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## Genetic Influences on Treatment Response in Rheumatoid Arthritis

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### 1. INTRODUCTION

The lack of clinical and laboratory markers that reliably predict response, side effects, or toxicity to therapeutic intervention poses a significant challenge in therapeutic decision-making. Consequently, rheumatologists and other physicians treating patients with rheumatoid arthritis (RA) must choose treatment regimens based on their own experience and assessment of the literature which usually consists of clinical trials of heterogeneous patient populations. With the US Food and Drug Administration's (FDA) approval of tumor necrosis factor (TNF) inhibitors such as etanercept (1) and infliximab (2), the era of targeted biological agents for the treatment of RA has begun. Biologic agents differ from traditional medications used for RA in their capacity to target specific pathophysiological pathways not previously accessible to focused therapeutic intervention. However, the expense of these medications (>\$10,000/yr), their lack of universally positive clinical responses, and the risk of immunosuppression with regard to infections make the identification of markers for clinically significant responses both clinically and practically important.

Although the mechanism of action of biologic agents may be through molecular events "downstream" from those being directly inhibited, there is rationale for searching for genetic markers of disease within the targeted molecules or their ligands. By identifying genetic markers of treatment response (either positive or negative), rheumatologists hope to be able to stratify patients according to genetic determinants of likelihood of

response or toxicity. Genetic markers that can stratify patients based on their likelihood of response or toxicity may have an impact on clinical trials. For example, incorporation of pharmacogenetic analyses into clinical trials may reduce the number of patients required in phase III trials, but may increase the number of patients to be studied in postmarketing studies. Thus, an understanding of the genetics of clinical responsiveness has the potential to improve safety, cost-effectiveness, and clinical response rates by allowing treatment regimens to be individualized (3,4). It should be noted that although genetic tests may provide guidelines for pharmacologic management, they should not be used by medical insurers to disallow reimbursement for treatments with a particular drug.

### GENETIC INFLUENCES ON TREATMENT RESPONSE AND TOXICITY IN HUMAN DISEASES

In the treatment of any disease, there are many factors that can influence response to drugs, including the severity and chronicity of the illness, liver and kidney function, patient age, concomitant treatment with other drugs, coexistent illnesses, and nutritional status (5). Genetic influences on response to drugs have been documented since the 1950s. For example, it was noted that inherited levels of erythrocyte glucose 6-phosphate dehydrogenase (G6PD) activity affected the likelihood of hemolysis after taking antimalarial medications (6). The explosive increase in human genetic information has influenced the field of pharmacology, fostering the burgeoning of pharmacogenetics and pharmacogenomics. For the purposes of this chapter, pharmacogenetics will be used in reference to the study of genetic variation underlying differential response to drugs; pharmacogenomics refers to the systematic application of genomics to discovery of drug-response markers (7).

Genetic markers useful in predicting treatment response or toxicity may lie in genes whose proteins are the target of the drug, are directly involved in the pathogenesis of the disease itself, or are enzymes that influence the metabolic or pharmacokinetic pathways of the drug (7). An example of a genetic marker in the drug target is the presence of coding and promoter polymorphisms in the serotonin receptor *5-HT<sub>2A</sub>* gene, which influence response rates to the antipsychotic drug clozapine (8). For example, there is a polymorphism at position 452 of the *5-HT<sub>2A</sub>* receptor in which either His or Tyr is encoded, based on the allele. In a sample of 153 schizophrenic patients, an association was found between the presence of the Tyr452 allele and poor clinical response to clozapine. A further analysis of multiple polymorphisms in the genes encoding adrenergic receptors, dopamine receptors, serotonin receptors, serotonin transporters, and histamine was performed. Genotypes at six polymorphisms (four in genes for serotonin receptors, one in a gene for serotonin transporter, and one in a histamine gene) yielded a sensitivity of 95% for predicting positive clinical response of schizophrenia to clozapine (9). In Alzheimer's disease, the apolipoprotein E (*apoE*) gene is associated with neurofibrillary tangles and  $\beta$ -amyloid protein in the senile plaques. The presence of particular alleles of the *apoE* gene are associated with response of Alzheimer's to treatment with tacrine (10). There are polymorphic variations in virtually all genes that encode enzymes involved in drug metabolism through modification of functional groups or through conjugation with endogenous substrates (reviewed in ref. 5).

