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REVIEW

Genetic factors that predict response and failure of biologic therapy in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) represents a significant disease burden marked by chronic inflammation and complications that adversely affect patients' quality of life. Effective diagnostic strategies involve clinical assessments, endoscopic evaluations, imaging studies, and biomarker testing, where early diagnosis is essential for effective management and prevention of long-term complications, highlighting the need for continual advancements in diagnostic methods. The intricate interplay between genetic factors and the outcomes of biological therapy is of critical importance. Unraveling the genetic determinants that influence responses and failures to biological therapy holds significant promise for optimizing treatment strategies for patients with IBD on biologics. Through an in-depth examination of current literature, this review article synthesizes critical genetic markers associated with therapeutic efficacy and resistance in IBD. Understanding these genetic actors paves the way for personalized approaches, informing clinicians on predicting, tailoring, and enhancing the effectiveness of biological therapies for improved outcomes in patients with IBD.

Key Words: Inflammatory bowel disease; Genetic predictors; Inflammatory bowel disease treatment; Biologic therapy; Biologic therapy response; Genetic markers in inflammatory bowel disease; Inflammatory bowel disease treatment failure; Pharmacogenomics; Biologic therapy efficacy; Genetic variability

Core Tip: Understanding the genetic factors that influence the response and failure of biological therapy in inflammatory bowel disease (IBD) is crucial for optimizing treatment strategies. Identifying specific genetic markers can help predict patient outcomes, tailor personalized therapies, and improve efficacy while minimizing adverse effects. This approach enhances clinical decision-making, leading to better management of IBD and improved patient quality of life. Future research should focus on expanding genetic profiling to refine therapeutic interventions.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that comprises two entities: ulcerative colitis (UC) and Crohn's disease (CD). The inflammation in UC continuously affects the colonic mucosa, with no granulomas detected on biopsy[1]. On the other hand, CD is characterized by transmural inflammation and granulomas that can affect any part of the gastrointestinal tract, most commonly the terminal ileum[2]. IBD is considered one of the most frequently diagnosed gastrointestinal diseases, with its incidence and prevalence constantly rising since the second half of the 20th century. This is true for both Europe and North America, as well as the newly industrialized countries of Asia, Africa, and South America. The highest incidence of 505 UC cases and 322 CD cases per 100000 persons has been reported in Norway and Germany, respectively[2]. IBD undoubtedly impairs quality of life, with fatigue, lack of energy, and sleep disturbances being the most common complaints. This is predominantly encountered in women, in patients suffering from CD, and in materially deprived persons[3]. IBD poses a significant disease burden characterized by chronic inflammation, pain, and complications that can severely impact patients' quality of life. Effective diagnostic strategies for IBD include clinical assessments, endoscopic evaluations, imaging studies, and biomarker testing to identify and differentiate the disease accurately. Early diagnosis is crucial for managing IBD effectively and preventing long-term complications, emphasizing the need for ongoing advancements in diagnostic approaches[3].

The treatment of IBD includes conventional therapy with 5-American Society of Anesthesiologists, corticosteroids and non-targeted immunosuppressants, and biological therapy. The biological rationale for using biologics in IBD is based on the known aspects of the disease pathophysiology. In patients with IBD, dysregulation of the immune response leads to the infiltration and accumulation of immune cells, which stimulate the release of various cytokines, chemokines, and growth factors[2]. This cascade may further impact the inflammation and carcinogenesis processes. Immune cells such as regulatory T cells (Tregs), type 2 macrophages, CD4+ T helper 17 cells, CD8+ T cells, and natural killer cells can play roles in either sustaining inflammation in IBD or contributing to disease progression[2].

Traditional gold standard methods for diagnosing IBD, such as endoscopy and histological examination, provide critical insights into mucosal inflammation and tissue morphology but can be invasive and uncomfortable for patients. By contrast, advanced techniques such as capsule endoscopy and biomarkers (*e.g.*, fecal, serum, genetic) offer non-invasive alternatives that enhance patient comfort and convenience[4]. While capsule endoscopy allows visualization of the entire small intestine, fecal calprotectin (FC) testing enables the quick assessment of inflammation levels. Each approach has its advantages and limitations, and the choice of diagnostic method should be tailored to individual patient needs and clinical scenarios to ensure accurate and effective diagnosis[4,5].

