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REVIEW

Genetic and clinical markers for predicting treatment responsiveness in rheumatoid arthritis

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Abstract **Although many drugs and therapeutic strategies have been developed for rheumatoid arthritis (RA) treatment, numerous patients with RA fail to respond to currently available agents. In this review, we provide an overview of the complexity of this autoimmune disease by showing the rapidly increasing number of genes associated with RA. We then systematically review various factors that have a predictive value (predictors) for the response to different drugs in RA treatment, especially recent advances. These predictors include but are certainly not limited to genetic variations, clinical factors, and demographic factors. However, no clinical application is currently available. This review also describes the challenges in treating patients with RA and the need for personalized medicine. At the end of this review, we discuss possible strategies to enhance the prediction of drug responsiveness in patients with RA.**

Keywords rheumatoid arthritis; gene; clinical markers; therapy

Introduction

Rheumatoid arthritis (RA) is a common immune-mediated disease characterized by chronic inflammatory arthritis and synovitis that destroy the bone and the cartilage. In the United States, the incidence of RA is approximately 1.3 million adults [1,2]. Patients with RA may also suffer from joint damage, functional impairment, and decreased quality of life.

Insufficient evidence has been published to determine the overall RA pathogenesis. However, an increasing number of studies have demonstrated the involvement of genetics, environmental cues, and autoimmune system dysfunction in the mechanism of RA and provided emerging new targets for treatment. Biologics, such as antitumor necrosis factor (TNF) agents, the B-cell depleting agent rituximab (RTX), the selective co-stimulation modulator abatacept, and the anti-IL-6 receptor monoclonal antibody tocilizumab, have been effective treatments for RA [3–6]. These drugs can be used individually or in combination with disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine [7]. However, some patients still fail to respond to treatment regardless of therapeutic options administered to patients with RA. As such, further studies should focus on how to identify these patients before therapy and how to predict treatment responses in patients with RA.

In this review, we provide an overview of the genes implicated in RA by mining MEDLINE/PubMed records. Despite many decades of research in the field of molecular biology and medicine, the number of genes implicated in RA is increasing rapidly, indicating the underlying complexity of this autoimmune disease. We then systematically review various factors, including genetics, clinical characteristics, and demographics, which have a predictive value for determining the potential response to different drugs in RA treatment. These results highlight the challenges in treating patients with RA and the need for personalized medicine. Lastly, we discuss possible strategies to predict drug responsiveness during RA treatment effectively.

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Overview of genes implicated in the pathogenesis of RA

To provide an overview of previous RA research, we employed a text-mining technique to search MEDLINE/PubMed abstracts for genes associated with RA and used keywords, such as "associated" and "implicated," to identify studies that examined genes that were differentially expressed in patients versus healthy controls or in patients who responded well to treatment versus those who did not. This approach allowed us to identify 3500 associations between 610 human genes and RA (Supplementary Table 1). Grouping the results by the year of publication, we found that the number of relevant publications per year has increased dramatically since the 1980s, and the number of implicated genes has accumulated (Fig. 1). These results, especially the increasing number of associated genes, suggest that RA pathogenesis has yet to be fully elucidated, and this disease may be even more complicated than it currently appears.

To provide an overview of the broad functional categories of the 610 RA-associated genes, we categorized the genes into gene families based on their annotated InterPro [8] functional domains (using the data from Ensembl BioMart [9]). As expected, immunoglobulin (Ig)-like genes are the most abundant gene family in our gene set; as shown below, 5 of the top 10 largest gene families contain genes that encode Ig-domain-containing proteins and cytokines. The 5 other families are all related to various kinases (Table 1). Kinases often participate in signal transduction cascades, regulate a large number of downstream proteins, and play important roles in RA pathogenesis [10,11]. The large number of kinases associated with RA further emphasizes the complexity of this autoimmune disease.

Consistent with these observations, our results revealed that the top 10 most studied genes, ranked by the number of MEDLINE/PubMed records in which these genes were mentioned, include mostly Igs, cytokines, and kinases (Table 2).

