Pharmacogenomics of Autoimmune Diseases

13

Melvin George, Sandhiya Selvarajan, and Suresh Kumar Srinivasamurthy

Abstract

Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis cause a considerable degree of morbidity worldwide. Although the treatment of these conditions has shown progress over the last decade with the steady trickle of new drug molecules, drug therapy is far from satisfactory due to the reduced efficacy and maximal toxicity in certain patients. Several factors are known to influence the efficacy and toxicity of these drugs such as age, gender, liver and kidney function, and concomitant drug therapy. Another crucial factor influencing drug response of the patient is the genetic constitution of the patient. For example, polymorphisms in the gene MTHFR such as *677T>C* can increase methotrexate serum levels and lead to toxicity in a patient with RA. Similarly polymorphisms in the drug transporter ABCB1 are associated with decreased efficacy to methotrexate. Polymorphisms within the *TNF* promoter region have been shown to modify the clinical efficacy and toxicity of anti-TNF therapy in RA patients. SLE patients with polymorphic *TPMT* gene may require a reduced dose of azathioprine to circumvent the catastrophe of fatal bone marrow suppression. Polymorphisms in the *TYMS* gene could lead to reduced efficacy with methotrexate in psoriatic arthritis patients. Although our understanding of autoimmune diseases has improved considerably over the last decade and several studies in pharmacogenomics of autoimmune diseases have been carried out, the only clinical application is *TPMT* testing for azathioprine. Yet with improved methodology adopted in pharmacogenomics studies coupled with novel technologies, the field of pharmacogenomics does appear to offer significant promise in the coming years towards the dream of personalized medicine in autoimmune diseases.

M. George, MD., DM. (✉)
Department of Cardiology, SRM Medical College and Hospital Research Centre, Kattankulathur, Kancheepuram District, Tamil Nadu, India
e-mail: melvingeorge2003@gmail.com

S. Selvarajan • S.K. Srinivasamurthy
Division of Clinical Pharmacology, JIPMER, Pondicherry, India
e-mail: sandhiyaselvarajan@yahoo.com; sandhiyaselvarajan@gmail.com

D. Barh et al. (eds.), *Omics for Personalized Medicine*,
DOI 10.1007/978-81-322-1184-6_13, © Springer India 2013

1 Introduction

Autoimmune diseases are one of the major causes of morbidity in developed and developing countries among young and middle-aged women (Cooper and Stroehla 2003). In women, autoimmune diseases constitute one of the top ten causes of death. Most autoimmune diseases have an unequal preponderance in females, being almost 65 %. Rheumatoid arthritis, psoriasis, systemic lupus erythematosus, Hashimoto's thyroiditis, Sjogren's syndrome, scleroderma, Wegener's granulomatosis, and systemic vasculitis are some of the major autoimmune diseases. The annual direct healthcare costs related to these diseases are more than hundred billion US dollars. As our understanding of these diseases has increased over the last few decades, it has also led to a number of new molecules entering the market. Although several new drugs have entered the market which target specific pathways of these diseases, the treatment of these disease conditions is far from satisfactory owing to the frequency of adverse drug reactions and variable and limited efficacy in different population. Several factors contribute to the variation of the drug response seen among these patients such as age, gender, presence of earlier drug therapy or concomitant drug therapy, stage of disease, and the genetic status of the individual. Pharmacogenetics is the branch of medicine which deals with the study of how genetic factors contribute to the variation in drug response of the individual. Apart from improving our ability to predict the variability of drug response and toxicity, pharmacogenomics also helps us to develop new biomarkers and new targets for drug development (Fig. 13.1). This chapter attempts to highlight the recent advances in the pharmacogenetics of some of the common autoimmune diseases.

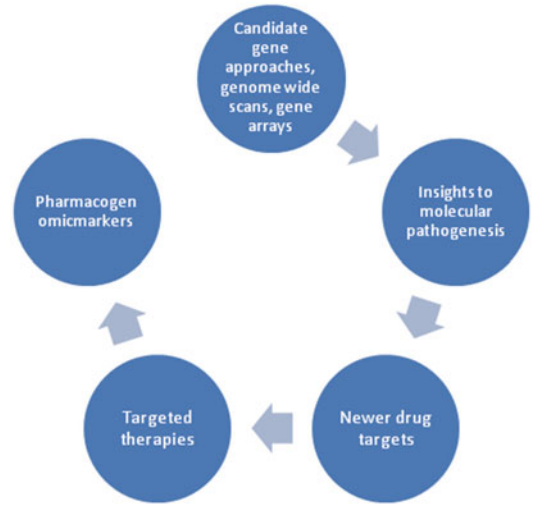

Fig. 13.1 Differing facet of pharmacogenomics in autoimmune diseases which includes development of newer targeted therapies with pharmacogenomic markers

2 Pharmacogenomics of Rheumatoid Arthritis

Rheumatoid arthritis is one of the most common autoimmune diseases worldwide with its prevalence hovering between 0 and 1 % in different regions. The disease causes untold suffering to millions of people every year. The symptoms of the disease, such as joint swelling and tenderness involving more than five joints, which are accentuated in the early hours of the day cause tremendous morbidity in these patients. Rheumatoid arthritis is also known to cause increased mortality due to the increased association with cardiovascular disease, malignancy, and infections in these patients (Owlia et al. 2012). The diminished quality of life and the added economic burden in terms of hospitalizations make this an important health problem to contend with. Some of the common drugs for rheumatoid arthritis include corticosteroids, methotrexate, sulfasalazine, and TNF-alpha inhibitors such as infliximab, etanercept, and adalimumab. Some of the new additions to this array of molecules which have been recently approved by US FDA include golimumab, certolizumab pegol, and tocilizumab (Reichert 2012). Although these new molecules appear promising in phase 2 and 3 clinical trials, as demonstrated by favorable safety and efficacy data, they are yet to become common place in drug therapy of rheumatoid arthritis owing to their prohibitive cost and limited availability in most nations (Hoebert et al. 2012). Hence, it is not surprising that the older drugs

