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Review

The genetics of rheumatoid arthritis

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Abstract

RA is a chronic systemic inflammatory disease that primarily affects the small joints of the hands and feet, and results in a mean reduction in life expectancy of 3–10 years. RA is a multigene disorder with a substantial genetic component and a heritability estimate of 60%. Large-scale Genome-Wide Association Studies (GWAS) and meta-analyses have revealed common disease-associated variants in the population that may contribute cumulatively to RA pathogenesis. This review identifies the most significant genetic variants associated with RA susceptibility to date, with particular focus on the contribution of the HLA class II genes across different ethnic groups. Also discussed are the potential applications of pharmacogenomics to RA management by identifying polymorphisms associated with variation in treatment response or toxicity. The use of genetic variants to guide treatment strategy has the potential to not only reduce National Health Service costs, but also drastically improve patient experience and quality of life.

Key words: rheumatoid arthritis, heritability, genetics, methotrexate, biologics, sequencing, polymorphism, pharmacogenomics

Rheumatology key messages

- Rheumatoid arthritis is associated with many common polymorphisms that contribute cumulatively to disease pathogenesis.
- Response to treatment varies widely between patients and has a genetic component.
- Polymorphisms associated with improved or reduced treatment response could be used to guide clinical practice.

Introduction

RA is a chronic systemic inflammatory disease that primarily affects the small joints of the hands and feet [1]. It has a prevalence of ~1% in European populations and is associated with premature mortality, with a mean reduction in life expectancy of 3–10 years [2]. RA is a multigene disorder with a substantial genetic component and a heritability estimate of 60%, at least 30% of which is likely attributable to genes in the HLA class II family [3]. Large-scale Genome-Wide Association Studies (GWAS) and meta-analyses have revealed common disease-associated variants in the population that may contribute in a cumulative fashion to RA pathogenesis. The identification of variants that are associated with increased RA susceptibility and severity could have diagnostic and clinical applications, not only to enable clinicians to anticipate those at greatest risk of disease, but also to direct drug choice for greatest efficacy and success in patients. This review identifies the most significant genetic variants associated with RA susceptibility to date, with particular focus on the contribution of the HLA class II genes across different ethnic groups. Also discussed are the potential application of these findings to the treatment of RA, and the use of pharmacogenomics in predicting patient response to RA drugs.

Background

RA is characterized by symmetrical peripheral polyarthritis due to an autoimmune inflammatory response focused in the synovium, and results in deformity of the joints, particularly the MCP, PIP and MTP joints (Fig. 1). Prevalence in women is at least twice that in men, and peak age of onset is in the fifth to sixth decades of life. RA presents initially with peripheral joint inflammation, causing inflammatory pain that is worse in the mornings and eases throughout the day. As the disease progresses it can result in joint damage and deformity, particularly subluxation of the wrist and fingers and ulnar deviation of the MCP joints [5]. RA is also associated with a 2–3-fold increase in cardiovascular disease and presents a significant disease

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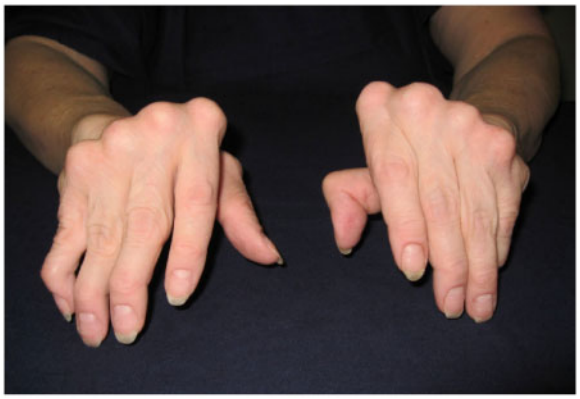
Fig. 1 Hand deformity in RA



The hands of an RA patient showing swelling, subluxation and ulnar drift of the MCP joints, characteristic of late-stage disease. Reprinted with permission from RheumExam Atlas (2015) [4].

burden with higher morbidity and mortality in those affected [5, 6].