There are many associations between drug response and genetic variations in the metabolic or pharmacokinetic pathways of the drug. The best studied of these associations is that of the cytochrome P450 system. Six cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) mediate the oxidative metabolism of most drugs in common use (reviewed in ref. 11), including some of those used in the treatment of RA, such as nonsteroidal anti-inflammatory drugs (12,13) and cyclosporin (14). Some of these enzyme systems (e.g., CYP2C19, CYP2D6) are polymorphic, with specific alleles that are associated with altered (i.e., reduced, deficient, or increased) enzyme activity, which may influence the likelihood of drug toxicity or therapeutic failure (11). A comprehensive discussion of the influence of cytochrome P450 genetic variations is beyond the review of this text, but is reviewed in ref. 15. In addition, a list of drugs metabolized through this system is available at the Cytochrome P450 Drug Interaction Table on the website of the Georgetown University Medical Center Pharmacology Department <<http://dml.georgetown.edu/depts/pharmacology/davetab.html>>.

Another example of genetic variations in enzymatic pathways affecting toxicity of drugs is the case of alleles in the thiopurine *S*-methyltransferase (*TPMT*) gene. This enzyme metabolizes the immunosuppressive drug azathioprine (as well as mercaptopurine and thioguanine), and genetic variants in its gene predict hematologic toxicity with use of the drug (16,17). Mutations *TPMT*\*3A or *TPMT*\*2 are found in 80–95% of Caucasians with intermediate or low enzyme activity. In a study from two rheumatology units, 6 of 67 patients (9%) treated with azathioprine for rheumatic diseases were found to be heterozygous for mutant thiopurine methyltransferase alleles. Of note, 5 of the 6 heterozygous patients discontinued therapy within 1 mo of starting treatment because of low leukocyte counts; the sixth patient did not adhere to treatment. In contrast, patients with wild-type *TPMT* alleles received therapy for a median duration of therapy of 39 wk (range 6–180 wk). None of 61 patients with homozygous for the wild-type *TPMT* allele discontinued therapy (17). Genotyping of the *TPMT* gene is now routinely performed on all patients with acute lymphoblastic leukemia (ALL) at the Mayo Clinic; patients with genotypes associated with low *TPMT* are treated successfully with lower doses of thiopurines (18–20). Perhaps rheumatologists should be using a similar strategy to identify patients with RA and systemic lupus erythematosus (SLE) who require lower doses of azathioprine to avoid toxicity.

Several requirements must be fulfilled for a pharmacogenetic assay to be useful for practicing clinicians (21). First, the test must discriminate between significantly different clinical responses. In RA, a pharmacogenetic assay for efficacy should be able to stratify patients according to improvement in the number of swollen and tender joints, e.g., those meeting American College of Rheumatology (ACR) 50% response criteria vs those failing to meet ACR 20% response criteria. Second, the test must be adequately sensitive. In an assay for toxicity, for example, a sensitivity approaching 100% is desirable whereas in a test of efficacy, identification of 60–80% of responders is clinically useful. The number of false positives (specificity of the test) is also a parameter that influences clinical utility. Finally, the test must be relatively inexpensive, rapid, and yield clear results that are interpretable by practicing physicians. An ideal pharmacogenetic test would require a small blood sample, provide fast and reliable genotype analysis, and accurately predict the treatment response or toxicity to one or more treatment alternatives (22).

