), following HLA-DRB1. Notably, this gene has also been implicated in a range of other autoimmune diseases, including type 1 diabetes, Graves' disease, myasthenia gravis, systemic sclerosis, systemic lupus erythematosus, and Addison's disease. A functional single nucleotide polymorphism (SNP), C1858T, results in an amino acid substitution from arginine to tryptophan at position 620 (R620W), and is considered a major risk factor for these conditions, particularly among Caucasian populations. This variant has been consistently associated with anti-citrullinated protein antibody (ACPA)- and rheumatoid factor (RF)-positive RA, and is thought to correlate with a more severe disease course. Although some studies have suggested a link between PTPN22 and RA severity, this association appears modest and has not been uniformly replicated. The

presence of the C1858T polymorphism, especially when combined with the shared epitope (SE) and ACPA positivity, may significantly enhance the accuracy of early RA diagnosis. Unlike the SE, however, PTPN22 polymorphism does not appear to be strongly associated with smoking [21,24,25].

Based on recent genome-wide association studies (GWAS), TRAF1, located within the TRAF1-C5 region, is considered the third most strongly associated genetic locus with rheumatoid arthritis (RA). This region is predominantly linked to ACPA-positive RA. TRAF1 encodes the tumor necrosis factor receptor-associated factor 1, an adaptor protein that mediates signal transduction from TNF family cytokines—such as TNF-α—to downstream signaling pathways. Functionally, TRAF1 is involved in regulating cell proliferation, survival, apoptosis, bone remodeling, and cytokine production, thereby playing a crucial role in RA pathogenesis. Notably, TRAF1 has been associated with increased radiographic disease progression; however, the TRAF1-C5 region does not appear to be significantly associated with RA-related mortality [20,22,31].

The association between STAT4 and rheumatoid arthritis (RA) is relatively modest compared to other major susceptibility loci. However, this gene is also implicated in several other autoimmune diseases, including systemic lupus erythematosus (SLE), scleroderma, type 1 diabetes, juvenile idiopathic arthritis, and possibly inflammatory bowel disease (IBD). Signal transducer and activator of transcription 4 (STAT4) plays a pivotal role in cytokine signaling, particularly in interleukin-12 (IL-12) pathways via JAK2. Notably, distinct single nucleotide polymorphisms (SNPs) in the STAT4 gene have been associated with increased susceptibility to both ACPA-positive and ACPA-negative RA [22,30].

The PADI4 gene encodes the enzyme peptidylarginine deiminase type 4, which catalyzes the conversion of arginine residues to citrulline—a process central to the formation of citrullinated neoantigens in RA. A strong association between PADI4 and RA was initially demonstrated in large Japanese and Korean cohorts. However, this genetic association appears significantly weaker in Caucasian populations and could not be confirmed in Hungarian cohorts, as discussed earlier [20,22,27,28].

Fc gamma receptors (FcγRs) are critical mediators of immune complex handling and inflammatory responses. In a study involving 945 RA patients, the FCGR3A 158 V/F polymorphism was analyzed. The homozygous VV genotype was significantly associated with ACPA-positive RA in Caucasian populations, whereas no such association was observed in Asian cohorts [19,22,32].

The CD40 gene, which encodes a member of the TNF receptor superfamily, plays an essential role in immune regulation, particularly in B-cell maturation and costimulatory signaling. CD40 has been identified as a genetic risk factor for RA, and specific SNPs at this locus have also been linked to increased disease severity [21,22,29].

In conclusion, several HLA and non-HLA genes have been implicated in susceptibility to or protection against RA. To date, more than 30 genes have been associated with the disease and these genetic factors account for about 50 % of the genetic variants linked to RA susceptibility [17–19, 20, 34,22].

IV. Environmental factors of RA

The environmental factors that affect the development and progression of rheumatoid arthritis (RA) are as follows:

1. Smoking

It is one of the common and major environmental factors that causes RA, especially for ACPA-positive RA (36). Smoking induces citrullination of proteins in the lungs, leading generation of neoantigens that trigger autoimmune responses in genetically susceptible individuals especially in individuals with HLA-DRB1 shared epitopes (37). It also activates the pathways such as NF-KB, AhR, and Th17 and also increases production of pro-inflammatory cytokines such as TNF-α, IL-6(35). It leads to increase in levels of autoantibodies such as RF and ACPA (40).

2. Infections

Many pathogens have been implicated in triggering RA, e.g. Epstein-Barr virus, parvo virus B19, Proteus mirabilis, Mycoplasma, etc. Chronic and recurrent low-grade infections are particularly risky in preclinical phase of RA.

Infections cause:

a. Stimulation of pro-inflammatory cytokine production (IL-1, IL-6, TNF-α)
b. Formation of citrullinated peptides, enhancing autoimmunity
c. Activate NF-KB and JAK/STAT signalling, leading to immune dysregulation (38, 41).