Genetic variants as predictors of responsiveness to RA treatment

TNF has been extensively studied in RA [12] because it is a cytokine produced by the immune system and responsible for inflammation. TNF expression is inhibited in healthy individuals. Conversely, in patients with RA or similar autoimmune conditions, the TNF expression in the blood often increases, leading to more inflammation [13]. Thus, anti-TNF agents or TNF-blocking drugs have been

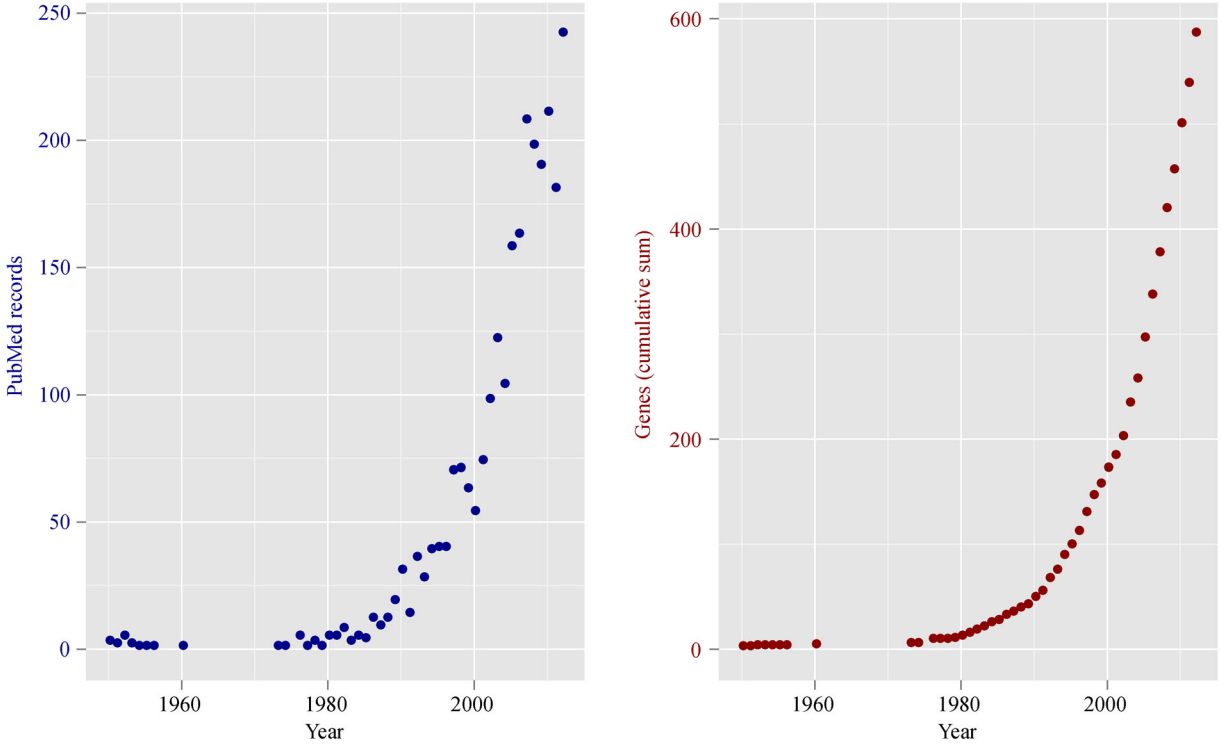

Fig. 1 Overview of the MEDLINE/PubMed records related to RA (left panel) and the associated human genes (right panel), stratified by the year of publication. The left panel shows the number of related publications per year from the 1950s to 2013, whereas the right panel shows the total number of genes that are known to be associated with RA in a particular year and the years prior (cumulative sum). Related data are provided in Supplementary Table 1.

Table 1 Top 10 most frequently occurring protein families and functional domains (according to InterPro) in the 610 RA-associated genes

Interpro ID	Annotation	No. of genes
IPR007110	Immunoglobulin-like domain	68
IPR003599	Immunoglobulin subtype	51
IPR011009	Protein kinase-like domain	40
IPR000719	Protein kinase domain	37
IPR001245	Serine-threonine/tyrosine-protein kinase catalytic domain	37
IPR002290	Serine/threonine/dual specificity protein kinase, catalytic domain	37
IPR020635	Tyrosine-protein kinase, catalytic domain	37
IPR013106	Immunoglobulin V-set domain	34
IPR001811	Chemokine interleukin-8-like domain	30
IPR003598	Immunoglobulin subtype 2	25

Table 2 Top 10 most studied RA genes according to their associated MEDLINE/PubMed records

NCBI Entrez ID	No. of PubMed abstracts	HGNC gene symbol	Note
7124	574	*TNF*	Cytokine
3123	173	*HLA-DRB1*	Immunoglobulin
3569	157	*IL6*	Cytokine
3605	68	*IL17A*	Cytokine
26191	64	*PTPN22*	Kinase
7422	61	*VEGFA*	Cytokine
920	56	*CD4*	Immunoglobulin
4790	53	*NFKB1*	Transcription factor
8797	50	*TNFRSF10A*	TNF receptor
3586	47	*IL10*	Cytokine

widely used to treat inflammatory conditions, including RA [3,4]. The commonly used anti-TNF drugs are infliximab, etanercept, and adalimumab [5,6]. These drugs can be used individually or in combination with DMARDs, such as methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine [7].