Conventional therapy of IBD can induce a clinical response and maintain remission mainly in mild to moderate forms [4,5]. However, a recent meta-analysis showed a modest effect in terms of both induction and maintenance of remission in moderate to severe IBD[6]. Hence, biological therapy emerged as a new class of drugs with the potential to influence treatment failure with conventional therapy. The initial drugs, infliximab and adalimumab, showed excellent clinical and endoscopic efficacy. Still, the subsequent follow-up of patients revealed up to 30% response failure, 50% loss of response over time, and 10% surgical treatment requirement[7].

The new drugs available on the market also show incomplete responses. Vedolizumab, an anti-integrin antibody, achieved endoscopic improvement and remission in 51% and 29% of patients with UC in week 52, respectively. In CD, the same treatment goals were observed in 76% and 48% of cases, respectively[8]. For ustekinumab, an anti-interleukin (IL) 12/23 antibody, clinical response and remission at 1 year were seen in 76.8% and 50.6% of patients with UC, respectively[9]. For CD, the percentage of patients in clinical remission in week 44 was approximately 50%[10]. The non-selective Janus kinase (JAK) inhibitor, tofacitinib, which has only been approved for the treatment of UC, achieved clinical remission in 40.6% of cases in week 52[11]. In comparison, the clinical and endoscopic remission rates of the selective JAK1 inhibitor upadacitinib were 33% and 15% for UC *vs* 41% and 24% for CD, respectively[12]. In keeping with those mentioned above, there seems to be wide interindividual variation in the efficacy of biological treatment, which can be genetically determined. A recent systematic review published in 2024 by Plaza *et al*[13] showed that single nucleotide polymorphisms (SNPs) may be associated with a different treatment response towards anti-tumor necrosis factor (TNF),

anti-integrins, and anti-IL-12/23 inhibitors. Therefore, a more individualized approach is needed for every patient with IBD.

In this review article, we identify and analyze genetic factors that predict patient response and failure to biologic therapy in IBD, facilitating personalized treatment strategies and improving clinical outcomes for the patients.

SEARCH STRATEGY

A comprehensive literature search was conducted across multiple databases, including PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar, covering the period to May 2024. The search terms used were combinations of key words and Boolean operators: "Inflammatory Bowel Disease" AND ("Genetic Predictors" OR "Genetic Markers") AND ("Biologic Therapy" OR "Biologic Therapy Response" OR "Biologic Therapy Failure") AND ("Pharmacogenomics" OR "Genetic Variability") AND "IBD Treatment". Approximately 500 papers were retrieved, and relevant articles were selected based on their relevance to the topic, focusing on studies that explored the genetic factors influencing the efficacy and failure of biological therapies in IBD.

GENETIC FACTORS INFLUENCING RESPONSE TO BIOLOGICAL THERAPY IN IBD

Role of genetic variations in drug metabolism

Cytochrome P450 (CYP) enzymes are involved in drug metabolism, and genetic polymorphisms in CYP2C19 significantly influence drug metabolism. Variations can result in different enzyme activity levels, categorizing individuals into poor, intermediate, extensive, and ultra-rapid metabolizers. This impacts drug efficacy and safety. For example, poor metabolizers may have higher drug levels, increasing the effectiveness or risk of toxicity for medications metabolized by CYP2C19[14]. Variations in CYP3A4 also affect the metabolism of many drugs used in IBD, contributing to variability in treatment outcomes[15].

Regarding the impact on drug levels and efficacy, thiopurine S-methyltransferase (TPMT) polymorphisms influence the metabolism of thiopurines. Low TPMT activity leads to higher active metabolite levels, increasing efficacy but also the risk of toxicity. TPMT genotyping helps tailor dosing to improve outcomes and reduce side effects[16]. Similarly, N-acetyltransferase 2 polymorphisms can affect the metabolism of certain IBD drugs, impacting their levels and effectiveness[17].

Pharmacogenetics of drug receptors and targets

The relevance of genetic variations in drug targets is described for several genes. Polymorphisms in TNF receptors (TNF receptor superfamily member 1A [TNFRSF1A] and TNFRSF1B) can affect the binding and efficacy of anti-TNF therapies such as infliximab and adalimumab. Specific polymorphisms are associated with better or worse responses to these treatments[18].

Variations in the IL-23 receptor (IL-23R) gene influence responses to biologics targeting the IL-23 pathway, such as ustekinumab. Specific IL-23R genotypes are linked to improved treatment responses[19].