Chronic and recurrent infections have been observed in preclinical phase in at-risk individuals. (37)

3. Air pollution and Occupational Exposure

Air pollutants such as silica dust, asbestos and traffic related air pollutants increase RA risk, especially in individuals with genetic susceptibility. Pollutants mainly activate the AhR pathway which promotes the differentiation of Th17 cells and production of osteoclasts, contributing in joint destruction(35, 36). People involve in occupations like mining, construction and farming, where exposure to dust and chemicals is significant have higher risk of RA (42).

4. Obesity

It is a pro-inflammatory state in which adipose tissues releases adipokines and cytokines (e.g. IL-6, TNF-α) which promotes chronic systematic inflammation and aggravate autoimmune responses in RA. Obesity is associated with :

a. Increased RA risk (especially in women)
b. Poorer response in RA treatment ‘
c. More severe disease activity and joint damage (35)

It has been observed that people with higher body mass index are correlated with increased RA incidence, especially women. (39)

5. Diet and Nutrition

Most of the western foods or diets are high in red/processed meat, saturated fats, sugar and excess of sodium and iron. These factors links to increased RA risk.

Anti-inflammatory dietary factors :

a. Omega-3 fatty acids (from fish): It reduces the pro-inflammatory cytokines and inhibit the Th1/Th17 pathway
b. Antioxidants (vitamin A,C,E): It reduces the oxidative stress in joints
c. Vitamin D : its deficiency links to increased RA risk and severity

Studies show that regular consumption of fish, Mediterranean diet and vitamin D supplementation may protect against RA (37, 38)

6. Mental stress and Psychological Factors

It has been observed that stress precede flares in established RA and may trigger disease onset in genetically at-risk individuals.

Chronic mental stress leads to :

a. Dysregulation of hypothalamic-pituitary-adrenal (HPA) axis
b. Increased production of cortisol, which may suppress immune regulation
c. Upregulation of IL-6 and TNF-α, which contributes in joint inflammation (40)

7. Sleep Deprivation

Sleep disorders like insomnia and obstructive sleep apnea have been associated with increased RA risk and worse quality of life in RA patients

Chronic sleep loss leads to :

a. Reduction in immune tolerance
b. Increase in systemic inflammation
c. Elevation of cytokines like IL-β and IL-6

8. Hormonal and Reproductive Factors

RA is 2-4 times more common in women than men due to hormonal influence.

a. Pregnancy : temporary improvement in RA may be observed during pregnancy due to high estrogen /progesterone levels
b. Postpartum period : there is high risk of RA during this period due to abrupt hormone drop
c. Breastfeeding : particularly in first pregnancy there is high risk in RA due to prolonged estrogen suppression (38)
d. Oral contraceptives and hormone replacement therapy : still in studies and debatable and controversial but some studies shows that it is protective against RA

9. Microbiome Dysbiosis and Mucosal Inflammation

Dysbiosis in gut, oral, and lung microbiota may lead to breakdown of mucosal immune tolerance and generation of ACPA and RF autoantibodies. Porphyromonasgingivalis (oral bacterium) produces PAD enzyme which catalyses protein citrullination . Altered gut microbiota may influence systemic immunity and inflammation. (36, 39).

10. Ethnicity and Geography

Some ethnic groups such as Native Americans have higher RA prevalence (up to 6-7%) likely due to gene-environment interactions. Some migration studies show that environmental adaption in new countries may increase or reduce RA risk, even in genetically similar populations. (42)

Summary : Environmental factors modulate immune system particularly in genetically susceptible individuals. Factors such as smoking, pollution, infections, diet, stress, sleep, and hormonal fluctuations show significant contribution to RA initiation and progression.

V.Treatment of Rheumatoid Arthritis

Pharmacological Management

NSAIDs relieve pain and inflammation by inhibiting cyclooxygenase and reducing prostaglandin synthesis [44]. Common NSAIDs (ibuprofen, naproxen, celecoxib) improve symptoms, but their use is limited by adverse gastrointestinal and cardiovascular effects [44].

Glucocorticoids (e.g., prednisone) are used for rapid symptom relief and as bridging therapy while DMARDs take effect [45]. However, prolonged use can cause osteoporosis, weight gain, diabetes, hypertension, and immunosuppression [46].

Opioids (e.g., tramadol, codeine) may be used briefly for severe pain. However, their benefits are modest and they carry risks of dependence and side effects, making them unsuitable for long-term RA management [47].

Second-line: Conventional DMARDs

Methotrexate (MTX) is the anchor drug in RA therapy. It is a folate antagonist that inhibits nucleotide synthesis and suppresses immune responses [48]. MTX reduces disease activity and slows joint damage progression. However, it requires liver and blood monitoring due to risks such as hepatotoxicity and bone marrow suppression. Folic acid supplementation reduces these risks [48].

