Pharmacogenetics of inflammatory bowel disease

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The therapeutic efficacy and toxicity of many commonly employed drugs show interindividual variations that relate to several factors, including genetic variability in drug-metabolizing enzymes, transporters or targets. The study of the genetic determinants influencing interindividual variations in drug response is known as pharmacogenetics. The ability to identify, through preliminary genetic screening, the patients most likely to respond positively to a medication should facilitate the best choice of treatment for each patient; drugs likely to exhibit low efficacy or to give negative side-effects can be avoided. Among the medications used for inflammatory bowel disease, the best studied pharmacogenetically is azathioprine. The hematopoietic toxicity of azathioprine is due to single nucleotide polymorphisms in the thiopurine S-methyltransferase enzyme. Additionally, likely gene targets have been investigated to predict the response to glucocorticoids and infliximab, a monoclonal antibody against tumour necrosis factor that induces remission in approximately 30–40% of patients. However, no genetic predictor of response has been identified in either case.

Key words: AZA/6-MP; CD; glucocorticoids; infliximab; NOD2; pharmacogenetics; TPMT; UC.
event. Ideally, benefit–risk ratios can be determined individually and used to select an optimal dosage and schedule of medication resulting in a safer, more effective and more cost-efficient medicine.

In addition to interindividual variation, pharmacogenetic studies investigate the geographic distribution of genetic variants associated with potential differences in drug response across different populations.3–5

As an example, the frequency of the ‘poor metabolizer’ phenotype of debrisoquine oxidation varies dramatically, occurring with an incidence of approximately 10% in the United Kingdom6, 1% in Arabic and Japanese populations, and up to 30% in Hong Kong.7,8 This phenotype results from polymorphisms in CYP2D6, the gene coding for cytochrome P-450 2D6, a member of the cytochrome P450 super-family of enzymes. Duplications of the CYP2D6 gene, associated with the ‘ultra-rapid metabolizer’ phenotype9, also vary in frequency. Across Europe, this phenotype varies in incidence from approximately 10% in Spain to 2% in Sweden.10,11 The frequency in East African populations is approximately 30%.12

Another example of population-specific variation in polymorphism frequency directly relevant to IBD genetics is represented by the three single nucleotide polymorphisms (SNPs) in the NOD2/CARD15 gene (IBD1) associated with CD (‘SNP8’ R702W, ‘SNP12’ G908R and ‘SNP13’ 3020insC).13 The allele frequencies of these three SNPs range from approximately 4 to 14% in CD patients and from 1 to 4% in healthy individuals of Caucasian origin.13– 21 However, these SNPs are not detectable in Korean22, Japanese23 and Chinese individuals.24

ALLELIC VARIATIONS ASSOCIATED WITH DIFFERENT DRUG RESPONSE

Variable drug response can result from allelic variants in genes involved in the uptake, distribution, metabolism, transport, receptor and target of the drug. Pharmacogenetics research has largely focused on allelic variants in drug-metabolizing enzymes (DMEs).

Common autosomal recessive variants at the previously mentioned cytochrome P450 CYP2D6 locus, interfering with the metabolism of several commonly used drugs, provide classic examples of polymorphisms in a DME associated with variable drug response. These polymorphisms include SNPs that change the amino acid sequence, alter mRNA splicing resulting in altered or absent protein, and frame-shift mutations, resulting in non-functional protein.25,26 An additional example of DME variants affecting drug response are the missense SNPs in the N-acetyltransferase 2 gene (NAT2), which generate the slow acetylator phenotype present in more than 50% of Caucasians27 and are associated with drug toxicity due to accumulation of the active drug. Further important examples are the SNPs in the TPMT gene, which contribute to the toxicity of thiopurine drugs.28,29

Variable drug response has been associated not only with polymorphisms affecting protein structure but also with genetic variants in promoter regions that can affect binding sites and gene expression. One such case is the association between the variable number of Sp1 binding motifs (GGGCGG) in the ALOX5 core promoter locus and response to antiasthma treatments that specifically inhibit the 5-lipoxygenase pathway (ALOX5). In a placebo-controlled, double-blinded clinical trial involving 114 patients receiving a high dose of ABT-761 (a potent and selective ALOX5 inhibitor), it was observed that homozygotes and heterozygotes bearing the wild-type allele (5 Sp1 tandem repeats) exhibited significantly greater improvement in response
to inhibition of 5-lipoxygenase than individuals homozygous for any of the alternative variants (3, 4 or 6 Sp1 tandem repeats). The latter also showed diminished activity in reporter constructs ($P < 0.0001$).