## GENETIC INFLUENCES ON SUSCEPTIBILITY TO RA AND ITS SEVERITY

Genes important in susceptibility or severity of RA may also influence treatment response. There is a genetic component to susceptibility to RA, as there is with virtually every form of arthritis, including familial osteoarthritis (23), ankylosing spondylitis (24), SLE (25), and gout (26). Because of the complexity and redundancy of the human immune system and the large number of cell types and molecules involved in its pathogenesis, there are a multitude of genes that may influence RA susceptibility. In addition to contributing to susceptibility, genetic factors may have an effect on disease phenotype as defined by particular clinical manifestations (e.g., erosions or extra-articular manifestations), or may influence response to particular treatments. Potentially relevant genes include those that encode proteins involved in antigen recognition, cell-cell interactions, intracellular signaling, inflammation, apoptosis, cell trafficking, hormonal interactions, and others (reviewed in ref. 27). A genome-wide screen of 257 multiplex RA families by the North American Rheumatoid Arthritis Consortium (NARAC), revealed evidence for linkage to a number of non-HLA loci on chromosomes 1, 4, 12, 16, and 17 (27a).

### *Class II MHC Alleles*

RA susceptibility is known to be associated with genes in the class II major histocompatibility complex (MHC) (28,29). An association between HLA DR alleles and RA was first reported in 1978 (30) and has been confirmed in multiple studies (reviewed in ref. 31). It is now generally accepted that particular class II MHC alleles (DR4 subtypes Dw4 [*DRB\*0401*], Dw14 [*DRB\*0404*], and Dw15 [*DRB\*0405*], and some DR1 alleles) are associated with susceptibility to RA in Caucasians. Nucleotide sequence analysis led to the hypothesis that these alleles confer susceptibility to RA based on shared homology at amino acid residues 70–74 of the third hypervariable region of the DRB1 chain, the so-called shared epitope (32). The predisposition to and severity of RA in African-Americans appears to be independent of the presence and dose of the shared epitope in class II MHC alleles (33) (*see below*).

In addition to having a role in susceptibility to RA, MHC class II DR4 alleles have been reported to have an affect on disease severity (such as more erosions on radiographs) (34,35). Rheumatoid factor (RF)-positive Caucasians with RA who bear two susceptibility alleles have been shown to be more likely to have severe disease and extra-articular manifestations than heterozygous individuals, suggesting a gene dosing affect (36).

### *TNF Polymorphisms*

In RA, there may be enrichment for genetic polymorphisms that lead to higher levels of cytokines with predominantly proinflammatory effects or lower levels of predominantly anti-inflammatory cytokines. Tumor necrosis factor (TNF), for example, plays a substantial role in the pathogenesis of RA (37,38). There are conflicting reports of the roles of TNF genetic variations in RA, possibly as a result of population admixture and multiple-hypothesis testing (39). Some studies have shown no association between RA susceptibility and the TNF locus (40–43). One study reported an association between the genotypes at the promoter polymorphisms at –238 and –308 and the mean

age at disease onset and the presence of rheumatoid nodules, respectively (43). The TNF -238 G/A heterozygous genotype has been reported to be associated, independent of the presence of HLA DR4 alleles, with a paucity of erosions early in the course of the disease (44) and with a lower rate of joint damage on hand radiographs as the disease progresses (45). However, functional assays revealed no significant differences in the level of inducible reporter-gene expression between the TNF -238 A and G alleles.

Microsatellite markers in the TNF locus (TNFa, b, c, d, and e) have also been studied with regard to RA susceptibility and severity. Studies have shown an association of TNF microsatellite alleles with RA independent of the MHC locus (46,47), and an association with RA with possible synergy with the MHC locus (48). Criswell and colleagues studied the effect of TNF microsatellite polymorphisms on likelihood of severe RA (defined by rheumatologists' assessments of disease course, joint replacement, hospitalization for RA other than for joint replacement, and severity of erosions on hand/wrist radiographs). Allele 11 of the TNF microsatellite polymorphism TNFa (TNFa11) appeared to be associated with RA severity through an interaction with the MHC shared epitope (48). Most of the severe outcomes were observed among individuals who had inherited both TNFa11 and the shared epitope, whereas individuals who had inherited TNFa11 in the absence of the shared epitope had the best outcomes. Although the mechanism for this interaction remains unclear, both the MHC shared epitope and the TNF-LT $\alpha$  locus appear to be important determinants in RA severity.