The combination of methotrexate and TNF-blocking agents is commonly prescribed for RA treatment [14] and has demonstrated positive results in most clinical trials. However, up to 45% of patients are slightly responsive or nonresponsive to methotrexate [15], suggesting that treatment responses vary among individuals. However, other studies have shown that this particular combination may increase RA remission rates [16].

Genetic polymorphisms, such as single nucleotide polymorphisms (SNPs), copy number variations, and insertion/deletions (indels), have been implicated in RA treatment responsiveness. Table 3 provides a shortlist of genes, their associated genetic variations, and effects on RA treatment.

TNF polymorphisms and their effects on responsiveness to DMARDs and TNF-blocking agents have been extensively studied because of the central role of TNF in RA treatment [3,4,13]. Many studies have focused on SNPs in the promoter region at positions −238 and −308 of the TNF gene. The −238 promoter polymorphism has been associated with RA severity, unresponsiveness to methotrexate [33], and treatment response to infliximab [34]. Conversely, the promoter SNP at −308 is not associated with treatment responses to infliximab [34] or etanercept [32]. However, SNP −308 has been linked to treatment responses to adalimumab [31]. These promoter SNPs contribute to treatment responses by presumably altering TNF gene expression [31]. An SNP at position 489 of the coding region has also been studied, but no remarkable contribution to methotrexate responsiveness has been revealed [33].

TNFRSF1B, a member of the TNF family, has been associated with the treatment responses to infliximab [35]. A previous study in a French population showed that the M196R SNP results in decreased responses to infliximab therapy, although this SNP and another one investigated in the same study are not related to RA susceptibility [35].

Polymorphisms in other cytokines have been associated with responses to DMARDs and TNF-blocking agents. For example, promoter microsatellite polymorphisms in the *IL10* gene can be used to predict clinical responses to etanercept [25].

Many Ig genes are implicated in RA. A major histocompatibility complex, class I, G (HLA-G) gene in the Ig family can be induced by methotrexate activation [21]; thus, its polymorphisms may influence the efficacy of methotrexate treatment. Indeed, a 14 bp indel polymorphism in exon 8 at the 3′ UTR in HLA-G is clinically advantageous in methotrexate responsiveness [22]. However, controversial results have been observed in a follow-up study [23]. In addition, polymorphisms in Ig receptor genes may affect their interactions with Ig genes, which may influence the efficacy of Ig-based therapies [19]. For example, Cañete *et al.* reported the association of several functional SNPs in two Fc γ receptor (FcγR) genes (FCGR2A and FCGR3A) and responses of patients with RA to infliximab [19]. Interestingly, treatment responses are remarkably associated with polymorphisms in the two genes at different timepoints, highlighting the dynamic nature of the interactions between FcγR and Ig [19]. Another study has confirmed the association between FCGR3A and the response to infliximab [20].

The effectiveness of methotrexate is largely due to its dihydrofolate reductase inhibitor activity. Its metabolites also inhibit other folate enzymes, including 5,10-methylenetetrahydrofolate reductase (MTHFR) [36]. Therefore,