**Azathioprine toxicity and TPMT genotype**

Among the established therapies for IBD, which include 5-aminosalicylic acid (5-ASA), azathioprine/6-mercaptopurine (AZA/6-MP), glucocorticoids, the antimetabolite methotrexate and the immunosuppressive cyclosporine\textsuperscript{31}, the most extensive pharmacogenetics research has aimed to explain the hematopoietic toxicity of AZA/6-MP medication.\textsuperscript{32} The thiopurine drugs 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TG), and their prodrug azathioprine (AZA), are immunosuppressive. Among other conditions, they are used to treat patients with autoimmune diseases, neoplasia\textsuperscript{34} and recipients of transplanted organs.\textsuperscript{35} The therapeutic benefit of azathioprine for the treatment of IBD, in the induction and maintenance of remission as well as closure of fistulae, is well documented.\textsuperscript{31,36–40} During treatment, up to 10\% of patients develop side-effects, which include allergic reactions, pancreatitis and bone marrow suppression. The last is relatively common, potentially life-threatening and often requires withdrawal from AZA/6-MP.\textsuperscript{41–43}

After absorption, AZA is converted by a non-enzymatic reaction into 6-mercaptopurine (6-MP)\textsuperscript{44}, which is the substrate for three competing intracellular pathways. Two of these pathways are catabolic and produce inactive metabolites. The third is anabolic and generates the active metabolite. The first catabolic route is catalyzed by xanthine oxidase (XO) and produces 6-thiouric acid, the second by TPMT and produces 6-MMP. The anabolic reaction is catalyzed by hypoxanthine phosphoribosyl-transferase (HPRT) and produces two classes of active metabolite: 6-thioguanine nucleotides (6-TGN) and 6-thioinosine monophosphate (6TIMP).

![Figure 1. Metabolic pathway of azathioprine/6-mercaptopurine (AZA/6-MP) metabolism. AZA is converted into 6-MP, which is the substrate for two catabolic pathways generating the inactive metabolites 6-MMP and 6-TU and one anabolic pathway generating the active metabolite 6-TIMP.](image-url)
6-methylmercaptopurine ribonucleotides (6-MMPR). Incorporation of the purine antagonist 6-TGN into DNA and RNA inhibits further nucleic acid synthesis; incorporation of 6-MMPR inhibits further purine synthesis, resulting in the cytotoxic and immunosuppressive properties of AZA/6-MP (Figure 1).

The activity of TPMT exhibits inherited variation following an autosomal codominant model. Approximately 90% of Caucasians and African-Americans display high enzymatic activity (homozygote wild type), about 10% intermediate activity (heterozygotes for any of the low-activity variants) and approximately 1 in 300 individuals low or no activity (homozygote for any of the low-activity variants). The enzymatic activity of TPMT determines the rate of 6-MMP formations and therefore, contributes to the relative production of 6-MMP versus the active compound 6-TGN. Low TPMT activity can lead to overproduction of 6-TGN and concomitant cytotoxic/oversuppression of the immune system. Several polymorphic alleles of the TPMT gene have been described and some have been associated with low enzymatic activity. The wild-type allele, with high enzymatic activity, is referred to as TPMT*1 and the low activity alleles are designated TPMT*2, TPMT*3 (*/3A, */3B, */3C, */3D), TPMT*4, TPMT*5, TPMT*6 and TPMT*7. TPMT*2 is characterized by the transversion G238C (Ala80Pro), TPMT*3A by the transitions G460A (Ala154Thr) and A719G (Tyr240Cys), TPMT*3B by the G460A transition only, TPMT*3C by the A719G transition only, TPMT*3D by both transitions and the G292T transition, TPMT*4 by a G to A transition in intron 9 at the intron/exon splice junction required for mRNA processing, TPMT*5 by the transition T146C (Leu49Ser), TPMT*6 by the transversion A539T (Tyr180Phe) and TPMT*7 by the transversion T681G (His227Glu). Among the low-activity variants, the most common are TPMT*2 and TPMT*3A. Other alleles bearing silent or intronic variants are not associated with reduction of enzymatic activity.