## DNA MICROARRAYS IN MOLECULAR GENOTYPING AND PHENOTYPING

One of the most exciting biotechnologies to impact on genetics is the development of DNA microarrays, which allow analysis of thousands of genes simultaneously (49). DNA chip technology has facilitated discovery of single nucleotide polymorphisms (SNPs) as well as genotyping of a large number of SNPs in a rapid, accurate fashion (50,51). In addition to SNP discovery and genotyping, DNA microarrays can be used to characterize which of thousands of genes are preferentially expressed in particular tissues (expression profiling) (52). This is a powerful technique that allows molecular comparison of diseased cells or tissues to their normal counterparts and to detect changes in gene expression in response to cytokines, growth factors, and drugs. Thus, DNA microarrays are likely to have a substantial impact on identification of new molecular targets and drug discovery (53). Among the most important potential applications of gene chips is to identify molecular classification of diseases, which may ultimately allow optimization of treatment strategies. For example, Golub et al. used DNA microarrays to profile expression of 6817 genes in bone marrow aspirates of patients with acute myeloid leukemia (AML) and ALL (54). Using 50 informative genes, classification into AML vs ALL, as well as identification of subclasses, was possible. One of the informative genes was topoisomerase II, the target for the anti-leukemia drug etoposide, which illustrates the potential usefulness of molecular classification in pharmacogenetics.

Because RA is a heterogeneous disease, molecular phenotyping may someday be useful for determining optimal treatment. Synovial tissue may be obtained through arthroscopic or percutaneous biopsy and expression profiling performed. For results to be interpretable and clinically meaningful, artifacts owing to varying proportions of different cell types must be avoided. There are many ways to exclude this problem,

including histologic examination of synovial samples to ensure comparability, or purification of cells of a particular lineage (e.g., T cells, B cells, monocytes, or fibroblasts) by flow sorting or laser-capture microdissection (54).