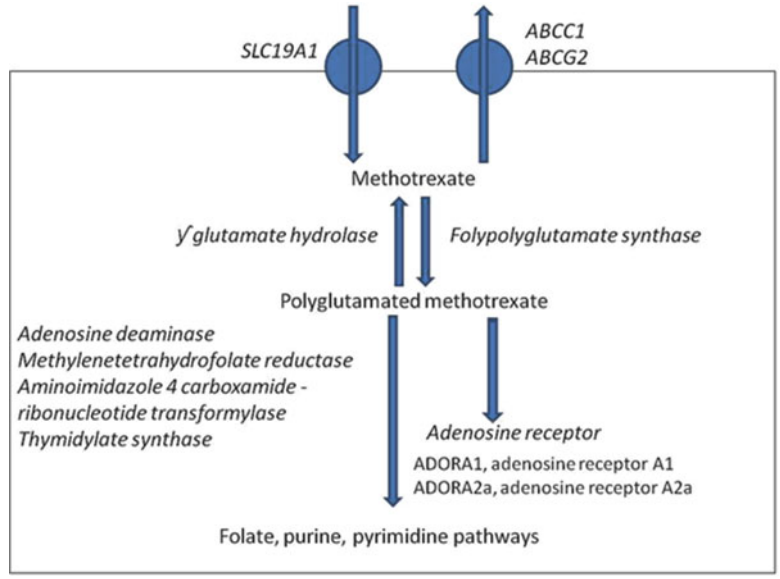

Fig. 13.2 Metabolism of methotrexate within the cell

such as methotrexate still occupy a pivotal role in the management of rheumatoid arthritis. The major adverse effects of methotrexate include neurologic toxicity, gastrointestinal complications including nausea, vomiting and diarrhea, liver dysfunction, hematologic abnormalities, rash, stomatitis, and alopecia (Mittal et al. 2012).

2.1 Effect of Methotrexate on Folate and Other Pathways

The entry of methotrexate into the cell is directed by a solute carrier family protein such as SLC19A1, while the efflux of the drug is mediated by ATP-binding cassette family transporters, also termed as MDR transporters. The enzyme folylpolyglutamate synthase helps in converting the methotrexate into its different polyglutamate forms (MTXPG), which helps in the retention of intracellular methotrexate (Fig. 13.2). This reaction can also be reversed by the enzyme gamma-glutamyl hydrolase. The MTXPG that are formed will in turn inhibit dihydrofolate reductase that converts dihydrofolate to tetrahydrofolate. Tetrahydrofolate further undergoes methylation to result in the formation of 5-methyltetrahydrofolate which acts as a carbon donor for several reactions such as conversion of homocysteine into methionine (Davila and Ranganathan 2011).

Methotrexate also has additional effects by acting on the pyrimidine and purine synthesis. It inhibits the thymidylate synthetase thereby preventing conversion of deoxyuridylate to deoxythymidylate. It also inhibits the enzyme AICAR transformylase that leads to intracellular accumulation of aminoimidazole carboxamide adenosine ribonucleotide (AICAR). AICAR and its metabolites inhibit the enzymes involved in the metabolism of adenosine such as adenosine deaminase and AMP deaminase, resulting in a rise in adenosine that has a powerful anti-inflammatory effect (Davila and Ranganathan 2011).

2.2 Genetic Polymorphisms and Methotrexate in RA

Methotrexate is well known to exhibit variable efficacy and toxicity in the treatment of rheumatoid arthritis. Several studies have been done to illustrate the role of genetic polymorphisms in influencing the response of methotrexate in terms of both efficacy and toxicity (Table 13.1). For example, polymorphisms of the gene

Table 13.1 Effect of genetic polymorphisms on methotrexate efficacy and toxicity in rheumatoid arthritis

Gene	Polymorphism	Functional significance	Clinical outcome
MTHFR	*677C>T*	Decreased MTHFR enzyme levels	Increased toxicity
	1298A>C	Decreased MTHFR enzyme activity	Increased efficacy and toxicity
SLC19A1	*80G>A*	Higher levels of MTXPG	Increased efficacy
ABCB1	*3425C>T*	Increased intracellular uptake of MTX	Decreased efficacy
TYMS	*5-UTR repeat element*	Increased TYMS activity	Decreased efficacy
ATIC	*347C>G*	Increased AICAR levels	Increased toxicity
IL-1R	*IL-1RN*3*	Alters IL-1 synthesis	Decreased efficacy

Abbreviations: *AICAR* aminoimidazole carboxamide ribonucleotide, *ATIC* aminoimidazole carboxamide ribonucleotide transformylase, *IL-1R* interleukin 1 receptor, *MTHFR* methylenetetrahydrofolate reductase, *MTXPG* methotrexate polyglutamate, *SLC* solute carrier, *TYMS* thymidylate synthase

encoding *MTHFR*, *677C>T* and *1298A>C*, are in linkage disequilibrium and lead to reduced levels, and thus activity, of MTHFR. A study done in 125 RA patients of European descent showed that RA patients with *DHFR-317AA* genotype had less favorable response to MTX as measured by DAS (Disease Activity Scoring) (Milic et al. 2012). A study in US population revealed that an SNP in the *ATIC* gene, rs4673993 was associated with low disease activity in patients on MTX (Lee et al. 2009). Methotrexate-induced liver dysfunction was found to be significantly correlated with non-*TT* genotype polymorphism at *GGH T16C* gene in a study done in Japanese children with juvenile idiopathic arthritis (Yanagimachi et al. 2011). A meta-analysis was done to determine the influence of pharmacogenetics on the efficacy and toxicity of methotrexate. Although as many as 12 genetic polymorphisms in the methotrexate pathway were studied, sufficient data was available only with respect to two polymorphisms, namely, *C677T* and *A1298C* in *MTHFR* gene. The *C677T* polymorphism was found to be significantly associated with methotrexate toxicity, while *A1298C* was not associated with toxicity. No polymorphisms could be positively correlated with efficacy in this meta-analysis (Fisher and Cronstein 2009). Besides these polymorphisms in recent years, there have also been studies which have attempted to build a model that combines clinical parameters with genetic polymorphisms. For example, clinical parameters such as rheumatoid factor status, smoking status, gender, and disease activity were compared with polymorphisms in adenosine pathway genes and folate pathway genes to predict efficacy of methotrexate. The *MTHFR 677C>T* variant has been found to be the most widely reported polymorphisms that is positively correlated with methotrexate toxicity (Schmeling et al. 2005; Aggarwal et al. 2006; Wessels et al. 2006; Ranganathan et al. 2008; Hughes et al. 2006). Yet quite number of studies have not shown an association between these polymorphisms and methotrexate efficacy and toxicity (Taraborelli et al. 2009a, b). A meta-analysis failed to prove a positive association between *C677T* and *A1298C* polymorphisms of MTHFR and the toxicity and efficacy of methotrexate in RA (Lee and Song 2010).

2.3 Genetic Polymorphisms and Sulfasalazine in RA

This drug has been used in RA treatment for more than 30 years. The drug is activated into 5-aminosalicylic acid and sulfapyridine after ingestion. Sulfapyridine is metabolized by N-acetyltransferase 2. Based on polymorphisms in *NAT2* gene, individuals can be classified as rapid and slow acetylators. Studies have demonstrated that toxicity with sulfasalazine such as headache, nausea, abdominal discomfort, and rash is more frequent in patients who are slow acetylators (Davila and Ranganathan 2011). Those patients without the wild-type haplotype at *NAT2* were more likely to experience adverse events by sulfasalazine (Taniguchi et al. 2007).