The presence of autoantibodies to the Fc region of immunoglobulin G (RF) and to citrullinated cyclic peptide (ACPAs) distinguish seropositive RA from seronegative RA. Patients with RF or ACPAs typically present with more aggressive and severe disease. This often leads to worse disease outcome, particularly in patients who smoke [7–9].

The disease activity in RA is quantified by DAS28, a scoring system based on the number of swollen and tender joints, the amount of inflammation indicated by blood tests, and by the patient's own sense of wellbeing. DAS28 scoring is often used to determine when a referral to a rheumatologist may be necessary [7]. Corticosteroid injections into an acutely swollen joint can rapidly reduce inflammation, and NSAIDs may be used as pain relief, but neither have any effect on disease activity. Early management with DMARDs and biologics can slow disease progression and improve outcomes. DMARDs are the first line of treatment for RA, and include MTX, sulfasalazine and azathioprine. They are frequently used in combination, and can take 6–12 months to produce symptomatic improvement [5]. NICE guidelines mandate that patients may be prescribed biologics only if they continue to present with active RA despite having tried at least two different DMARDs [9]. Biologics include TNF-α inhibitors (infliximab, etanercept, adalimumab), B-cell depletors (rituximab), IL-1/IL-6 inhibitors (tocilizumab), and inhibitors of T-cell co-stimulation (abatacept). They are often used in combination with MTX [5]. Response to DMARDs and biologics is highly variable between patients, and biologics are still prescribed on a largely trial-and-error basis [10].

The genetics of rheumatoid arthritis

It has long been acknowledged that having a family history of RA increases an individual's likelihood of developing the disease, and the heritability of RA has been estimated to be around 60% [1]. Early twin studies and linkage analyses seeking to identify disease-associated genes consistently highlighted one gene family in particular – the HLA *DRB1* alleles, found within the human MHC on chromosome 6. The *HLA* region contains class I and class II genes, the latter of which (*HLA-DR, DQ* and *DP*) produce the alpha and beta chains of the corresponding MHC class II molecule. This molecule is found on antigen-presenting cells and is responsible for the presentation of extracellular pathogens to T cells, resulting in an immune response [11].

The *HLA-DRB1* alleles constitute the single strongest genetic association for RA, and likely contribute at least 30% of the total genetic component of this disease [12]. The disease-associated alleles have a conserved sequence of five amino acids, termed the 'shared epitope' [13]. The shared epitope hypothesis suggests that certain alleles with this conserved sequence are associated with, and in fact directly contribute to, the pathogenesis of RA by permitting the incorrect presentation of autoantigens to T cells by antigen-presenting cells, resulting in a T-cell-mediated autoimmune response [12, 13]. The alleles of the shared epitope have been strongly associated with RA susceptibility and increased disease severity, as well as with an increased risk of developing extra-articular manifestations [12, 14]. These alleles appear to show a gene dosage effect, with RA susceptibility and severity increasing in proportion with the number of alleles present [15]. Jawaheer *et al.* (1994) showed that twins with the shared epitope, particularly the *HLA-DRB1*04* (*HLA-DR4*) alleles, have increased disease concordance. Twins who are homozygous for the shared epitope have five times higher concordance than those lacking the shared epitope completely. The researchers concluded that the shared epitope is 'the most important factor in determining RA concordance' [16].