Preliminary genetic screening allows the identification of individuals who are homozygous for the low-activity TPMT alleles and would therefore experience a toxic effect under AZA/6MP treatment. Heterozygous individuals for whom a reduction of dose is required can also be identified. Nevertheless, the presence of a wild-type genotype for the TPMT enzyme is not sufficient to guarantee the non-occurrence of myelosuppression during AZA/6MP treatment. A recent study investigating myelosuppression during AZA therapy in 41 CD patients who had developed leukopenia (n = 24), thrombocytopenia (n = 3) or both (n = 14) during AZA (n = 33) or 6-MP (n = 8) therapy, and were therefore required to withdraw from treatment (83% of patients) or reduce doses by more than 50% (17% of patients), revealed that only 27% of patients carried a TPMT allele associated with low enzymatic activity. Therefore, although the genotyping of TPMT can provide a reliable method of identifying patients at risk of hematopoietic toxicity, one must bear in mind that myelosuppression can be multifactorial and that monitoring of leukocytes and thrombocytes is always required during AZA/6MP treatment. In addition, increasing evidence suggests that 6-TGN levels above a certain threshold might be associated with reduced risk of relapse in CD.

5-Aminosalicylates and sulfasalazopyridin

AZA/6-MP can be used in combination with 5-ASA agents. Sulfasalazine and its metabolite 5-ASA inhibit TPMT. This raises the possibility of clinically significant drug-to-drug interactions and underlines the importance of both TPMT genotyping and leukocyte monitoring during AZA/5-ASA dual therapy.

5-ASA itself undergoes rapid acetylation, which in part commences in the intestinal mucosa. Little pharmacogenetic research has focused directly on 5-ASA metabolism.
In a recent study on patients with UC, no association was found between common variants in the N-acetyltransferase 1 gene (NAT1), which are responsible for the N-acetylation of 5-ASA, and the response to mesalamine ($n = 52$) or sulfasalazine ($n = 64$). In the same study, no association between variants in the N-acetyltransferase 2 gene (NAT2), which result in the rapid and slow acetylator phenotypes, and toxicity rates among the 64 patients treated with sulfasalazine was observed.$^{50}$

**Glucocorticoids**

Glucocorticoids as a short-term treatment of acute relapse are effective in most patients with UC$^{51,52}$ or CD.$^{53,54}$ However, glucocorticoids are associated with potentially serious side-effects. In addition to systemic glucocorticoids, topical formulations (budesonide) have been developed to reduce side effects. However, because of its release characteristics, the indication of budesonide is restricted to mild–moderate ileal inflammation in CD. Glucocorticoid therapy of acute inflammatory bowel disease results in the development of glucocorticoid-refractory or glucocorticoid-dependent disease in up to 30% of cases.$^{55,56}$ Glucocorticoids have low efficacy for the long-term maintenance of remission.$^{53,57}$ No clinical parameters to predict glucocorticoid responsiveness are available. In severe attacks of UC, persistence of high C-reactive protein and low serum albumin levels after several days of treatment might suggest treatment failure.$^{58}$ In a study of 300 patients with active CD, glucocorticoid resistance was found to be associated with the following parameters: prior bowel resection, perianal disease and a high initial Crohn’s disease activity index (CDAI).$^{59}$

Over-expression of the human glucocorticoid receptor β (hGRβ), produced by alternative splicing of the primary transcript of the glucocorticoid receptor mRNA, has been found to be associated with steroid-refractory UC. hGRβ binds glucocorticoids but does not transduce the signal. It therefore acts as a dominant negative regulator. In a study by Honda and co-workers$^{60}$ involving 23 patients with UC (11 glucocorticoid responsive and 12 glucocorticoid resistant), amplification of total RNA from peripheral blood mononuclear cells using hGRβ-specific primers (with confirmation by Western blot analysis), revealed the presence of hGRβ mRNA in 9.1% of the glucocorticoid-responsive patients and in 83.3% of the glucocorticoid-resistant patients ($P = 0.0019$). hGRβ mRNA was present in 10% of healthy controls, an almost identical incidence to the glucocorticoid-responsive patients.