2.4 Genetic Polymorphisms and Leflunomide in RA

Leflunomide is metabolized into an active metabolite A771726 that causes reversible inhibition of the rate-limiting enzyme in pyrimidine synthesis, namely, dihydroorotate dehydrogenase (DHODH). Thus, a missense polymorphism in the human *DHODH* gene will reduce the DHODH enzyme activity (Davis et al. 1996). In a study carried out in 147 RA patients, remission was found to be more common in patients with *C* allele rather than *A* allele. However, this polymorphism has also found to be linked with a sevenfold increased risk of adverse events from leflunomide such as hepatotoxicity and gastrointestinal and mucosal toxicity (Pawlik et al. 2009). Based on in vitro studies, estrogen was found to interfere in the suppression of cytokine production by leflunomide. This led to exploration of the association between estrogen receptor polymorphisms and leflunomide response. Polymorphisms in the estrogen receptor could potentially alter the estrogen receptor expression. In a prospective study done in 115 patients with RA, the *ESR1* rs9340799 *AA* and rs2234693 *TT* genotype were associated with better response to leflunomide therapy. Leflunomide is converted into its active metabolite by CYP1A2. *CYP1A2*1F* polymorphism was found to be correlated with leflunomide toxicity as it accentuates the conversion of leflunomide to its active metabolite (Grabar et al. 2009; Dziedziejko et al. 2011).

2.5 Genetic Polymorphisms and Tumor Necrosis Factor Antagonists in RA

Polymorphisms in the *TNF* gene locus such as *−308G>A* and *−238A>G* influence TNF production. A study reported increased efficacy of TNF-alpha antagonists in patients having *−308G>A* polymorphism (Cuchacovich et al. 2004). A meta-analysis of 13 studies revealed an association between treatment response to infliximab and the TNF-alpha *−238 A/G* polymorphism, but no associations between treatment response and the TNF-alpha *−308 A/G* polymorphism (Lee et al. 2010). Polymorphism in *TNFRSF1B 196T>G* is associated with decreased efficacy as it influences receptor shedding and ligand binding. DNA microsatellites which are nothing but repeat sequences of A and T in the intronic portions of DNA can sufficiently influence gene transcription. There are five microsatellites in the TNF locus, namely, TNFa to TNFe, and they influence the production of TNF production. There have been studies that have shown TNFd and TNFa2 increase TNF production while low level of TNF is associated with TNFa6. However, a study done in 457 patients with RA showed that response to etanercept was not dependent on any TNF microsatellite markers (Criswell et al. 2004).

TNF antagonists are antibodies, and the Fcδ portion binds to the Fcδ receptors. Polymorphisms in the FcδR mediate antibody-dependent cellular cytotoxicity (ADCC). For instance, an SNP in FCGR3A which encodes a Val158Phe variant will influence the binding affinity of IgG1 and promote increased ADCC and apoptosis resulting in drug toxicity. The TNF promoter *−308* allele was found to be a selective marker which influences the response to TNF antagonists such as etanercept, infliximab, and adalimumab in RA patients. In a meta-analysis of TNF-alpha promoter *−308 A/G* polymorphism and responsiveness to anti-TNF therapy, individuals with RA who carry the *A* allele did not respond as well to TNF antagonists as those with the *G* allele (Lee et al. 2006). A meta-analysis of polymorphisms in *TNFAIP3* revealed that these patients were at a greater predilection to develop rheumatoid arthritis (Lee et al. 2012).

Besides TNF, there are other genes that have also been explored to look for the influence of their polymorphic variants that affect response to biologic agents. The PTPRC is a CD45 tyrosine protein phosphatase C that regulates BCR and TCR signaling which influence the secretion of several cytokines. In a prospective study of 1,283 patients with rheumatoid arthritis, the *rs10919563* variant was found to be associated with favorable response to biologic therapy (Cui et al. 2010). The MAPK14 is an important signaling molecule involved in the production of

several proinflammatory cytokines and matrix metalloproteinases. Patients with RA having SNPs in *MAPK14* gene were found to have improved efficacy with infliximab and adalimumab. However, there was no improved response with etanercept in these patients with variant polymorphisms in the MAPK14 pathway (Coulthard et al. 2011).

An important confounding factor in the interpretation and application of pharmacogenetic studies is that the same genetic variants which are markers of severe disease are also found to be associated with better response to anti-TNF therapy. This can complicate the predictive value of pharmacogenetics markers in autoimmune diseases. An ideal tissue to use in pharmacogenetics of rheumatic diseases is to obtain the synovial tissue. However, this is seldom accessible and so one has to contend with the less reliable DNA from peripheral blood. Another limiting factor in most pharmacogenetic studies is the lack of power due to smaller sample size and racially homogenous nature of the population making it difficult to generalize the results in the other populations. So there is a definite onus on pharmacogenetic researchers to carry out larger prospective, multicentric, and multiethnic studies to overcome these problems. Although there has been an increasing trend in the rise of genome-wide association studies, this approach is equally daunting with its own potential limitations.

One of the reasons that has been argued for the variable results in correlation between efficacy and different polymorphisms is that rheumatoid arthritis is a waxing and waning disease, and since most of the studies that are carried out are snapshot studies, they may not reflect the true picture as to whether a patient is a responder or a nonresponder to drug therapy. A better way of investigating this correlation would be to perform long-term longitudinal studies to correlate efficacy variables with polymorphisms (de Rotte et al. 2010).

3 Pharmacogenomics of SLE

SLE is an autoimmune, multisystemic disease which is defined by the presence of autoantibodies to self-antigens and to antigens present inside the nucleus which leads to progressive destruction of several organs. The disease is more commonly seen in Asians, African Americans, and Hispanics. The various features of the disease include skin rashes, arthralgia, and hematologic, renal, and immunologic abnormalities. In SLE both the innate and acquired immune responses are deranged resulting in impaired T cell response, production of autoantibodies, and apoptosis. The disease is characteristically associated with exacerbations and remissions. The disease is conventionally treated with NSAIDs, antimalarials, corticosteroids, high-dose immunoglobulins, and immunosuppressants such as azathioprine, cyclophosphamide, methotrexate, and mycophenolic acid.

3.1 Genetic Polymorphisms and Hydroxychloroquine in SLE

Polymorphisms in TNF and IL-10 can influence the response to hydroxychloroquine in SLE patients. The basal production of IL-10 can be influenced by three polymorphisms (*IL-10-1082A>G*, *-IL-10-819C>T*, *−592C>A*). Those patients having the genotype which causes high TNF production and low IL-10 production were found to have better response to hydroxychloroquine (Davila and Ranganathan 2011). A study done in patients with discoid lupus erythematosus showed that the response of patients to hydroxychloroquine was not influenced by *CYP2C8* or *CYP2D6* polymorphisms (Wahie et al. 2011). Yet the data for the application of pharmacogenetics in guiding the use of hydroxychloroquine for SLE remain sparse (Table 13.2).