When we discuss the implications for treatment outcomes, we should focus on the human leukocyte antigen (HLA)-DQA1*05 allele associated with developing anti-drug antibodies (ADA) against infliximab and adalimumab, reducing their efficacy. Patients with this allele may need closer monitoring and therapy adjustment[20]. Variants in Fc gamma receptor 3A (FCGR3A) can also affect the response to anti-TNF agents by altering drug binding to immune cells, impacting clinical outcomes[18].

GENETIC MARKERS ASSOCIATED WITH BIOLOGICAL THERAPY RESISTANCE IN IBD

To date, more than 240 non-overlapping genetic loci have been identified as significant risk factors of IBD[21-23]. Among them statistically significant genes include autophagy-related 16-like 1 (*ATG16L1*), E-cadherin, *HLA*, hepatocyte nuclear factor 4 alpha, *IL-10*, *IL-10RA*, *IL-10RB*, *IL-23R*, leucine-rich repeat kinase 2, nucleotide oligomerization domain 2 (*NOD2*), protein tyrosine phosphatase non-receptor type 2, TNF superfamily member 15, immunity-related GTPase family M, caspase recruitment domain protein 9, and RING finger protein 186, which are linked to innate and adaptive immunity, autophagy, epithelial barrier, innate mucosal defense, Tregs, oxidative stress, IL-10 and IL-23 signaling, and cell apoptosis, among others[22-24].

Identification of genetic variants linked to treatment resistance

First, we start by describing the genetic mutations in drug targets. A critical point in IBD treatment is identifying genetic variants associated with an individual's drug response. Mutations in genes encoding drug targets can significantly impact drug efficacy and contribute to treatment resistance. IBD-causing alleles are rich in non-synonymous mutations in their coding region, modulating the protein structure and function and thus affecting drug binding affinity or downstream signaling pathways. Furthermore, 80%-90% of IDB loci are non-synonymous variants due to mutations in their non-coding regions exerting pathogenic effects by modulating the gene expression[25].

Extensive meta-analyses combined with genome-wide association studies (GWAS) have identified specific variants and polymorphisms associated not only with the onset and severity of IBD but also with a role in treatment response in patients undergoing drug therapy[26]. The clinical trials and real-life practice demonstrate the association of some genetic variants with no or limited response (primary non-response or secondary loss of response) to drug treatment[21,26,27] and, in some cases, even worsen it[28].

Altered pathways leading to reduced drug efficacy

Genetic variants leading to altered target structure or gene expression are not the only cause of reduced drug effectiveness, as additional causes include drug interactions, development of resistance, and drug quality. For example, changes in physiological conditions, such as the potential of hydrogen and blood flow, can influence drug distribution and metabolism, affecting drug efficacy. The use of multiple drugs can lead to the inhibition or induction of drug-metabolizing enzymes, competition for binding sites, or synergistic or antagonistic effects on drug targets[29].

INFLUENCE OF GENETIC POLYMORPHISMS ON IMMUNOGENICITY OF BIOLOGICAL THERAPY IN IBD

Some biological drugs can induce immune reactions, leading to the formation of antibodies that neutralize the therapeutic effects of the drug. Immunogenicity with the formation of ADA to biological products is one of the causes of treatment failure in IBDs. The drug concentration, inadequate drug exposure, and high drug clearance can also be responsible for undesirable therapeutic outcomes in patients with IBD. Other factors besides immunogenicity can accelerate the clearance of biologics such as increased body weight, low serum albumin, and even disease status and medications[30]. Biologics have long been used to treat IBD, but guidelines regarding their optimal use are still being researched and developed. Over the past few decades, IBD-related costs have significantly increased due to the frequent administration of TNF-α antagonists and other biological products for treatment[31]. This gives reason to assume that the optimal use of these products is essential to improve the efficacy of therapy and reduce adverse effects.

Various strategies to prevent ADA formation have been investigated. Combining a biological product with an immunomodulator was found to preclude the formation of ADA[32,33]. ADAs decrease by adding or changing immunomodulators[34,35]. It has also been shown that fewer ADAs are detected at higher anti-TNF dosing[36].