Expression of the multidrug resistance 1 (MDR1) gene in peripheral blood lymphocytes has been found to be significantly elevated in patients requiring surgical resection following the failure of medical therapy: UC ($n = 28$) and CD ($n = 15$) compared with patients who did not require surgery: UC ($n = 40$) and CD ($n = 32$) as well as with healthy controls ($n = 50$).$^{51}$ MDR1 codes for a 170-kDa P-glycoprotein (Pgd-170)—a pump that actively transports cytokines and xenobiotics, including glucocorticoids$^{62}$, out of the cell.

SNPs in the transporter of antigenic peptide (TAP2) gene have been associated with response to glucocorticoids in 148 CD patients (although not with susceptibility to CD itself).$^{63}$ TAP2 is a member of the ATP-binding cassette super-family and of the MDR/TAP (multi drug resistance) subfamily.

HLA-DR and IL1RA polymorphisms have been tested for association with the outcome of budesonide treatment in 243 CD patients.$^{64}$ HLA-DR8 appeared to be associated with treatment failure but, because this allele has a low frequency, this association needs to be replicated in a larger cohort of patients. In the same
study, the IL1RA polymorphism did not appear to be associated with therapy response.

**PHARMACOGENETICS OF IMMUNOTHERAPY TARGETING TNF IN CROHN'S DISEASE**

Because of the central role of macrophages, T helper I (Th-1) lymphocytes and, in particular, the proinflammatory cytokine tumour necrosis factor (TNF) in the pathogenesis of CD, agents interfering directly with TNF have been suggested as a specific immunotherapy with potentially high efficacy, rapid onset of action and prolonged effect. An increased production of proinflammatory cytokines, including TNF, in the intestinal mucosa is pivotal for the development of inflammatory relapses and for sustaining chronic inflammatory activity. Several ways of reducing available TNF, by blocking TNF production and secretion or by binding and neutralizing TNF, have been proposed. Agents binding and neutralizing TNF include monoclonal antibodies against TNF (infliximab65, CDP57166 and CDP870, adalimumab) and the TNF-binding proteins etanercept (TNFRp75-Fc) and onercept (recombinant human soluble TNFRp55). Different levels of experimental and clinical development characterize each of these agents.67,68 Other agents blocking TNF production directly or indirectly include: oxpentifylline (pentoxifylline, PTX), a strong suppressor of TNF transcription and translation; thalidomide, which enhances TNF mRNA degradation in macrophages; CNI-1493 and BIRB 796 (inhibitors of mitogen-activated protein kinase (MAPK) pathways)69 and nuclear factor-κB (NFκB) antisense oligonucleotides.

It appears that clinical efficacy depends on more than just blockade of TNF. Although infliximab is highly effective in CD, other agents have a smaller or no efficacy: pentoxifylline, a xanthine oxidase inhibitor that reduces TNF transcription and protein production by increasing intracellular cyclic AMP concentration in different cell types, including monocytes and T lymphocytes, in vitro and in vivo70,71, has shown no effect on clinical, laboratory or endoscopic activity in an open-label pilot study of 16 glucocorticoid-dependent, chronic active CD patients.72 As far as can be concluded from open-label pilot studies, thalidomide might be effective and well tolerated.73,74 CNI-1493, a guanylhydrazone inhibitor of the stress-activated MAPKs JNK (c-Jun N-terminal kinase) and p38 appeared to be safely tolerated and effective in an open-label pilot trial of 12 patients with severe CD.75 The use of an antisense oligonucleotide to the p65 subunit of NFκB has been shown to abrogate experimentally induced intestinal inflammation in a mouse model;76 human studies are ongoing.

Most interesting is the therapeutic experience with etanercept, a genetically engineered fusion protein consisting of two recombinant chains of the human extracellular TNFR2 (p75) component fused to the Fc domain of human IgG1 and binding both TNF and TNF-β. It showed efficacy in a double-blind, placebo-controlled trial involving 234 patients with refractory, active rheumatoid arthritis77 but not in CD. Sandborn and collaborators78 report that subcutaneous administration of etanercept, at the same dose approved for rheumatoid arthritis, appeared safe but not effective in a placebo-controlled trial of 45 patients with moderate to severe CD.