3.2 Genetic Polymorphisms and Cyclophosphamide in SLE

Cyclophosphamide is a DNA alkylating agent used in the treatment of SLE and glomerulonephritis secondary to SLE. It is broken down by the enzyme CYP2C19 in the liver. One of the adverse effects known to occur in patients with cyclophosphamide is ovarian failure. In a study done in Thai patients with SLE, polymorphism in *CYP2C19*

Table 13.2 Genetic polymorphisms affecting drug therapy in SLE

Gene	Polymorphism	Clinical outcome
CYP2C19	*CYP2C19*2*	Reduced toxicity with cyclophosphamide
CYP2B6	*CYP2B6*5*	Reduced toxicity with cyclophosphamide
GSTP	*Ile 105Val*	Increased toxicity with cyclophosphamide
IL-10	*1082A>G*	Increased efficacy with hydroxychloroquine
	819C>T	
	592C>A	
NAT2	*NAT2*4*	Increased toxicity in slow acetylators to sulfasalazine
TNF	*308A>G*	Increased efficacy with hydroxychloroquine

Abbreviations: *CYP* cytochrome P450 enzyme system, *GSTP* glutathione *S*-transferase, *Il-10* interleukin 10, *NAT* *N*-acetyl transferase, *TNF* tumor necrosis factor

such as *CYP2C19**2 reduced the likelihood of ovarian toxicity as compared to those with wild-type *CYP2C19*1*1* (Ngamjanyaporn et al. 2011). Patients with SLE who were heterozygous for this polymorphism also were observed to have greater risk of developing cyclophosphamide-induced end-stage renal disease complicating the lupus nephritis. Polymorphisms of *GSTP* gene were also said to play a major role in the metabolism of cyclophosphamide in the liver. In a study performed in 102 patients, individuals with GSTP polymorphisms were noticed to have a greater risk of developing adverse effects to cyclophosphamide. The *GSTP1* variant gene polymorphisms in *105* codon due to a substitution of isoleucine to valine results in a reduction in the catalytic activity of GST protein as well as its inherent stability. Myelotoxicity and gastrointestinal toxicity were more common in patients with *GSTP1*- *105 I/V or *GSTP1*-105*V/V* genotype than in patients with the *GSTP1* wild-type genotype (Zhong et al. 2006).

3.3 Genetic Polymorphisms and Rituximab in SLE

Rituximab is a monoclonal antibody that targets CD20 B cells and mediates antibody-dependent cellular cytotoxicity. The *FcγR IIIA Val158Phe* polymorphism was helpful in predicting the response to drug therapy in one study. But the sample size for this study was small, and these findings were not replicated by any other investigators. Although the number of studies which dealing with SLE pharmacogenomics are scant, the data on the role of genetic factors in determining the prevalence of the disease is abundant (Davila and Ranganathan 2011).

4 Pharmacogenomics of Psoriasis

Psoriasis is a complex genetic disorder which has diverse manifestations from skin to joints that affects 2–3 % of Caucasian population. The skin lesions of psoriasis are distinct and very well circumscribed, circular, red papules or plaques with a grey or silvery-white, dry scale, which are typically distributed symmetrically on the scalp, elbows, knees, lumbosacral area, and in the body folds (Langley et al. 2005). Patients with psoriatic arthritis start with oligoarticular disease and progress on to severe polyarticular disease. Distal joints are frequently affected in psoriatic arthritis. A ray pattern of distribution is observed in which all the joints of a single digit are more likely to get affected than the same joints on both sides, which is typical of RA. Other classical features of psoriatic arthritis include erythema over affected joints, the presence of spinal involvement, the presence of enthesitis (inflammation at the point where tendon gets attached to bone), and lower level of tenderness (Gladman et al. 2005). The nails are additionally affected in several patients. The quality of life in patients with psoriasis is diminished when compared to the general population (Jankovic et al. 2011).

Genome-wide association studies have identified the loci involved in disease susceptibility. At present, 16 loci have been identified, as being associated with susceptibility to psoriasis (Hebert et al. 2012). A study showed that the combined genetic risk involving 10 loci could account for 11.6 % of the genetic variance in psoriasis (Chen et al. 2011). The *HLA-C*, *IL-12B*, *TRAF3IP2*, and *FBXL19* genes have been associated with psoriatic arthritis susceptibility in genome-wide

association studies (Bluett and Barton 2012). Apart from genetic susceptibility, not much is explained about genetic heritability, which remains to be explored. There is emerging evidence that the different psoriasis subtypes have different genetic makeup such as increased association of *PSORS1* in psoriasis vulgaris and guttate psoriasis, which may be of pharmacogenetic importance (Vasku et al. 2007). Genome-wide approach may also be promising in identifying the genetic predictors of treatment response. Treatments available for psoriasis act mainly as immunosuppressants and inhibitors of inflammation. As pathogenesis and genetic predisposition varies from person to person, concept of personalized medicine is more relevant in management of psoriasis. Further currently available drugs mainly control the disease activity, and there is no evidence of change in long-term course of the disease with these drugs.

Variation in drug response is another prime concern in the management of psoriasis. Both lack of response and adverse drug reactions occur in significant proportion of patients. Therapies for psoriasis are broadly divided as topical, phototherapy, systemic agents, and biologics. The choice of drugs depends on severity, site, adverse drug reactions, and drug response in the patient. Thus, if genetic makeup of individual would help to tailor these drugs to the person to whom it is appropriately matched, then the overall cost and even adverse drug reactions could be prevented. It is reported that 15–30 % of interindividual variation in drug response can be attributed to the genes coding the proteins involved in pharmacokinetics and pharmacodynamics (Table 13.3) (Hebert et al. 2012).

Table 13.3 Genetic polymorphisms affecting drug therapy in psoriasis

Gene	Polymorphism	Clinical outcome
ABCC1	*1219–176T>C*	Improved methotrexate efficacy
	rs35592	
	3391–1960G>A	
	rs2238476	
	4009A>G	
	rs28364006	
ABCG2	*204–592C>T*	Improved methotrexate efficacy
	rs17731538	
	1194+928A>T	
	rs13120400	
ADORA2A	*4205975G>A*	Increased methotrexate toxicity
IL-6	*–174G/C*	Reduced efficacy to TNF-α blockers
MTHFR	*1289A>C*	Reduced toxicity to methotrexate
SLC19A1	*80G>A*	Increased methotrexate toxicity
TPMT	*TPMT *2, TPMT*3B, TPMT*3C*	Increased azathioprine toxicity
TYMS	*28bp repeat rs34743033*	Reduced efficacy to methotrexate
VDR	*Fok1 F, Taq1 T, A-1012G A*	Enhanced response to calcipotriol
VEGF	*+405, –460*	Reduced efficacy to TNF-α blockers