Table 3 Gene polymorphisms and associations with response to DMARDs and drugs

NCBI Entrez ID	HGNC gene symbol	Associated variations	DMARD/TNF-blocking agent	Note (reference and statistics)
1544	*CYP1A2*	SNP	Leflunomide	CYP1A2*1F allele is associated with leflunomide toxicity [17]; CC vs. A allele: OR = 9.7 (95% CI = 2.276–41.403), $P = 0.002$
s1557	*CYP2C19*	SNP	Leflunomide	CYP2C19*2 allele influences leflunomide metabolite concentrations that are associated with treatment responses but not with leflunomide-induced toxicity [18]; leflunomide metabolite concentration was ~71% higher in carriers in the CYP2C19*2 allele than in noncarriers
2212	*FCGR2A*		Infliximab	Infliximab treatment in patients with RA is influenced by the FCGR2A and FCGR3A genotypes; this effect is observed at different times during follow-up (6 and 30 weeks, respectively) [19]; in patients with low-affinity homozygotes, FCGR2A and FCGR3A alleles could achieve better responses to infliximab ($P<0.05$ for both cases)
2214	*FCGR3A*		Infliximab	Stated in the comment above and also in the reference [19]
		SNP rs396991	Infliximab	The wild-type allele is associated with better treatment responses, and the strength of the response depends on the type and stage of disease [20]; patients with homozygous V158F polymorphism achieved better response to infliximab ($P<0.05$)
3135	*HLA-G*	Indel	Methotrexate	A −14bp deletion in the 3′-unstranslated region (3′ UTR) of HLA-G was clinically advantageous for methotrexate treatment; however, the results were controversial among studies [21–23]; for example, one study showed that the −14/−14 bp deletion was enriched in the responder group (OR = 2.46 with 95% CI = 1.26–4.84, $P = 0.009$) [21], whereas another study reported the lack of significant results [23]
3569	*IL6*	SNP; −174	Rituximab	−174 CC genotype is associated with a lack of response to rituximab [24] (OR = 2.83; 95% CI = 1.10–7.27; $P = 0.031$)
3586	*IL10*		Etanercept	Promoter polymorphisms in IL10 are useful in predicting clinical response to etanercept treatment [25]
4524	*MTHFR*	SNP; C677T and A1298C	Methotrexate	C667T polymorphism is associated with responses to methotrexate; however, controversial results were recorded among different populations [26–29]
5243	*ABCB1*	SNP; C3435T	Methotrexate	More nonresponders to methotrexate were found in patients with the TT allele than the CC allele [30] (OR = 8.78, $P = 0.038$)
7124	*TNF*	SNP; −308	Adalimumab	Promoter SNP −308 is associated with treatment responses to adalimumab [31]; 88.2% of G/G versus 68.4% of G/A for the −308 polymorphism were responders ($P = 0.05$)
		SNP; −308	Etanercept	Promoter SNP −308 is not associated with treatment responses to etanercept [32]
		SNP; −238 and +489	Methotrexate	Promoter SNP −238 GG homozygosity is associated with severity and unresponsiveness, but the coding +489 polymorphism is not; the −238 AG genotype is absent in severe-unresponsive RA but present in mild-responsive RA subjects; thus, −238 GG homozygosity is associated with severity and unresponsiveness [33]
		SNP; −308 and −238	Infliximab	Promoter SNP −238 is associated with treatment responses to infliximab, but the −308 SNP is not; A allele carrier state was significantly lower among responders (OR 0.344, 95% CI = 0.152–0.779, $P = 0.01$) [34]
7133	*TNFRSF1B*	SNP; M296R	Infliximab	The M196R SNP leads to lower responsiveness to infliximab [35]
7298	*TYMS*	Indel	Methotrexate	3′ UTR indel is associated with responses to methotrexate [27]; in patients with RA with the CC genotype, the OR (95% CI) for the risk of toxicity was 3.8 (2.29–6.33) for the CT genotype and 4.7 (2.40–9.04) for the TT genotype)

Note: OR = odds ratio; CI = confidence interval.

variations in MTHFR may influence the effectiveness of methotrexate treatment. Several studies have confirmed this association and shown that the C667T SNP in the coding region of MTHFR is related to an increased methotrexate toxicity in Spanish [28], Korean [27], African-American, and Caucasian individuals [26]. Ethnic differences influence the response to methotrexate treatment [26]. Conversely, in a study involving Japanese subjects, C667T SNP does not remarkably contribute to methotrexate responses [29]. The A1298C SNP has also

been studied [26,29] and found to be associated with methotrexate treatment responses in African-American and Caucasian individuals [26] but not in Korean individuals [27]. Polymorphisms in the 3′ UTR of thymidylate synthetase, another member of the folate pathway, are also associated with responses to methotrexate [27].