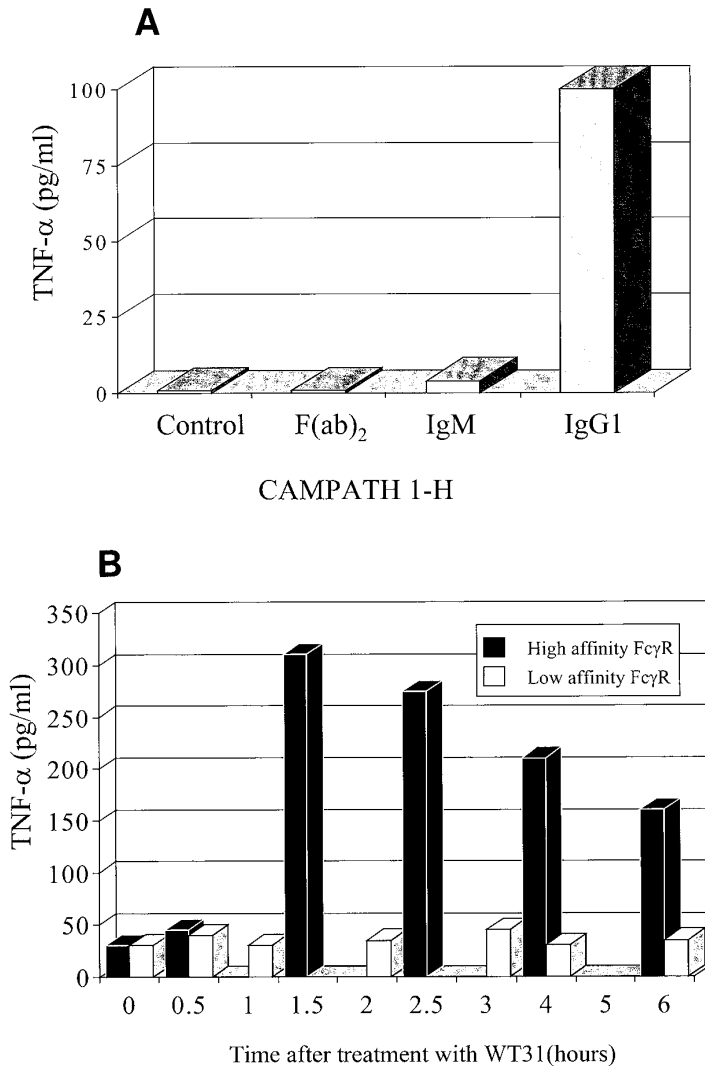
## PHARMACOGENETIC STUDIES IN RA

In approaching pharmacogenetic studies in RA, there are some genetic associations for which the mechanism of side effects or toxicity is unknown. For others, the genetic association may influence drug metabolism or pharmacokinetics. For still others, responsiveness may associate with variations in specific pathophysiologic pathways or with the underlying severity of disease.

Gold salts have been used in the treatment of RA for many years, and can cause side effects such as bone marrow suppression, proteinuria, and mucocutaneous lesions. HLA DR3 may be associated with gold toxicity in RA (55). Further studies indicate that HLA-DQA region genes (56) or HLA-B8 and DR3 antigens (57) may play an important role in susceptibility to gold-induced nephropathy and that HLA-DR1 (58) or HLA-DR5 (57) may be involved in susceptibility to mucocutaneous side effects. Although the mechanisms and genes involved remain unknown, such studies helped to set the stage for pharmacogenetics in understanding drug effects in RA. Affecting drug-metabolism genetic variability in the *G6PD* and *TPMT* genes may influence toxicity of antimalarials or azathioprine, respectively, in the treatment of RA. Susceptibility to sulfasalazine-induced agranulocytosis may be influenced by polymorphisms of *NAT2* (59).

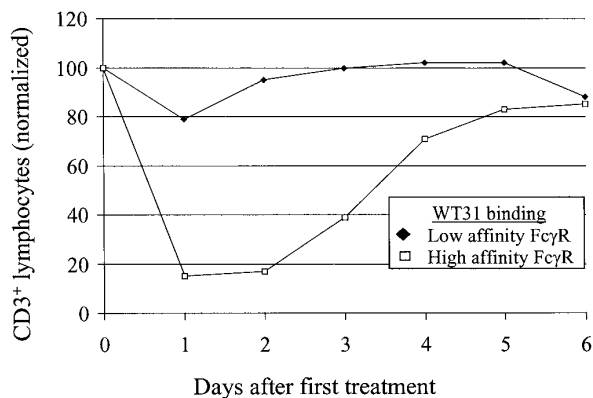
With the use of immunoglobulin-based biologics, naturally occurring polymorphisms in receptors for immunoglobulins may influence pharmacokinetics and side effects. The efficacy of some of these immunoglobulin-based therapeutics in model systems is Fcγ receptor dependent (60,61). Similarly, the cytokine-release syndrome induced by at least some humanized monoclonal antibodies (MAbs) is also Fcγ receptor-dependent (62) (Fig. 1). Tax and colleagues (63,64) have shown that in organ transplant recipients, the cell depletion induced by the anti-CD3 MAb, WT31, varies predictably with Fcγ receptor genotype (Fig. 2). Although the effect of naturally occurring polymorphisms in Fcγ receptors on the efficacy of current therapeutic agents in RA has not been explored in depth, an influence on minor infections as an adverse events in both treated and control subjects has been demonstrated (65). Such observations suggest that the genetics of the study population may influence adverse events and impact on formulation strategies as well as affect responsiveness of pathophysiological pathways. Because of the role of TNF in RA and the availability of anti-TNF therapy, TNF and TNF-receptor loci may yield useful pharmacogenetic markers as an example of the latter (27).