Abbreviations: *ABC* ATP-binding cassette protein, *ADOR* adenosine receptor, *IL-6* interleukin 6, *MTHFR* methylenetetrahydrofolate reductase, *SLC* solute carrier, *TPMT* thiopurine methyl transferase, *TYMS* thymidylate synthase, *VDR* vitamin D receptor, *VEGF* vascular endothelial growth factor

4.1 Genetic Polymorphisms and Vitamin D Analogues in Psoriasis

Topical vitamin D is well used in mild psoriasis. They exert antiproliferative, prodifferentiation of keratinocytes with localized immunosuppressive effects in dermis. This action is mainly by binding to vitamin D receptors. For unknown reasons, certain patients do not respond well to vitamin D. Since vitamin D acts through nuclear receptors, studies have explored the relationship between vitamin D receptor polymorphism and response to vitamin D. There was a significant difference in the genotypes *Ff*, *ff*, and *TT* between vitamin D3 therapy responders and nonresponders. Haplotype analysis of the results showed that certain haplotypes were less responsive to therapy (Acikbas et al. 2012). Three polymorphism of VDR gene *Fok1* F allele, *Taq1* T allele, and *A-1012G* A allele are identified to be associated with an enhanced response to calcipotriol (Halsall et al. 2005).

4.2 Genetic Polymorphisms and Methotrexate in Psoriasis

Methotrexate is an effective drug for moderate to severe psoriasis. Some patients are refractory to treatment and other sustains adverse drug reactions. Several studies have addressed the pharmacogenomics involved in methotrexate therapy of psoriasis. Common genetic polymorphisms of genes coding adenosine deaminase (ADA), 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC), 5,10-methylenetetrahydrofolate reductase (MTHFR), solute carrier family 19, member 1 (SCL19A1), and thymidylate synthase (TS) were studied in retrospective cohort of 203 patients with psoriasis on methotrexate therapy. A specific polymorphism in *SLC19A1(80A allele)* which is involved in influx of methotrexate into cells and TS (3′ untranslated region six base pair deletion) involved in pyrimidine synthesis were associated with toxicity. *Methylenetetrahydrofolate reductase* polymorphism has been shown to predict methotrexate toxicity for psoriasis patients treated with methotrexate (Hebert et al. 2012). However, these findings were not replicated in another study that looked at single-nucleotide polymorphisms (SNPs) across four genes that are relevant to methotrexate metabolism [*folylpolyglutamate synthase* (*FPGS*), *gamma-glutamyl hydrolase* (*GGH*), *methylenetetrahydrofolate reductase* (*MTHFR*), and *5-aminoimidazole-4-carboxamide ribonucleotide transformylase* (*ATIC*)]. No significant association was found between clinical outcomes with methotrexate and the SNPs studied (Warren et al. 2009).

4.3 Genetic Polymorphisms and Cyclosporine in Psoriasis

Cyclosporine is metabolized by CYP3A4 and CYP3A5, and efflux transporter protein ABCB1 is involved in transporting out of cell. Pharmacogenetics of cyclosporine has been studied in renal transplant patients, which has shown no effect on drug response (Press et al. 2010). Pharmacogenetics of cyclosporine in psoriasis is yet to be studied. Recently, the study has identified 220 early response genes (day 14 post treatment) that were downregulated by cyclosporine in psoriasis. This also demonstrated modulation of genes from activated T cells and the "type 1" pathway, Th17 pathway. Cyclosporine also reduced TNF and inducible NO synthase in dendritic cells. It is also hypothesized that myeloid-derived genes contribute to pathogenic inflammation in psoriasis as cyclosporine modulated more myeloid-derived genes than activated T cell genes in responders (Haider et al. 2008).

4.4 Genetic Polymorphisms and Azathioprine in Psoriasis

The use of azathioprine in psoriasis has been superseded by other drugs. The active metabolite of azathioprine is 6 mercaptopurine which is deactivated by the intracellular enzyme thiopurine methyltransferase. Polymorphisms in *TPMT* such as *TPMT *2*, *TPMT*3B*, *and TPMT*3C* significantly vary the enzyme activity, such that it correlates inversely with myelotoxic adverse effects. Azathioprine in individuals with reduced/absent TPMT is associated with early myelosuppression. Thus, pretreatment assessment of *TPMT* in peripheral blood specimen guides the titration of azathioprine, such that azathioprine can be totally avoided in absent/very low TPMT activity.

4.5 Genetic Polymorphisms and Synthetic Retinoids in Psoriasis

Acitretin is a synthetic retinoid that is used in moderate to severe psoriasis. It is hypothesized that acitretin interacts with cytosolic proteins and nuclear receptors such as retinoic acid receptors and retinoid X receptors to alter gene transcription. Thus, it results in normalization of epidermal cell proliferation, differentiation, and cornification (Montrone et al. 2009; Young et al. 2006). The pharmacological relevance of the polymorphisms of these receptors with treatment response has not been investigated.

Psoriatic plaques have shown to have elevated levels of vascular endothelial growth factor (VEGF) which is involved in promoting angiogenesis. Retinoids inhibit VEGF production. Two *VEGF* gene polymorphisms, namely, *+405* and *−460* have been implicated in retinoid blockade of VEGF production. A study demonstrated increased prevalence of the *−460 TT* genotype among nonresponders (Young et al. 2006).

4.6 Genetic Polymorphisms and TNF Antagonists in Psoriasis

TNF antagonists are effective treatment for severe forms of psoriasis causing disease remission in 80 % of cases. Nearly 44 polymorphisms in the TNF gene have been identified. Two SNPs in the promoter region *G to A* transitions at the *−238* and *−308* sites appear to be functionally related to TNF expression in rheumatoid arthritis. Studies have shown many genetic loci as markers of TNF antagonist response, such as genes encoding transcription factors (AFF3), cell surface membrane proteins (CD226), and components of the Toll-like receptor and NF-kB pathways (Tan et al. 2010; Potter et al. 2010). Further, SNPs at the *−238* and *−308* TNF gene loci have been associated with disease susceptibility; however, there is need to explore the pharmacogenetic/genomic significance of these polymorphisms (Louis et al. 1998). In 15 psoriasis patients on etanercept therapy, patients were categorized as "responders" or "nonresponders" (Zaba et al. 2009).

Gene clusters expressed in the lesional biopsy were identified by gene arrays. The downregulation of genes involved in Th17 lymphocyte activity and IL-17 signaling was associated with treatment response. Thus, it is inferred that for etanercept response, downstream Th17 suppression is necessary, also increasing the understanding of the pathogenesis of psoriasis. Allelic variance at the genes *IL-12B* (encoding the p40 subunit common to IL-12 and IL-23), *IL-23A* (encoding IL-23 p19 subunit), and *IL-23R* (encoding IL-23 receptor subunit) is shown to be associated with susceptibility to psoriasis by genome-wide association scans (Cargill et al. 2007; Liu et al. 2008; Nair et al. 2009).