Genes with protein products that can directly interact with administered drugs, such as those involved in drug resistance or metabolism, can influence treatment efficacy. For example, ATP-binding cassette, subfamily B (MDR/TAP), member 1 (ABCB1) is a multi-drug resistance gene that encodes an ATP-dependent drug efflux pump. A C3435T polymorphism in ABCB1 affects methotrexate sensitivity in patients with RA, and patients with the 3435TT allele are significantly more nonresponsive than those with the 3435CC allele [30]. Leflunomide is also a commonly used DMARD, and its metabolism involves genes in cytochrome P450, mainly CYP1A2 and CYP2C19 [18,37]. Polymorphisms in both genes are associated with the response to leflunomide [17,18,37]; in particular, certain CYP2C19 genotypes can hasten leflunomide degradation [18].

In addition to anti-TNF drugs, many other drugs targeting the interleukin family, a group of cytokines that play central roles in the regulation of immune and inflammatory responses, and genes important in immune cell development have been used to treat RA. For example, RTX is a chimeric monoclonal antibody against CD20, which is a B-cell surface protein, and has been used to treat RA [38]. A promoter polymorphism at −174 in an *IL6* gene is associated with the response to RTX treatment, but patients with the IL6 −174CC genotype often show no response to this drug [24]. Nevertheless, associations between genes and relatively new non-TNF blocking drugs are seldom reported. The latter have been proven to be useful in treating RA, and many researchers proposed cocktail therapies for RA by using combinations of anti-TNF drugs and other cytokine antagonists [39].

In addition to genetic factors, epigenetic factors, such as DNA methylation and histone modifications, can be used to predict responses to drugs in RA treatment. Plant *et al.* summarized this topic in a recent review [14]. Considering the technical complexity in identifying epigenetic modifications and the recently revealed links between epigenetic factors and drug responses during RA treatment, we will explore this topic in our future studies and request our readers to consult the review by Plant *et al.* and the references therein.

Differential gene expression as predictors of responsiveness in RA treatment

Many genetic variations affect gene expression. Thus, determining differentially expressed genes by comparing between patients with RA and healthy controls or among patients with different responses to RA treatment may provide useful information for identifying the predictors of drug responsiveness. Gene expression is often measured at a transcriptome level by using microarray or quantitative real-time polymerase chain reaction (qPCR) or at a proteome level from blood samples by conducting enzyme-linked immunosorbent assay (ELISA) and comparative serum proteome analyses.

The TNF −308 G/G promoter polymorphism contributes to adalimumab responsiveness by altering serum TNF levels; the median serum TNFα level of the G/G group was remarkably higher than that of the G/A group [31]. In addition to TNF expression levels, the expression levels of other cytokines, such as interferon (IFN) and IFN receptor genes, have been extensively studied and linked to RA treatment responsiveness. For example, using the data from whole-blood qPCR analysis, van Baarsen *et al*. [40] found that a high IFN signature, that is, an abundant expression of genes activated by type I IFNs, is associated with poor responses in infliximab-treated patients with RA. de Jong *et al.* [41] reported that the use of prednisone, a synthetic immunosuppressant drug, suppresses the IFN signature and increases the responsiveness to RTX in patients with RA. The use of the IFN signature as a predictor of drug response has also been reviewed [42].

The use of drugs in RA treatment can lead to immunogenicity, which can lead to the development of antidrug antibodies (ADAbs) and low effective drug levels. Jani *et al.* recently reported that patients who have developed ADAbs and low drug levels after 3 months of adalimumab treatment respond poorly to continued treatment [43]. Thus, early responses to a particular drug can predict the long-term outcomes of patients administered with the same drug or possibly other drugs. Similar results have been observed in Japanese patients with RA [44].

By applying comparative serum proteome analyses in TNF-antagonist responders and nonresponders, Blaschke *et al.* [45] identified four genes, namely, haptoglobin-α1 (Hp-α1), -α2 (Hp-α2), vitamin D-binding protein (VDBP) and apolipoprotein C-III (ApoC-III), as predictors of etanercept responses in RA treatment. After 6 months of etanercept treatment, the first three genes (Hp-α1, Hp-α2, and VDBP) are remarkably more upregulated in the serum samples of the responders than that of the nonresponders. By contrast, ApoC-III is considerably downregulated. Therefore, high-throughput techniques can accelerate the discovery of genes essential for the clinical outcomes in RA treatment.