The MHC class II shared epitope, which can influence disease severity, may also affect the clinical response of RA to treatment (66). In a study by O'Dell and investigators in the Rheumatoid Arthritis Investigational Network (RAIN), patients were randomized to receive three disease modifying anti-rheumatic drugs (DMARDs) (methotrexate [MTX], hydroxychloroquine, and sulfasalazine), MTX alone, or hydroxychloroquine plus sulfasalazine (67). The three drug regimen was found to be superior to the other two. In a follow-up analysis, all patients were genotyped for the presence of DRB1 \*0401, \*0404/\*0408, \*0405, \*0101, \*1001, and \*1402 alleles to determine if there was an influence of the shared epitope on treatment response. Patients with the shared epitope were more likely to achieve ACR 50% response criteria to triple DMARD therapy than



**Fig. 1.** Role of Fc $\gamma$ R in cytokine release syndrome. **(A)** Ex vivo whole-blood cultures demonstrate the central role of Fc $\gamma$  receptors in TNF- $\alpha$  release by the anti-CD52 MAb, CAMPATH 1-H. Adapted with permission from Wing et al. (62). **(B)** Fc $\gamma$  receptor-binding affinity for MAb varies with receptor genotype and influences TNF- $\alpha$  production in patients receiving MAb WT31. Adapted from Tax et al. (64).

to MTX alone (94% responders vs 32%,  $p < 0.0001$ ) (66). In contrast, patients without the shared epitope did equally well regardless of treatment (88% responders to triple DMARD therapy vs 83% for MTX alone). Although the number of patients was small, this study suggests that knowing whether or not the patient has alleles containing the shared epitope may be useful in selecting among treatment options.



**Fig. 2.** Percentage of circulating CD3<sup>+</sup> lymphocytes during anti-CD3 treatment with MAb WT31. The donor with the FcγRIIA genotype which binds WT31 with high affinity showed a more pronounced decrease in circulating CD3<sup>+</sup> lymphocytes. Adapted from Tax et al. (64).

There are likely to be important racial differences in allele frequencies of genes important in the pathogenesis of RA. As mentioned earlier, MHC class II shared epitope appears to have less of an influence on susceptibility to RA in African-Americans than it does in Caucasians (33). In addition, there are marked differences between African-Americans and Caucasians with regard to the prevalence of an SNP in the *IL-6* gene that appears to play a role in susceptibility to juvenile RA (68–70). Among Spaniards (71) and Israeli Jews (72), DR10 alleles appear to be the most important MHC susceptibility genes. Although there are no known racial differences in the overall frequency of mutant TPMT alleles compared to wild-type alleles, it has recently been reported that Caucasians mutant alleles are usually TPMT\*3A, whereas Kenyans have the TPMT\*3C allele (73). Thus, race should be considered an important variable in genetic analyses of susceptibility, severity, and treatment response in RA.

When pharmacogenetics will be translated to the bedside in the treatment of RA remains to be established, but the future of molecular medicine, and its potential to enhance the management of our patients, appears bright. New agents, including those directed against IL-1 (74,75), and other biologic targets such as costimulatory molecules (e.g., CD40/CD40L, and CTLA4), are being developed, and identification of genetic markers of clinical response or toxicity may provide more efficient and cost-effective therapies.

## CONCLUSIONS

There has been an explosion of knowledge of genetic variations among different populations and the influences of genetics on complex autoimmune and inflammatory diseases such as RA. Although class II MHC alleles are important contributors, there are likely to be multiple other genes that modulate the disease phenotype. In addition, genetic markers may allow determination of treatment response, especially in light of the growing number of biologic agents undergoing clinical trials.



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