Infliximab is a chimeric murine–human (75% human and 25% murine) monoclonal antibody of the IgG1 subclass that exerts its therapeutic effect by binding specifically to and neutralizing TNF. In contrast to etanercept, infliximab has been shown to be an effective treatment for moderately to severely active therapy-refractory CD and
closure of fistulae in several placebo-controlled trials.\textsuperscript{55,79–83} A single infusion of infliximab results in a remission rate (CDAI $< 150$) of approximately 30–40\% in CD, without any statistically significant differences between different dose groups (5, 10 and 20 mg/kg bodyweight).\textsuperscript{65}

Infliximab binds to both soluble and transmembrane TNF but not to the closely related cytokine TNF-$\beta$. It has been suggested that infliximab specifically induces apoptosis in activated immune cells through binding to transmembrane TNF. This mechanism might differentiate the compound from other TNF binding agents and could result in a differential clinical efficacy.\textsuperscript{84} Lugering and co-workers\textsuperscript{85} showed that at therapeutic concentrations, infliximab induces apoptosis in monocytes through the activation of members of the caspase-family.

Infliximab infusions are generally well tolerated although acute allergic reactions occur in about 15\% of cases.\textsuperscript{86} However, concerns remain about infliximab's long-term and reinfusion safety and efficacy. Treatment with infliximab could result in the formation of human antichimeric antibodies against infliximab, which are associated with increased risk of reinfusion reactions and reduced duration of response to treatment.\textsuperscript{87} Additionally, several cases of tuberculosis\textsuperscript{88}, fungal and other opportunistic infections, as well as a possible association with development of lymphoma, have been reported in connection with infliximab therapy.\textsuperscript{89}

As the therapeutic response to infliximab in CD appears to be a stable trait, with repeated administration inducing only very limited benefit in primary non-responders,\textsuperscript{65,80,81,83} pharmacogenetic investigation of therapeutic efficacy appears warranted. Pharmacogenetic research on response to infliximab in CD has focused on polymorphisms potentially associated with variations in TNF expression, metabolism or signal transduction. Polymorphisms in the TNF and TNF-$\beta$ genes, located on chromosome 6p21.3 within one of the linkage regions established for CD, have been investigated with contradictory results. Taylor and co-workers\textsuperscript{90} studied polymorphisms in the TNF-$\alpha$ and TNF-$\beta$ genes (TNF-$\alpha$-238 and TNF-$\alpha$-308; TNF-$\beta$ Ncol, a13 and a26 and the TNF microsatellites) as well as the presence of antineutrophil cytoplasmic antibodies (ANCA) in 75 CD patients who participated in a placebo-controlled trial (59 receiving infliximab and 16 placebo).\textsuperscript{65} Individuals (n = 6) homozygous for the TNF-$\beta$ haplotype Ncol-TNFc-a13-a26 1-1-1-1 (1 being the higher frequency allele) did not respond to infliximab. Positive response to infliximab was associated with presence of speckled antineutrophil cytoplasmic antibody (sANCA) and the response of patients with pANCA did not differ significantly from that of the placebo group. In another study, including 279 CD patients, neither presence of anti-Saccharomyces cerevisiae antibody nor pANCA could predict response.\textsuperscript{91}

SNPs in the TNF promoter at nucleotide positions $-238$, $-308$, $-376$, $-857$, $-1031$; in the TNFR1 (CD120a) at positions $-609$ and $+36$ (Pro12Pro) and in the TNFR2 (CD120b) at positions $+168$ (Lys56Lys), $+587$ (Met196Arg), $+1663$ and $+1690$ (5'UTR) were tested in CD patients from two prospective, multicenter clinical trials: 90 patients from an open-label trial including 39 German centers\textsuperscript{92} and 444 patients from the ACCENT I trial.\textsuperscript{83} Such a design results, in the case of a double-positive but also a double-negative result, in a high level of reliability.\textsuperscript{93}