Other studies seeking to explain the remaining heritability of RA have identified strongly associated loci outside of the shared epitope, such as those involving *PTPN22*, *CTLA4* and *PADI4* [17–19]. However, the candidate gene approach used by most of these studies has limitations, chiefly that it is wholly dependent on the appropriate selection of genes known (or thought) to contribute to disease pathogenesis, and is therefore reliant on a prior thorough understanding of disease mechanisms. This is difficult for studies of RA, which has a complex pathogenesis and polygenic inheritance pattern, and this strategy will inevitably miss contributions from significant loci. Researchers have therefore turned increasingly to Genome Wide Association Studies (GWAS) to look for common variants that may contribute, in small but cumulative ways, to increased RA susceptibility. GWA studies take advantage of regions of linkage disequilibrium (LD) across the genome. These are blocks of genes with lower rates of recombination than expected, which are inherited as haplotype blocks and can be tagged for single nucleotide polymorphisms (SNPs), common single base pair variations that occur throughout the genome [20]. This allows researchers to observe which polymorphisms are more common in cases than in controls.

In 2007, the Wellcome Trust Case-Control Consortium (WTCCC) carried out an extensive GWA study in the British population to look for common variants associated with susceptibility to seven major diseases, including RA [21]. The study confirmed the established association of the *HLA-DRB1* locus with RA, as well as the 1858 C/T polymorphism of the *PTPN22* gene previously associated by Begovich *et al.* (2004) [17, 21]. Of the non-*HLA-DRB1* loci, the *PTPN22* gene is by far the most significantly associated with RA susceptibility and, together with the *HLA-DRB1* alleles, is thought to be responsible for ~50% of the genetic component of RA [21, 22]. The PTPN22 protein product is lymphoid protein tyrosine phosphatase, an enzyme found only in immune cells where it plays an important part in reducing the responsiveness of T and B-cell receptors [17]. However, despite the significance of this variant in populations of European descent, it occurs very rarely in Asian populations, and is therefore unlikely to contribute substantially to RA risk amongst those groups [23–25].

The WTCCC GWA study identified and confirmed several other variants with moderate disease-association. An SNP mapping to the alpha and beta chain regions of the IL2 receptor (*IL2RA* and *IL2RB*) is of particular note [21]. The IL2 receptor is responsible for regulating IL2 stimulation of T cells, and is therefore important for inhibiting autoimmune responses. The association with *IL2RA* was later refined and confirmed by Stahl *et al.* (2010) [26]. This SNP, as well as a variant in *STAT4*, has been associated with susceptibility to several other autoimmune-related diseases, including systemic lupus erythematosus and type 1 diabetes, suggesting a common aetiology underlying these autoimmune disorders [10, 21].

Another GWA study in 2007 identified an SNP (rs3761847) significantly linked with the TNF receptor associated factor 1 and complement component 5 gene regions (*TRAF1/C5*) that is associated with increased risk of ACPA-seropositive RA in European populations [27]. Huang *et al.* (2019) identified another polymorphism (rs10818488) associated with RA not only in Europeans, but also Asians and Africans [28]. Subsequent analysis of eQTL data (a method of testing linkage between gene expression phenotype and genetic polymorphisms) strongly suggests that the association stems from the *TRAF1* region, rather than the *C5*, and *TRAF1* is now thought to be the more functionally-relevant gene associated with these variants [29].

The choice of SNPs used to tag regions of the genome is critical, and is determined by the microarray genechip used in the GWA study. Eyre *et al.* (2012) used Immunochip (an autoimmune disease-specific microarrary) to perform a meta-analysis, combining data from almost 50 000 individuals. By genotyping for 186 GWAS-confirmed loci, they were able to identify 14 new disease-associated loci, and pinpoint the association signal to a single gene for 19 of the 39 previously associated loci on Immunochip [30].

Through such strategies, researchers may gradually determine the true causal variants of RA susceptibility. However, certain microarrays are more appropriate for some ethnic groups than others, and failure to account for this variation can lead to unreliable results. Blocks of LD vary in structure between ethnicities, and this is responsible in part for the heterogeneity of associated polymorphisms between populations [31]. Additionally, care must be taken when selecting cohorts for these studies, as cases and controls must be of similar ethnic backgrounds to avoid effects of population stratification [32]. The results of GWAS are only applicable to the population studied, and cannot be reliably extrapolated to others.