The TNF-α antagonists infliximab, adalimumab, golimumab, and certolizumab pegol are used as anti-TNF therapies in the clinical setting of IBD[37,38]. They have different pharmacological profiles and efficacy and can improve remission [39]. However, some patients with IBD either do not respond or have loss of response to treatment over time. Genetic factors are responsible for this inability. Genetic profiling techniques and GWAS have enabled the identification of genetic variants that can influence the treatment response and development of adverse effects[24].

A study revealed genetic associations with primary non-response[40]. The authors found that SNPs in loci DENN domain containing 1B (rs2488397) and aryl hydrocarbon receptor (rs1077773) are most strongly associated with primary non-response. Similarly, they observed genetic associations with time to loss of response. In addition to a number of known IBD susceptibility loci, SNPs in PR domain zinc finger protein 1 (rs62421049), chromosome 21q22.2 (rs2836866), cluster of differentiation 28 (rs3116494), *SMAD3* (rs17293632), and interferon (IFN) induced with helicase C domain 1 (rs1990760) were associated[40].

Usually, SNPs with long-term responses are associated with responsiveness to infliximab or adalimumab therapy in patients with IBD. However, some SNPs such as rs396991-GG (*FCGR3A*), rs6100556-TT (phosphatase and actin regulator 3 [*PHACTR3*]), rs2241880-AA, rs10210302-CC, and rs2241880-GG (*ATG16L1*) have shown a reduced clinical response at the end of treatment in pediatric patients with IBD (pIDB)[27,41].

In some cases, the presence of certain variants in the genotype of patients with IDB may worsen the drug treatment. In their research, Zapata-Cobo *et al*[28] demonstrated that specific SNPs such as rs6908425 (cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1), rs2241880 (*ATG1L1*), rs2188962 (IFN regulatory factor 1 antisense RNA 1), and rs6100556 (*PHACTR3*) were associated with long-term worse response to anti-TNF drugs in children with IBD.

SNPs with short-term responses do not show a response to drug treatment. For example, rs976881-AA+GA (*TNFRSF-1B*), which is related to the TNF-α pathway, and rs1813443-CC and rs1568885-TT (contactin 5) from the immunoglobulin superfamily are associated with non-response to infliximab, and rs4645983-GG (caspase-9 [*CASP9*]) is associated with non-response to adalimumab[27]. Studies on the association between some variants and drug treatment response have shown controversial outcomes, probably due to population or age differences or insufficient analyses. For example, the SNP rs1061624-AA+GA in *TNFRSF1B* in Spanish patients with CD is related to beneficial long-term response to infliximab, whereas in Italian patients, it is linked to a short-term non-response[27].

BIOMARKERS FOR PREDICTING THE BIOLOGICAL THERAPY RESPONSE

Overview of biomarkers in IBD

The International Organization for the Study of IBD STRIDE-II recommendations from 2021 confirmed that the most critical long-term achievable treatment targets for patients with IBD are clinical remission, endoscopic healing, restoration of quality of life, and absence of disability. With accumulating clinical evidence, serum and fecal biomarkers have been validated as intermediate- or medium-term feasible treatment goals, meaning that at times, treatment could be revisited solely based on these tests to facilitate care in the clinical setting[42].

Based on their low cost and availability, FC and C-reactive protein (CRP) are the two most widely used classical biomarkers in IBD. A meta-analysis that summarized the performance of FC when using all available data, whatever the cutoff values used, showed a pooled sensitivity of 82%, specificity of 72%, and area under the curve of 0.84 for FC in reflecting endoscopic disease activity in CD[43]. The evidence suggests that a reduction in FC and target below a certain threshold have clear prognostic significance, justifying the utilization of this biomarker as a treatment target. FC predicted long-term clinical outcomes when measured 12 weeks after initiating medical treatment[44]. A meta-analysis of six studies showed that patients with elevated FC had a 53% to 83% probability of relapse during the subsequent 2 months to 3 months[45]. Different studies that confirmed FC as a predictor of relapse at the time of anti-TNF discontinuation, predicted subsequent relapse at cutoff values of 50 mg/g to 150 mg/g[46].

Whereas FC has high sensitivity and lower specificity in identifying mucosal inflammation, CRP has the opposite characteristics of higher specificity but low sensitivity[47]. Consequently, high CRP values determined at the time of anti-TNF discontinuation are associated with a higher risk of relapse[48]. CRP normalization at 8 weeks to 14 weeks after treatment predicts remission at 1 year with vedolizumab[49] and anti-TNF success at 2 years[50]. Similarly, CRP > 5 mg/dL in week 22 has been shown to predict secondary loss of response to anti-TNF[51].