Hydroxychloroquine (HCQ) is an antimalarial drug that modulates antigen presentation and inhibits Toll-like receptor signaling [49]. It is generally well tolerated, but long-term use may cause retinal toxicity [49].

Sulfasalazine (SSZ) suppresses cytokines like IL-8 and MCP-1 and is useful in combination therapy. It may cause gastrointestinal upset, rashes, or hematologic issues [50].

Leflunomide blocks pyrimidine synthesis by inhibiting dihydroorotate dehydrogenase. Its efficacy is comparable to MTX, but it can cause hepatotoxicity, hypertension, and teratogenicity [51].

Biologic DMARDs

Biologics are used when conventional DMARDs fail and target specific immune pathways.

TNF-α inhibitors (etanercept, infliximab, adalimumab, certolizumab, golimumab) neutralize a key cytokine in RA pathogenesis. They are effective but increase susceptibility to infections such as tuberculosis [52].

IL-1 receptor antagonist (anakinra) is rarely used due to lower efficacy [52].

B-cell depleting agent (rituximab) targets CD20+ B cells and is effective in seropositive RA and vasculitis, particularly after TNF inhibitors fail [52].

T-cell co-stimulation blocker (abatacept) modulates the CD80/86:CD28 pathway and is useful in TNF-refractory patients [52].

IL-6 receptor blocker (tocilizumab) reduces systemic inflammation and is effective in severe or refractory RA [52].

Targeted Synthetic DMARDs

JAK inhibitors (e.g., tofacitinib, baricitinib, upadacitinib) inhibit Janus kinase pathways, disrupting cytokine signaling. These oral agents are convenient and effective, but may cause thrombosis, elevated lipids, infections, and possible malignancies [48][45][53].

Hormonal and Genetic Insights

RA is 2–3 times more common in women than men, implicating sex hormones in disease susceptibility [54].

A prospective study by Karlson et al. found that pre-RA testosterone, DHEAS levels, and hormone-related gene polymorphisms (AR, ESR2, PGR, CYP19) were not significantly associated with future RA risk [55].

Small trials suggest testosterone therapy may benefit postmenopausal women and hypogonadal men by suppressing pro-inflammatory cytokines like TNF-α and IL-6 [55].

Surgical Interventions

Surgery is reserved for advanced RA with severe joint damage. It aims to relieve pain, correct deformities, and restore function.

Synovectomy: removal of inflamed synovial tissue [56]

Tenosynovectomy: especially in hands to improve function [56]

Joint Fusion (Arthrodesis): stabilizes joints such as wrists or ankles

Osteotomy: realigns bones to reduce stress

Joint Replacement (Arthroplasty): common in knees, hips, and shoulders [56]

Radiosynovectomy: involves injecting radioactive isotopes to ablate synovium and reduce inflammation [57]

Non-Pharmacologic and Complementary Therapies

Physical and occupational therapy maintain mobility and reduce pain via exercise and adaptive strategies.

Exercise: Low-impact activities (swimming, walking, yoga, tai chi) improve function and well-being.

Nutritional support: Omega-3 fatty acids have modest anti-inflammatory effects. Calcium and vitamin D counteract steroid-induced bone loss. Folic acid reduces MTX toxicity [48].

Behavioral and lifestyle modifications: Stress reduction techniques, such as mindfulness and deep breathing, may reduce flare frequency.

Future Directions and Personalized Medicine

The 'treat-to-target' (T2T) approach involves setting specific disease activity goals and adjusting therapy accordingly, which improves long-term outcomes [58].

Personalized strategies using genetic and biomarker profiles may guide treatment selection. Trials of agents targeting new cytokines (e.g., IL-7, GM-CSF) are ongoing.

Nanomedicine and innovative drug delivery systems aim to enhance treatment precision and safety [59][58].

VI.CONCLUSION

Rheumatoid arthritis is a disease that develops due to combination of both genetic and environmental factors. Genes, especially those in the HLA-DRB1 group, play a major role in increasing the risk of RA. Other genes such as PTPN22, STAT4, and PADI4 also add to this risk, and their effects varies in different populations. On the other hand, lifestyle and environmental factors such as smoking, infections, stress, pollution, diet, and hormonal changes also influence the development and severity of RA.

By understanding both genetic and environmental factors, we can improve the diagnosis and treatment of RA. Modern treatments like DMARDs and biologic drugs have greatly helped in controlling the symptoms and slowing down the joint damage and newer approaches like JAK inhibitors and personalized medicine are helping to make treatment more effective and safer.

In the upcoming future, combing genetic testing with knowledge of lifestyle and environmental risks may help the doctors to predict who is likely to get RA and choose the best treatment for each patient. This can lead to earlier diagnosis and better outcomes which can improve the quality of life for people living with RA.

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