To address this issue, researchers have combined data from multiple GWA studies into meta-analyses, which benefit from increased statistical power compared with single GWA studies, and can allow for the detection of subtle associations across ethnic groups. One of the most significant contributions in this field is a meta-analysis by Okada *et al.* (2014), which used 29 880 RA cases and 73 758 controls from European and Asian cohorts to analyse around 10 million SNPs. The researchers discovered 42 novel loci that are associated with increased RA risk at genome-wide significance, 38 of which are significant at a trans-ethnic level [33]. Further GWA studies and meta-analyses have identified more loci, such as *PADI2* and *NFKBIE*, that are consistently associated across ethnicities (see Table 1 for summary) [25, 33, 38].

Meta-analyses have also shed further light on the MHC class II HLA alleles and their association with RA across ethnicities. The prevalence of RA itself is higher in some populations than others, with 1% of Europeans, 0.5% of Asians and Africans, and over 2% of some Native American populations suffering from the disease [40]. As discussed above, the most common SE-coding alleles are those in the *HLA-DR4* group, though RA in the absence of an *HLA-DR4* background appears to be more common in certain ethnic groups, particularly among Americans of African descent and Jewish Israelis [41, 42]. In patients lacking the *HLA-DR4* alleles, variants in other MHC class II-corresponding HLA genes, such as alleles *HLA-DRB1*01* and *HLA-DRB1*10:01*, are associated with increased RA susceptibility (though conferring lower relative risk than *HLA-DR4*) [13]. The *HLA-DPB1*02:01* and *HLA-DRB1*09:01* alleles are independently associated with disease in Japanese populations; while a variant in the *HLA-DOA* gene is associated with disease in Japanese and Europeans [36, 37, 43]. Conversely, alleles *DRB1*13:01* and *HLA-DRB1*13:02* have been found to have a negative association with RA in northern European and Japanese populations, respectively, suggesting they have a protective effect on ACPA-positive RA [44, 45]. Amongst Indigenous North Americans, a population with 2–3 times the prevalence of RA in Europeans and Asians, the *HLA-DRB1*14:02* allele has been shown to be associated with increased risk of ACPA-positive RA, independently of other HLA loci [35, 46, 47]. This allele is very uncommon in Caucasian and Asian ethnicities, but reaches a prevalence of 80% in some Native American populations [47].

Table 1 Significant genes associated with RA susceptibility

Gene	Protein Product	Population	Reference
HLA-DRB1	HLA class II histocompatibility antigen, DRB1 beta chain	Trans-ethnic African-AmericanIn digenous North American	[25, 33, 34, 35]
HLA-DPB1	HLA class II histocompatibility antigen, DP beta 1 chain	Japanese	[36]
HLA-DOA	HLA class II histocompatibility antigen, DO alpha chain	Japanese European	[37]
PADI4	Protein-arginine deiminase type-4	Trans-ethnic African-American	[25, 33]
PTPN22	Tyrosine-protein phosphatase non-receptor type 22	Trans-ethnic	[33]
CTLA4	Cytotoxic T-lymphocyte protein 4	Trans-ethnic African-American	[25, 33]
IL2RA	IL-2 receptor subunit alpha	Trans-ethnic African-American	[25, 33]
STAT4	Signal transducer and activator of transcription 4	Trans-ethnic	[33]
TRAF1-C5	TNF receptor-associated factor 1 - Complement C5	Trans-ethnic African	[28, 33]
CD40	C-C chemokine receptor type 6	Trans-ethnic	[33]
CCR6	IFN regulatory factor 5	Trans-ethnic	[33]
IRF4	Transcription regulator protein BACH2	Trans-ethnic	[33]
BACH2	DNA repair protein RAD51 homolog 2	European	[38]
RAD51B	Dipeptidyl peptidase 4	European	[38]
DPP4	RNA binding protein fox-1 homolog 1	Han Chinese	[39]
RBFOX1	Protein-arginine deiminase type-2	African-American	[25]
PADI2	CDK5 regulatory subunit-associated protein 2	African-American	[25]
CDK4RAP2	Protein LBH	Han Chinese European	[39]
LBH	HLA class II histocompatibility antigen, DO alpha chain	Trans-ethnic African-American	[25, 33]
COG6	Non-receptor tyrosine-protein kinase TYK2	Trans-ethnic African-American	[25, 33]
TYK2	Protein-arginine deiminase type-2	Trans-ethnic African-American	[25, 33]
PADI4	Trans-acting T-cell-specific transcription factor GATA-3	Trans-ethnic African-American	[25, 33]
GATA3	Conserved oligomeric Golgi complex subunit 6	European	[30]