Efficacy of infliximab was defined as response (CDAI decrease of at least 70 points) and achievement of remission (CDAI $< 150$), respectively. In the first cohort, the mutant allele at nucleotide position $+587$ in the TNFR2 appeared to be associated with lack of response to infliximab, but this data could not been replicated in the second, larger, cohort. None of the other investigated SNPs appeared to be associated with response to infliximab in either of the two cohorts. This can be regarded effectively as
an exclusion of these variants. TNF-$\alpha$-308 was not found to be associated with infliximab response in another study comprising 226 CD patients (136 patients with refractory luminal disease and 90 with refractory fistulizing disease). In the same study, an association between positive clinical response and higher CRP levels before treatment was observed. Among the clinical parameters investigated, response to infliximab appears positively correlated with isolated colitis and concomitant immunosuppressive treatment. The development of antibodies against infliximab has been found associated with increased risk of infusion reaction and reduced duration of response in a cohort of 125 patients with CD.97

**OTHER TARGETS FOR IMMUNOTHERAPY**

Many other immunological therapies for CD are presently under clinical development. They include ISIS-2302, an antisense oligonucleotide directed against intracellular adhesion molecule 1 (ICAM-1), human recombinant interleukin 10 (rhuIL-10) and natalizumab (monoclonal antibody directed against alpha4beta7 and alpha4beta7 integrin).

ICAM-1, a transmembrane glycoprotein, is an adhesion molecule expressed on various cell types including monocytes, tissue macrophages and a subset of T and B cells. Its expression is upregulated in response to proinflammatory mediators, including TNF, and facilitates leukocyte migration. ISIS-2302 is a 20 base-pair oligonucleotide that hybridizes to the 3' UTR region of ICAM-1 mRNA. The latter is subsequently cleaved by RNase H resulting in specific reduction of ICAM-1 mRNA and protein. ISIS-2302 appeared effective in a pilot placebo-controlled clinical trial including 20 patients with active, steroid-dependent CD. However, it failed to show clinical efficacy in other placebo-controlled clinical trials conducted in 75 and 299 steroid-refractory CD patients (with the exception of a small subgroup of females that had a higher level of exposure due to a high bodyweight).

Treatment with rhuIL-10, a potent anti-inflammatory cytokine, appeared safe, well tolerated and efficacious in an initial placebo-controlled study involving 46 CD patients receiving subcutaneous rhuIL-10 for 7 days. Two subsequent double-blinded, placebo-controlled clinical trials, involving 95 and 329 CD patients receiving subcutaneous treatment with rhuIL-10 over 28 days, confirmed its safety but showed only a low proportion of patients experiencing clinical improvement.

Natalizumab appeared well tolerated in pilot studies including patients with UC and CD, and has demonstrated to increase the rate of clinical remission and response in a double-blinded, placebo-controlled trial including 248 patients with moderate to severe CD.

These are typical examples of new drug developments in IBD that would greatly benefit from accompanying pharmacogenetic investigations to define markers or causative variants identifying potential responders.

**IMPORTANCE OF CAUSATIVE GENETIC VARIANTS FOR PHARMACOGENETICS**

In a polygenic disease such as CD, interindividual differences in response to therapy could be associated with different combinations of disease predisposing genes. Following
the identification of the first CD susceptibility gene, NOD2/CARD15 (16q12), three SNPs—a C insertion (3020insC) leading to a truncated protein and two missense mutations (R702W and G908R) that are independently associated with the disease—have been tested for association with response to infliximab. In addition, 3020insC has been found associated with increased NFκB activity in lamina propria mononuclear cells and, therefore, might be associated with altered production of inflammatory cytokines, including TNF. Two independent studies involving 534 and 245 patients with therapy-refractory active CD showed no association between the three mutations and response to infliximab (defined as CDAI drop of at least 70 points) and achievement of remission (defined as CDAI < 150 points). In both studies, the three SNPs were, as anticipated, strongly associated with susceptibility to CD itself (P < 0.001 in comparison with unrelated healthy controls).

CONCLUSIONS

Although it is still in its infancy, pharmacogenetics is likely to deliver causative variants in genes regulating efficacy or detoxification of anti-inflammatory drugs. The chronic disorder of inflammatory bowel disease will greatly benefit from rational treatment decisions through personalized medicine. The full picture will unfold with the further exploration of anti-inflammatory drugs specifically targeting single molecules in disease pathophysiology.

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<td>● pharmacogenetic variations in detoxifying mechanisms are likely to aid in the reduction of side effects</td>
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