Increasing molecular and cellular evidence suggests that the IL-23/Th17 axis is key to the pathogenesis of psoriasis. This leads to the hypothesis of targeting common p40 subunit of the cytokines IL-12 and IL-23 to block their actions by monoclonal antibodies (Mak et al. 2009). Ustekinumab is the IL-12/IL-23 antagonist developed, and it has been shown to have very good anti-psoriatic efficacy (Leonardi et al. 2008). However, the interaction between polymorphisms identified at the *IL-12B*, *IL-23A*, and *IL-23R* genes and the efficacy/toxicity of IL-12/IL-23 antagonists remains to be explored. Pharmacogenomics in psoriasis is presently devoid of clinical application in spite of significant research in this area over the last decade. However, it is hoped that with improved understanding of the disease, larger prospective studies, and improved cost-effective technology, pharmacogenomics would find definite clinical application in psoriasis as in other diseases.

5 Pharmacogenomics of Inflammatory Bowel Disease

Inflammatory bowel disease with its two subtypes, namely, Crohn's disease and ulcerative colitis, has been observed to have greater prevalence in Europe and North America. But recent reports indicate that the disease is also increasing in prevalence in the developing regions such as Asia and the Middle East (Molodecky et al. 2012; Loftus 2004; Niriella et al. 2010). The pathogenesis and exact etiology of IBD is yet to be elucidated, but an interaction between genetic susceptibility, environmental factors, and the host immune response is said to play a major role in the pathophysiology of the disease (Niriella et al. 2010). Abdominal pain and diarrhea are the most common symptoms of IBD. Systemic complaints that may be associated with IBD include fever, weight loss, malaise, and arthralgia. The symptomatology of the disease being nonspecific

may mimic irritable bowel syndrome and other intestinal disorders. Since the disease is associated with exacerbations and remissions, the two goals of therapy include achievement of remissions and prevention of disease flares. The common drugs used in the treatment of inflammatory bowel disease include corticosteroids, aminosalicylates, and biologic agents such as infliximab, adalimumab, and certolizumab pegol.

More than 30 susceptible novel IBD susceptible loci have been found in the last decade across several centers. Some of the genes include *NOD2*, *MUC3A*, *MST1*, *OCTN1*, *OCTN2*, *ABCB1*, *IRF5*, *IL-23R*, *and NKX2-3*. The first susceptibility gene described was the nucleotide-binding oligomerization domain 2 (*NOD2*) on chromosome 16 which encodes a protein involved in recognizing the muramyl dipeptide component of the peptidoglycan cell wall of bacteria. This leads to subsequent activation of NF-kB, an important mediator of the immune response. The discovery of NOD2 has led to the realization that the innate immunity is specifically disturbed in Crohn's disease. Polymorphisms in NOD2 such as *Arg702Trp*, *Gly908Arg*, and *Leu1007fsinsCNOD2* were found to impair NF-kB activation confer susceptibility to CD (Ishihara et al. 2009; Weizman and Silverberg 2012). In spite of this, only 22 % of patients with Crohn's disease carry a NOD polymorphism. Polymorphisms in IL-23R are associated with Crohn's disease and ulcerative colitis (Duerr et al. 2006). Although there is sufficient evidence for NOD2, it does not have sufficient sensitivity and specificity to enter routine clinical practice (Weizman and Silverberg 2012).

The most widely used application of pharmacogenomics in IBD is azathioprine use and *TPMT* polymorphisms in IBD similar to those described in earlier disorders (Table 13.4) (Chouchana et al. 2012). IBD patients with polymorphisms such as *Leu155His* in the NALP1 complex were found to develop steroid resistance more commonly than those without these polymorphisms (De et al. 2011). Individuals with variants in *IL-23R* were also associated with improved response to infliximab therapy (Jurgens et al. 2010). In a retrospective cohort of 700 patients, a genetic risk marker score based on 46 SNPs was developed that predicted patients' need for surgery due to refractoriness to medical therapy. On the basis of this score, four groups were identified, and the risk of colectomy in these patient groups was 0, 17, 74, and 100 % (Haritunians et al. 2010).

Table 13.4 Genetic polymorphisms affecting drug therapy in inflammatory bowel disease

Gene	Polymorphism	Clinical outcome
IL-23R	*rs1004819*	Increased/decreased efficacy with infliximab
NALP1	*Leu155His*	Reduced efficacy to steroids
TPMT	*TPMT*2*, *TPMT*3B*, *TPMT*3C*	Increased azathioprine toxicity

Abbreviations: *Il-23R* interleukin 23 receptor, *NALP1* NACHT leucine-rich-repeat protein 1, *TPMT* thiopurine methyl transferase

6 Limitations of Pharmacogenetic Studies

The major problems associated with pharmacogenomics of autoimmune diseases are the limited sample size, high degree of discordance between studies, and the lack of application in clinical practice settings of most the variant polymorphisms that have been discovered in relation to rheumatic diseases pharmacotherapy. Poor methodological rigor followed in designing pharmacogenetic studies was cited as one of the major reasons for failure of replication of positive findings of initial investigators (Jorgensen and Williamson 2008). For example, use of relative risk may be an inferior measure of outcome differences than taking the absolute risk difference to determine if genotype does make a difference in drug response. Most pharmacogenetic studies are observational in nature, but in order to differentiate if the genotype is a prognostic factor or a true effect modifier of the outcome, one should perform randomized controlled trials and collect the DNA samples from patients in a prospective fashion. If they are collected later, it could lead to selection bias and selective loss of genotype if they are associated with a poor outcome. The presence of drug-gene interaction could

complicate the analysis of the data gathered. Ideally drug-gene interactions are appreciated best when outcomes in the treatment and nontreatment group are compared within one genotype (Smits et al. 2005; Kelly et al. 2005; Cobos et al. 2011).

7 Conclusion

Rheumatic diseases such as rheumatoid arthritis, SLE, psoriasis, and other less common autoimmune diseases contribute to the increased morbidity and mortality worldwide. Although the pharmacological armamentarium to tackle these illnesses has steadily increased in the last two decades, some of these drugs are fraught with issues such as narrow therapeutic index, severe adverse reactions, and variable therapeutic response. Pharmacogenomic studies have appeared to elucidate some of the mechanisms that better predict an individual's response to these drugs. However, till date the only successful application for pharmacogenetic testing in clinical practice for autoimmune diseases is the *TPMT* testing for azathioprine in rheumatic diseases.