A summary of the most significant genes currently associated with RA susceptibility, and the populations within which they are significant. Variants found to be significant across both European and Asian ethnicities are classified as 'trans-ethnic'. Studies demonstrating the broadest association of the variant across ethnicities are referenced in each case.

The substantial contribution of *HLA-DRB1* alleles to the genetic component of RA and the increasing number of non-HLA loci associated with the disease have led researchers to investigate connections between these two groups. Diaz-Gallo *et al.* (2018) found significant enrichment in interactions between *HLA-DRB1* shared epitope alleles and SNPs associated with ACPA-positive RA. They suggested a 'dominion hypothesis', wherein the smaller effects of non-HLA variants on RA susceptibility are amplified through interaction with a central 'hub' of shared epitope alleles [48]. The researchers found that of all the loci, the most highly interactive SNPs were rs2476601 and rs1073958. eQTL analysis revealed that in shared-epitope carriers, the rs2476601 variant in the *PTPN22* gene shows the most significant interaction with the shared epitope alleles, while rs1073958 corresponds to *CDK5RAP2* (previously identified by Jiang L *et al.*) and *PSMD5* (Table 1) [39, 48].

GWA studies have contributed substantially to our understanding of the genetic aspect of RA, allowing researchers to cast a wide net without the restrictions of the candidate gene approach. However, these studies also have limitations integral to their design. While they can detect common variants associated with complex diseases, GWAS fail to identify contributing rare genetic variants [49]. This is often due to a lack of statistical power, as well as the limitations of SNPs in identifying larger sources of variation (such as copy number variants, deletions or rearrangements) [50]. GWA studies also suffer from a high rate of false positives due to the large number of statistical tests performed on the data and the presence of individuals in the control group who have not yet developed the disease, but will in the future. It is therefore crucial that studies adhere to a very low *P*-value as the threshold for significance – typically taken as less than 5×10^{-8} [32].

Determining the mechanism by which a SNP is associated with disease is difficult, as it may be causal itself, or simply in LD with the true causal variant. A strong association is not sufficient to prove causality, and identifying the truly causative genetic variant presents a challenge in this field. Fine mapping techniques may be of use in analysing disease-associated regions from GWA studies [51]. This involves exploring in detail the structure of each region tagged by a promising SNP, and may allow researchers to begin to identify true causal variants from the staggering number of disease-associated SNPs [52]. Farh *et al.* (2015) succeeded in developing a new statistical algorithm for fine-mapping, allowing them to identify over 5000 candidate causal SNPs for 21 autoimmune diseases [53]. They integrated these data with chromatin and transcription factor binding maps to determine function, and found that the majority of causal variants are non-coding, involved in

enhancer elements, and located near to immune transcription factor binding sites [53]. In fact, 80% of the >100 loci now associated with RA are in non-coding regions of the genome [54]. The researchers proposed that the effects of such variants could produce subtle but significant alterations in immune response that could predispose towards an autoimmune disease [53]. Effects on expression could be mediated through several mechanisms, including regulatory elements affecting promoter and enhancer activity, alternative splicing and chromatin configuration [54]. Such effects are difficult to elucidate and beyond the scope of this review, but are discussed in depth by Ding J *et al.* (2019) in their review of the use of functional genomics in RA [55].