Clinical and demographic factors as predictors of responsiveness in RA treatment

Clinical factors, such as disease histories, previous use of

certain drugs, and even RA severity, can serve as predictors of drug responsiveness in RA treatment. For example, Atzeni *et al.* [46] studied 1300 patients with various levels of RA disease severity. The authors evaluated the associations between several clinical factors and the response to anti-TNF agents and found that the enhanced responses of patients with severe RA are associated with no previous use of corticosteroids (an immunosuppressant), the use of adalimumab versus infliximab (both anti-TNF drugs), and the absence of comorbidities [46]. However, these associations are unremarkable in patients with moderate RA disease severity [46], indicating that disease severity itself can be a predictor of drug responsiveness in RA treatment. Gender and age at the start of treatment are also associated with responsiveness to anti-TNF therapy; in particular, males have been higher RA remission than females [47]. However, these results partly contradicted those of a study of Swedish patients with RA in which gender does not influence treatment responses to TNF-blocking therapy [48]. These discrepancies can be attributed to the different populations investigated.

The presence of rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) is a characteristic of RA [49,50]. Thus, the serum levels of these molecules in patients have been extensively studied and linked to drug responsiveness. Narváez *et al.* [51] investigated 108 Spanish patients with RA and found that patients with high levels of serum anti-CCP and/or RF achieve enhanced responses to RTX.

The serum levels of proteins/antibodies and the number of circulating cells can be used as predictors of drug responsiveness. Chara *et al.* [52] measured the number of circulating monocytes and CD14(+ high)CD16(−), CD14 (+ high)CD16(+), and CD14(+ low)CD16(+) subsets in treatment-naive patients with RA through flow cytometry. They found that patients who are nonresponsive to methotrexate treatment have a higher number of circulating monocytes and the subsets than those of responsive patients, who showed normal number of these cells [52]. Their study suggests a new strategy for predicting the clinical response to methotrexate in treatment-naive patients.

Lifestyle activities, such as smoking and drinking, have been associated with several autoimmune diseases, including RA [53–55]. Smoking has also been linked to drug responsiveness in RA treatment. For example, a study on British patients has revealed that nonsmokers tend to have higher responses to TNF therapy than smokers do [56].

Concluding remarks and future directions

Despite efforts devoted to identifying the genetic risk factors of RA, the number of associated genes has been rapidly increasing (Fig. 1), highlighting the complex pathogenesis of this autoimmune disease. In this review, we focused primarily on the genetic and clinical factors that have predictive power to determine drug responses during RA treatment, especially recent developments. On the basis of the collected research articles, we revealed that multiple factors, including genetic variation, gene expression abundance, comorbidities, the use of other drugs, treatment history, and even patient lifestyles, can influence treatment outcomes in RA. To date, most studies have focused on only a limited number of these factors, but combinations of these factors are clearly the most effective predictors of drug responsiveness.

How can we use the available information to predict drug responsiveness? A recent study utilizing machine-learning methods may provide insights into this topic. Lin *et al.* recently reported their efforts to diagnose RA by mining patient clinical data stored in Electronic Medical Records [57]. The authors extracted clinically relevant information from 2792 clinical notes with human diagnoses and used these data as a training set for machine-learning algorithms (MLAs). Then, they applied MLA-generated statistic models to a test set of 2093 clinical notes and obtained a machine-derived diagnosis of disease activity. Consequently, the MLAs achieved a performance similar to human diagnosis. Although drug responsiveness was not explicitly tested in the study, the methods can be applied to study responses to therapies. Interestingly, a rigorous community-based assessment of using SNP data for predicting anti-TNF treatment efficacy in patients with RA has shown no substantial improvement over clinical information [58]. In other studies, haplotypes of HLA-DRB1 gene are correlated with disease susceptibility, severity, and mortality but are inversely correlated with TNF inhibitor treatment response [59]. Nevertheless, these results may indicate that information other than SNP data, such as the expression abundance of target genes and the extent of DNA methylation, should be considered [60]. Dose and intervals of biologics during treatment should be taken into account [60].

In addition to pre-treatment screening, short-term drug response is a reliable predictor of long-term clinical outcomes. Hence, therapeutic strategies should be flexible during treatment and revised whenever necessary.

In summary, despite the availability of many drugs and therapeutic strategies, a considerable proportion of patients with RA fail to respond to currently available agents during treatment. As such, challenges in treating patients with RA should be addressed, and additional disease-associated genes and mutations should be identified. More omics data, including gene expression, DNA methylation, and post-translational modifications, should be obtained, and intelligent methods, such as MLAs, should be established to build predictive RA models with an enhanced performance.

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Compliance with ethics guidelines

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