Although newer biomarkers are emerging and being tested in practice, none have been successfully validated or proved reliable as a sole predictive tool in personalized medicine in IBD.

Genetic biomarkers for predicting response

Identifying predictive genetic markers is the first step in predicting the response to IBD biological treatment. Although genetic studies are not universally applicable in the clinical field, they can be used to diagnose IBD, predict therapeutic or toxic responses to drugs, and assess the risk, thereby enabling precision medicine for patients. Precisely understanding the underlying immunopathogenic mechanisms of IBD will lead to the development of targeted therapies. Effective and careful consideration of underlying factors, including immunogenicity potential, treatment safety profile, and optimal therapeutic duration in these patients, is needed.

Over the past decade, a range of predictive biomarkers has been identified that promise to provide personalized and effective treatments for patients[52]. There are also some limitations and clinical applications of these biomarkers in monitoring optimized patient outcomes and providing personalized care. Some of the predictive genetic markers are associated with predicting the response to biological treatment in patients with IBD. A favorable clinical response may be associated with polymorphisms in genes such as *FCGR3A*, *TNFRSF1A*, *IL-6*, and *IL-1B*; conversely, variants of Toll-like receptor 2 (*TLR2*) and *TLR9* show a negative correlation[53].

Some genetic variants in *TNFRSF1B* and nuclear factor kappa B (*NF-kB*) genes can affect TNF-α production or the binding of TNF-α blockers to the TNF-α receptor. These, in turn, may influence the primary response to anti-TNF therapy in patients with CD[54] or UC[55].

Polymorphisms in the IL-23R are associated with response in patients with UC, and a polymorphism in the *NOD2/CARD15* gene is associated with patients with CD[56]. These data[54] and the genetic variants described above are related to predicting positive, negative, or no response to biological treatment in patients with IBD[55-59].

It is also mandatory to integrate clinical and other biomarkers into clinical practice. Protein markers can provide valuable information for monitoring and therapeutic responses to anti-TNF therapy[60]. Markers such as CRP, human angiopoietin 1 (ANG1), ANG2, carcinoembryonic antigen-related cell adhesion molecule 1, extracellular matrix metalloproteinase inducer, transforming growth factor alpha, matrix metalloproteinases 1-3 (MMP 1-3), MMP-9, IL-6, and some apolipoproteins have been identified as predictive[61]. It should be noted that proteomics has great potential, but various factors influence protein levels and are individual in patients. Therefore, protein markers alone are not sufficient to be universal markers of therapeutic response in IBD patients.

FC, lactoferrin, and other fecal biomarkers can also be used as potential markers in patients with CD and UC on anti-TNF therapy[62,63]; however, the results of the studies are contradictory. In some cases, high calprotectin levels correlated with better treatment response[64], others inversely[65] or failed to confirm the data[66,67].

The correlation between the gut microbiome and anti-TNF therapy is complex. Still, there is evidence that some microbial markers may be associated with treatment response[68]. Patients with a more diverse gut microbiome respond better to anti-TNF-α therapy, whereas the presence of other species is associated with a negative response[69,70]. In dysbiosis, there is often no or poor response to anti-TNF therapy[71,72]. A recent study by Caenepeel *et al*[73] investigated different combinations of clinical and microbial data to predict the efficacy of TNF-α treatment. The authors examined certain clinical parameters and microbial dysbiosis, achieving a 73.9% accuracy rate in predicting treatment responses.

Fungi and viruses are also being studied for their correlation with responses to therapy[74-76]. The diversity of these different populations cannot be completely ruled out as misleading in clinical practice, as their amount and types also depend on different factors. Recently, microRNAs (miRNAs) have also been considered potential biomarkers for therapeutic responses in patients with IBD[77].

One study found significant changes in the expression of several miRNAs after anti-TNF treatment in patients with pIDB[78], but another study did not confirm the correlations[79]. Additional studies on miRNAs as possible predictive markers in patients with IBD are needed. Changes in blood or mucosal parameters can also be assessed for anti-TNF therapy's effectiveness. If there is a reduction in TNF-α and IFN-g levels and reduced inflammation at the mucosal level, then anti-TNF therapy is effective[65,80]. Some cytokines have also shown potential as candidate biomarkers in patients with IBD[81].