Pharmacogenomics and personalized medicine in the treatment of rheumatoid arthritis

Although the recent progress in identifying variants associated with RA susceptibility has potential to improve understanding of disease pathogenesis, separate large-scale studies investigating variants associated with treatment response will be more useful for advancing the fields of pharmacogenomics and personalized medicine. Personalized medicine seeks to tailor disease management to individuals based on biomarkers associated with drug response or toxicity. Research in pharmacogenomics aims to identify which genetic variants are associated with drug responses or reactions. Success in these areas would be revolutionary for the management of RA, as the majority of drugs currently prescribed for treatment produce highly variable responses in patients.

Several DMARDs are used to treat RA. MTX is considered to be a cornerstone of disease management, but only 46–65% of RA patients respond positively to its use [56, 57]. Its mechanism of action is unknown, but likely involves inhibition of the folate metabolism pathway [58]. Several genetic variants have been identified as associated with variation in clinical response to MTX, the most significant of which are discussed here (Table 2).

One of the most strongly associated variants is a minor allele of *ATIC* (rs4673993). Lee *et al.* (2009) found that the C allele is associated with increased response to MTX in RA patients on MTX monotherapy compared with the T allele, while another study in 2011 showed that the C allele is associated with lower disease activity [59, 60]. This was further supported by a meta-analysis by Chen *et al.* (2017), which showed significant association of this variant across Caucasian and non-Caucasian populations [61]. The *ATIC* C allele is therefore strongly associated with improved response to MTX in RA patients.

Other genetic associations with MTX response or toxicity are less clear and often controversial. Polymorphisms in genes such as *SLC19A1*, *ABCB1* and *MTHFR* have all been shown to be associated with increased, decreased or no change in MTX response or toxicity, making it very difficult to draw conclusions as to the true effects (if any) of these alleles (Table 2) [62–65, 79–81]. Chen *et al.* (2017) found only one other SNP associated with MTX responsiveness – the 34 C > T polymorphism in the *AMPD1* gene [61]. Significant association of the T allele with improved response was found across multiple ethnicities. The variant produces an enzyme (adenosine monophosphate deaminase) with lower activity, though it is unclear how this might affect MTX efficacy [82]. Most recently, Taylor *et al.* (2018) performed a GWA study using >1000 RA cases to evaluate patient response to MTX, and found that the only locus to suggest association was rs168201 in the *NRG3* gene; however, even this failed to achieve genome-wide significance [66]. This study represents the largest GWA study of RA patient response to MTX treatment to date, and its failure to identify any loci of substantial significance suggests that MTX response is highly polymorphic [66]. Larger, more extensive studies will be required to shed light on any true genetic associations.

Other DMARDs used in RA therapy include sulfasalazine and azathioprine. Patient response to sulfasalazine has long been associated with variants in the *NAT2* gene that affect the ability of the N-acetyltransferase 2 enzyme to metabolise sulfasalazine (Table 2) [67, 68, 71]. Homozygotes for variant alleles, including *NAT2*5B*, *NAT2*6A* and *NAT2*7B*, are 'slow acetylators', and recent studies have shown that these individuals are more likely to suffer adverse drug reactions from sulfasalazine treatment than those with the wild-type *NAT2*4* allele, and are more likely to show non-compliance [69–71]. Wiese *et al.* (2014) also found a polymorphism (C412A) in the *ABCG2* gene, which is associated with disease remission using sulfasalazine [69]. These findings suggest that *NAT2* and *ABCG2* genotyping could be useful in predicting clinical response and toxicity of sulfasalazine during treatment [70].