References

Acikbas I, Sanli B, Tepeli E, Ergin S, Aktan S, Bagci H (2012) Vitamin D receptor gene polymorphisms and haplotypes (Apa I, Bsm I, Fok I, Taq I) in Turkish psoriasis patients. Med Sci Monit 18:CR661–CR666

Aggarwal P, Naik S, Mishra KP, Aggarwal A, Misra R (2006) Correlation between methotrexate efficacy & toxicity with C677T polymorphism of the methylenetetrahydrofolate gene in rheumatoid arthritis patients on folate supplementation. Indian J Med Res 124:521–526

Bluett J, Barton A (2012) What have genome-wide studies told us about psoriatic arthritis? Curr Rheumatol Rep 14:364–368

Cargill M, Schrodi SJ, Chang M et al (2007) A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 80:273–290

Chen H, Poon A, Yeung C et al (2011) A genetic risk score combining ten psoriasis risk loci improves disease prediction. PLoS One 6:e19454

Chouchana L, Narjoz C, Beaune P, Loriot MA, Roblin X (2012) Review article: the benefits of pharmacogenetics for improving thiopurine therapy in inflammatory bowel disease. Aliment Pharmacol Ther 35:15–36

Cobos A, Sanchez P, Aguado J, Carrasco JL (2011) Methodological quality in pharmacogenetic studies with binary assessment of treatment response: a review. Pharmacogenet Genomics 21:243–250

Cooper GS, Stroehla BC (2003) The epidemiology of autoimmune diseases. Autoimmun Rev 2:119–125

Coulthard LR, Taylor JC, Eyre S et al (2011) Genetic variants within the MAP kinase signalling network and anti-TNF treatment response in rheumatoid arthritis patients. Ann Rheum Dis 70:98–103

Criswell LA, Lum RF, Turner KN et al (2004) The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum 50:2750–2756

Cuchacovich M, Ferreira L, Aliste M et al (2004) Tumour necrosis factor-alpha (TNF-alpha) levels and influence of −308 TNF-alpha promoter polymorphism on the responsiveness to infliximab in patients with rheumatoid arthritis. Scand J Rheumatol 33:228–232

Cui J, Saevarsdottir S, Thomson B et al (2010) Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. Arthritis Rheum 62:1849–1861

Davila L, Ranganathan P (2011) Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol 7:537–550

Davis JP, Cain GA, Pitts WJ, Magolda RL, Copeland RA (1996) The immunosuppressive metabolite of leflunomide is a potent inhibitor of human dihydroorotate dehydrogenase. Biochemistry 35:1270–1273

de Rotte MC, Luime JJ, Bulatovic M, Hazes JM, Wulffraat NM, de Jonge R (2010) Do snapshot statistics fool us in MTX pharmacogenetic studies in arthritis research? Rheumatology (Oxford) 49:1200–1201

De IS, Stocco G, Martelossi S et al (2011) Genetic predictors of glucocorticoid response in pediatric patients with inflammatory bowel diseases. J Clin Gastroenterol 45:e1–e7

Duerr RH, Taylor KD, Brant SR et al (2006) A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 314:1461–1463

Dziedziejko V, Kurzawski M, Safranow K, Chlubek D, Pawlik A (2011) The effect of ESR1 and ESR2 gene polymorphisms on the outcome of rheumatoid arthritis treatment with leflunomide. Pharmacogenomics 12:41–47

Fisher MC, Cronstein BN (2009) Metaanalysis of methylenetetrahydrofolate reductase (MTHFR) polymorphisms affecting methotrexate toxicity. J Rheumatol 36:539–545

Gladman DD, Antoni C, Mease P, Clegg DO, Nash P (2005) Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 64(Suppl 2): ii14–ii17

Grabar PB, Rozman B, Logar D, Praprotnik S, Dolzan V (2009) Dihydroorotate dehydrogenase polymorphism influences the toxicity of leflunomide treatment in

patients with rheumatoid arthritis. Ann Rheum Dis 68:1367–1368
Haider AS, Lowes MA, Suarez-Farinas M et al (2008) Identification of cellular pathways of "type 1," Th17 T cells, and TNF- and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. J Immunol 180:1913–1920
Halsall JA, Osborne JE, Pringle JH, Hutchinson PE (2005) Vitamin D receptor gene polymorphisms, particularly the novel A-1012G promoter polymorphism, are associated with vitamin D3 responsiveness and non-familial susceptibility in psoriasis. Pharmacogenet Genomics 15:349–355
Haritunians T, Taylor KD, Targan SR et al (2010) Genetic predictors of medically refractory ulcerative colitis. Inflamm Bowel Dis 16:1830–1840
Hebert HL, Ali FR, Bowes J, Griffiths CE, Barton A, Warren RB (2012) Genetic susceptibility to psoriasis and psoriatic arthritis: implications for therapy. Br J Dermatol 166:474–482
Hoebert JM, Mantel-Teeuwisse AK, van Dijk L, Bijlsma JW, Leufkens HG (2012) Do rheumatoid arthritis patients have equal access to treatment with new medicines?: tumour necrosis factor-alpha inhibitors use in four European countries. Health Policy 104:76–83
Hughes LB, Beasley TM, Patel H et al (2006) Racial or ethnic differences in allele frequencies of single-nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene and their influence on response to methotrexate in rheumatoid arthritis. Ann Rheum Dis 65:1213–1218
Ishihara S, Aziz MM, Yuki T, Kazumori H, Kinoshita Y (2009) Inflammatory bowel disease: review from the aspect of genetics. J Gastroenterol 44:1097–1108
Jankovic S, Raznatovic M, Marinkovic J et al (2011) Health-related quality of life in patients with psoriasis. J Cutan Med Surg 15:29–36
Jorgensen AL, Williamson PR (2008) Methodological quality of pharmacogenetic studies: issues of concern. Stat Med 27:6547–6569
Jurgens M, Laubender RP, Hartl F et al (2010) Disease activity, ANCA, and IL23R genotype status determine early response to infliximab in patients with ulcerative colitis. Am J Gastroenterol 105:1811–1819
Kelly PJ, Stallard N, Whittaker JC (2005) Statistical design and analysis of pharmacogenetic trials. Stat Med 24:1495–1508
Langley RG, Krueger GG, Griffiths CE (2005) Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 64(Suppl 2):ii18–ii23; discussion ii24–ii5
Lee YH, Song GG (2010) Associations between the C677T and A1298C polymorphisms of MTHFR and the efficacy and toxicity of methotrexate in rheumatoid arthritis: a meta-analysis. Clin Drug Investig 30:101–108
Lee YH, Rho YH, Choi SJ, Ji JD, Song GG (2006) Association of TNF-alpha −308 G/A polymorphism with responsiveness to TNF-alpha-blockers in rheumatoid arthritis: a meta-analysis. Rheumatol Int 27:157–161
Lee YC, Cui J, Costenbader KH, Shadick NA, Weinblatt ME, Karlson EW (2009) Investigation of candidate polymorphisms and disease activity in rheumatoid arthritis patients on methotrexate. Rheumatology (Oxford) 48:613–617
Lee YH, Ji JD, Bae SC, Song GG (2010) Associations between tumor necrosis factor-alpha (TNF-alpha) −308 and −238 G/A polymorphisms and shared epitope status and responsiveness to TNF-alpha blockers in rheumatoid arthritis: a metaanalysis update. J Rheumatol 37:740–746
Lee YH, Bae SC, Choi SJ, Ji JD, Song GG (2012) Associations between TNFAIP3 gene polymorphisms and rheumatoid arthritis: a meta-analysis. Inflamm Res 61:635–641
Leonardi CL, Kimball AB, Papp KA et al (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 371:1665–1674
Liu Y, Helms C, Liao W et al (2008) A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet 4:e1000041
Loftus EV Jr (2004) Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 126:1504–1517
Louis E, Franchimont D, Piron A et al (1998) Tumour necrosis factor (TNF) gene polymorphism influences TNF-alpha production in lipopolysaccharide (LPS)-stimulated whole blood cell culture in healthy humans. Clin Exp Immunol 113:401–406
Mak RK, Hundhausen C, Nestle FO (2009) Progress in understanding the immunopathogenesis of psoriasis. Actas Dermosifiliogr 100(Suppl 2):2–13
Milic V, Jekic B, Lukovic L et al (2012) Association of dihydrofolate reductase (DHFR) -317AA genotype with poor response to methotrexate in patients with rheumatoid arthritis. Clin Exp Rheumatol 30:178–183
Mittal N, Mittal R, Sharma A, Jose V, Wanchu A, Singh S (2012) Treatment failure with disease-modifying anti-rheumatic drugs in rheumatoid arthritis patients. Singap Med J 53:532–536
Molodecky NA, Soon IS, Rabi DM et al (2012) Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 142:46–54
Montrone M, Martorelli D, Rosato A, Dolcetti R (2009) Retinoids as critical modulators of immune functions: new therapeutic perspectives for old compounds. Endocr Metab Immune Disord Drug Targets 9:113–131
Nair RP, Duffin KC, Helms C et al (2009) Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 41:199–204
Ngamjanyaporn P, Thakkinstian A, Verasertniyom O et al (2011) Pharmacogenetics of cyclophosphamide and CYP2C19 polymorphism in Thai systemic lupus erythematosus. Rheumatol Int 31:1215–1218