Azathioprine is an immunosuppressant that works by inhibiting purine synthesis, particularly in white blood cells. The gene *TPMT* codes for the protein thiopurine methyltransferase (TPMT), which is involved in the metabolism of azathioprine [83]. Multiple studies have shown that patients with variations in the *TPMT* gene (alleles *TPMT*2*, *3A*, *3B*, *3C*, *4*) have deficient TPMT activity, resulting in decreased inactivation of thiopurines, and an increased risk of azathioprine toxicity compared with individuals homozygous for the wild-type *TPMT*1* allele [72, 84, 85] (Table 2). These variants are common, with ~10% of the Caucasian population heterozygous for one allele, and one in 300 homozygous (no TPMT activity) [86]. Patients with deficient TPMT activity are at greater risk of life-threatening myelotoxicity and pancytopenia with standard azathioprine dosing, and current NICE clinical guidelines recommend determining patient genotype or TPMT enzyme activity prior to prescribing azathioprine [72, 87]. The introduction of standard TPMT status assessment as a part of clinical decision-making represents one of the clearest demonstrations of the field of pharmacogenetics at work.

A promising addition to this field is the effect of a variant in the gene *NUDT15* on azathioprine toxicity

Table 2 Variants associated with response/toxicity to RA drugs

Drug	Gene	Polymorphism/Allele	Effect	Reference
MTX	*ATIC*	T675C (rs4673993)	C allele associated with lower disease activity and improved treatment response compared to TT	[59, 60, 61]
	SLC19A1	G80A (rs1051266)	G allele associated with increased risk of MTX-related gastrointestinal toxicity compared to AA	[62]
			No association	[63]
	ABCB1	C3435T (rs1045642)	C allele associated with increased risk of MTX toxicity	[64]
			No association	[65]
	MTHFR	C677T (rs1801133)	T allele associated with increased risk of toxicity after 12 months of MTX treatment	[64]
			No association	[63]
	AMPD1	35C>T (rs17602729)	T allele associated with increased response	[61]
			No association	[63]
	NRG3	G>A (rs168201)	Associated with improvement in DAS28 score	[66]
Sulfasalazine	*NAT2*	NAT2*5	Associated with increased risk of adverse drug reaction compared to wild-type allele	[67]
		NAT2*6		[68]
		NAT2*7		[69]
				[70]
			Associated with reduced efficacy	[71]
	ABCG2	C412A (rs2231142)	A allele associated with increased rates of remission after 12 months	[69]
Azathioprine	*TPMT*	TPMT*2 TPTM*3A TPMT*3B TPMT*3C TPMT*4	Associated with increased risk of toxicity	[72]
	NUDT15	T>C (rs116855232)	T allele associated with increased risk of toxicity	[73]
TNF-alpha inhibitors	*TNF*	−308 G/A (rs1800629)	A allele associated with poor response to adalimumab, etanercept and infliximab	[74]
				[75]
			No association with infliximab	[76]
Rituximab	*FGCR3A*	−236 A/C (rs396991)	C allele associated with improved response after 6 months of treatment	[77]
				[78]

A summary of the most significant variants associated with response or toxicity for DMARDs and biologic therapies used in RA.

(Table 2). While *TPMT* variations are relatively common in Caucasian populations, they are rare in Asians. Conversely, variants in *NUDT15* are more common in Asian populations. The T allele in the *NUDT15* gene has been shown to be strongly associated with azathioprine-induced leukopaenia in patients with inflammatory bowel disease compared with allele C [73]. The association is strong across both Asian and European ancestry groups, and researchers have estimated that *NUDT15* and *TPMT* variants together account for '∼50% of severe thiopurine-related hematotoxicity', suggesting that *NUDT15* genotyping could be a useful tool in the future for determining the risk of adverse drug reactions with azathioprine [88].

Patients who continue to suffer with active RA despite having tried at least two DMARDs are managed using biologics [9]. These drugs are synthesized from biological sources and vary drastically in efficacy between patients [89]. This variability has been partially associated with specific gene polymorphisms.

TNF-α inhibitors are the first type of biologic given to most RA patients, and act by suppressing the body's response to TNF, an essential component of the inflammatory response. There are several types, chiefly etanercept, infliximab and adalimumab. They are very effective for some, but as many as 30–40% of patients do not respond to treatment [90]. Several pharmacogenomics studies of TNF-α inhibitors have identified variants that may be associated with treatment response, including the common variant 308 G/A (rs1800629) in the *TNF-α* gene (Table 2) [74, 75]. Two separate meta-analyses identified the A allele as associated with decreased response to adalimumab, etanercept and infliximab in RA patients compared with the G allele [74, 75]. However,

not all studies agree, and a study by Maxwell *et al.* (2008) found that there is no association of this polymorphism with response to infliximab in particular [76]. A large GWA study on this topic in 2018 failed to identify any variants of genome-wide significance capable of predicting change in DAS28 score during the first 3–6 months of treatment [91]. The study did determine that a variant in the *FTO* gene (previously linked to BMI), is associated with improvement in the number of swollen joints in patients treated with infliximab, even when the results are controlled for BMI. Treatment non-compliance is a complicating factor for these studies, but the lack of substantial genetic association with treatment response suggests that response to TNF-α inhibitors is a highly polygenic trait, and greater statistical power is needed to elucidate associated variants [91].

The biologic rituximab is an anti-CD20 monoclonal antibody that depletes B-cell numbers. It is given to patients with severe disease resistant to other drugs. Although rituximab appears to successfully reduce B-cell count in almost all patients, 40–50% of patients still fail to improve [92]. A cohort study of 212 RA patients in 2014 found that RA patients with the V allele (158 V/F) of the *FCGR3A* gene have increased response to rituximab, and are less likely to have loss of response to the drug after 4–6 months of treatment (Table 2) [77]. These findings are supported by other smaller studies, suggesting that the *FCGR3A* 158 V polymorphism could be useful for determine efficacy of rituximab treatment [77, 78].

The ability to reliably identify genetic polymorphisms that have a substantial effect on treatment response in RA patients would revolutionize the management of this disease. This is particularly true for biologics, which are currently prescribed in a systematic manner based on price, wherein a patient must fail to respond to the first drug before they can try the next [9]. This can be a very slow and frustrating experience for patients, particularly those who fail to respond to multiple drugs and must continue living with uncontrolled RA while potentially experiencing the side effects of each new drug they try. It is also very cost-ineffective – TNF-α inhibitors, for example, are estimated to cost the National Health Service (NHS) over £9000 per patient per year [93]. The ability to better predict which patients are most likely to respond well or poorly would therefore make a profound difference to clinical management of RA, patient quality of life and NHS spending.

RA prognosis is intrinsically linked with early diagnosis and management [94]. While it is not possible to predict with certainty who will develop RA, identifying individuals at higher genetic risk of the disease could help clinicians to better advise patients about lifestyle factors prior to disease onset, and enable closer monitoring to begin treatment immediately at disease onset. Polygenic risk scores are one method of quantifying the cumulative effect of all gene variants associated with a disease. However, because they are specific to the ethnic groups used to identify them originally, clinical use of existing data could result in the neglect of certain populations (for example, Afro-Caribbean and Middle Eastern) who have not been studied so rigorously for disease-associated variants compared with European and Asian populations. This has the potential to create and/or exacerbate inequalities in healthcare, and more research targeting these under-studied populations is required to ensure equal distribution of resources [95].

Conclusion

Understanding the genetic basis of RA is important for prediction of disease severity, prognosis and response to treatment. Candidate gene and genome-wide studies have succeeded in identifying a large number of polymorphisms associated with increased RA susceptibility in different human populations. Focus on the use of functional studies to determine not only the causal variant in each case, but also the function of the causal variant, the genes affected by the causal variant, and how all of these factors contribute to disease pathogenesis, is perhaps now the more important area for study. This, combined with the use of pharmacogenomics in clinical practice, would represent a tremendous step forward in the management of RA, and would undoubtedly improve patient quality of life.

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