Niriella MA, De Silva AP, Dayaratne AH et al (2010) Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. BMC Gastroenterol 10:32

Owlia MB, Mostafavi Pour Manshadi SM, Naderi N (2012) Cardiac manifestations of rheumatological conditions: a narrative review. ISRN Rheumatol 2012:463620. doi:10.5402/2012/463620, Epub 2012 Oct 17

Pawlik A, Herczynska M, Kurzawski M, Safranow K, Dziedziejko V, Drozdzik M (2009) The effect of exon (19C > A) dihydroorotate dehydrogenase gene polymorphism on rheumatoid arthritis treatment with leflunomide. Pharmacogenomics 10:303–309

Potter C, Cordell HJ, Barton A et al (2010) Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. Ann Rheum Dis 69:1315–1320

Press RR, de Fijter JW, Guchelaar HJ (2010) Individualizing calcineurin inhibitor therapy in renal transplantation–current limitations and perspectives. Curr Pharm Des 16:176–186

Ranganathan P, Culverhouse R, Marsh S et al (2008) Methotrexate (MTX) pathway gene polymorphisms and their effects on MTX toxicity in Caucasian and African American patients with rheumatoid arthritis. J Rheumatol 35:572–579

Reichert JM (2012) Marketed therapeutic antibodies compendium. MAbs 4:413–415

Schmeling H, Biber D, Heins S, Horneff G (2005) Influence of methylenetetrahydrofolate reductase polymorphisms on efficacy and toxicity of methotrexate in patients with juvenile idiopathic arthritis. J Rheumatol 32:1832–1836

Smits KM, Schouten JS, Smits LJ, Stelma FF, Nelemans P, Prins MH (2005) A review on the design and reporting of studies on drug-gene interaction. J Clin Epidemiol 58:651–654

Tan RJ, Gibbons LJ, Potter C et al (2010) Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. Ann Rheum Dis 69:1029–1035

Taniguchi A, Urano W, Tanaka E et al (2007) Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. Pharmacogenet Genomics 17:383–390

Taraborelli M, Andreoli L, Archetti S, Ferrari M, Cattaneo R, Tincani A (2009a) Methylenetetrahydrofolate reductase polymorphisms in methotrexate treatment of rheumatoid arthritis patients. Review of the literature and personal experience. Reumatismo 61:98–106

Taraborelli M, Andreoli L, Archetti S, Ferrari M, Cattaneo R, Tincani A (2009b) Methylenetetrahydrofolate reductase polymorphisms and methotrexate: no association with response to therapy nor with drug-related adverse events in an Italian population of rheumatic patients. Clin Exp Rheumatol 27:499–502

Vasku V, Bienertova VJ, Pavkova GM, Vasku A (2007) Three retinoid X receptor gene polymorphisms in plaque psoriasis and psoriasis guttata. Dermatology 214:118–124

Wahie S, Daly AK, Cordell HJ et al (2011) Clinical and pharmacogenetic influences on response to hydroxychloroquine in discoid lupus erythematosus: a retrospective cohort study. J Investig Dermatol 131:1981–1986

Warren RB, Smith RL, Campalani E et al (2009) Outcomes of methotrexate therapy for psoriasis and relationship to genetic polymorphisms. Br J Dermatol 160:438–441

Weizman AV, Silverberg MS (2012) Have genomic discoveries in inflammatory bowel disease translated into clinical progress? Curr Gastroenterol Rep 14:139–145

Wessels JA, de Vries-Bouwstra JK, Heijmans BT et al (2006) Efficacy and toxicity of methotrexate in early rheumatoid arthritis are associated with single-nucleotide polymorphisms in genes coding for folate pathway enzymes. Arthritis Rheum 54:1087–1095

Yanagimachi M, Naruto T, Hara T et al (2011) Influence of polymorphisms within the methotrexate pathway genes on the toxicity and efficacy of methotrexate in patients with juvenile idiopathic arthritis. Br J Clin Pharmacol 71:237–243

Young HS, Summers AM, Read IR et al (2006) Interaction between genetic control of vascular endothelial growth factor production and retinoid responsiveness in psoriasis. J Investig Dermatol 126:453–459

Zaba LC, Suarez-Farinas M, Fuentes-Duculan J et al (2009) Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. J Allergy Clin Immunol 124:1022–1030

Zhong S, Huang M, Yang X et al (2006) Relationship of glutathione S-transferase genotypes with side-effects of pulsed cyclophosphamide therapy in patients with systemic lupus erythematosus. Br J Clin Pharmacol 62:457–472