Many identified biomarkers indicate inflammation and are not specific to IBD alone. Various factors such as age, sex, genetics, biochemical profile, microbial composition, and mucosal conditions influence the therapy response, which may explain why none of these biomarkers have been included in routine clinical practice. For this to happen, future efforts

should focus on the robust validation of certain biomarkers in large numbers of patients with IBD.

CLINICAL APPLICATIONS OF GENETIC PREDICTORS

Personalized medicine approaches in IBD treatment

It is a well-established fact that one-third of patients with IBD are primary non-responders to inceptive treatment despite new targeted therapies that have been available recently in clinical practice. Another troubling fact is that half of patients on therapy lose treatment response with time[82]. Presently, there is an insufficient number of biomarkers that can be useful in predicting treatment failure. In clinical practice, validating equitable biomarkers, which can predict treatment response or failure, would greatly help clinicians tailor personalized therapeutic algorithms for managing patients with IBD.

Personalized medicine is the idea that the appropriate medication may be given to the relevant patient at the proper time. This process could only be possible with precise knowledge of the underlying molecular processes causing IBD. Better rates of patient outcomes, reduction of morbidity due to improper treatment, and decline in healthcare costs would all be made possible by such an approach. Creating a personalized medicine approach in IBD is connected with identifying, developing, and validating novel biomarkers to support individualized treatment[83].

Tailoring therapy based on genetic profiles

A study by Park and Jeen[22] established 240 susceptibility loci for IBD. Understanding the role of these genes in IBD pathogenesis will help to identify novel therapeutic targets. Recently, a plethora of data on the connection between genetic markers and therapeutic response has been published. For example, a study by Jürgens *et al*[56] demonstrated that therapeutic responses to infliximab were detected in adult patients with CD who were homozygous for the high-risk IL-23R variant compared to low-risk IL-23R variants. Unfortunately, a low percentage of patients have these IL-23R variants; thus, using this marker in clinical practice is unreliable[56].

The *CASP9* gene regulates activation of the caspase cascade and the process of cell apoptosis. Thus, polymorphism in *CASP9* could affect the process of apoptosis in peripheral blood lymphocytes in patients with IBD. It has been established that polymorphism in the *CASP9* gene (rs4645983) is related to short-term non-response to adalimumab[84].

Some data have shown a better response to infliximab in patients with CD with polymorphisms in the *CASP9* gene and FAS ligand gene[85]. According to some GWAS, there has been conflicting evidence about the relationship between treatment response and polymorphisms in TNF-encoding genes. Two polymorphisms in the *TNF* promoter were linked to the responsiveness of patients with IBD to TNF inhibition, according to a 2013 meta-analysis: More often occurring alleles were linked to higher response rates[86].

Better clinical responses have been found to be positively correlated with polymorphisms in the *FCGR3A*, *TLR4*, *TNFRSF1A*, *IFN-g*, *IL-6*, and *IL-1B* genes, whereas variants of *TLR2* and *TLR9* have shown a negative correlation[87]. In individuals with IBD receiving anti-TNF medication, polymorphisms in TNF, NF-kB, and other cytokine pathways have been connected to better outcomes. For instance, a study by Bank *et al*[88] demonstrated that in patients with IBD receiving anti-TNF therapy, polymorphisms in TNF, NF-kB, and other cytokine pathways were correlated with a better response to treatment.

A study by Koder *et al*[84] investigated SNPs in genes that regulate the cell division cycle (cyclin Y; rs12777960 CC), chromatin organization (chromosome 11 open reading frame 30; rs7927894 CC), and synthesis of some proinflammatory cytokines (*IL-13*; rs1295686 TT). The authors established that these SNPs are related to long-term response to adalimumab [84]. Furthermore, in patients with CD receiving anti-TNF therapy, the HLA-DQA1*05 allele, HLA-DRB1 allele, and polymorphisms at the *FCGR3A* locus (encoding immunoglobulin G Fc receptor IIIa) have been linked to a higher risk of ADA production[89-91]. Monoclonal antibodies represent large, complex proteins; they can lead to the synthesis of ADA, which are linked to therapy inefficacy. One such chimeric antibody is infliximab[92]. Finding patients at high risk of developing ADA would be very beneficial since concurrent immunosuppression (with thiopurines and methotrexate) lowers the likelihood of developing them[93].

IL-13R alpha 2 is another marker that has been previously discovered by gene array investigations in the mucosal biopsies of patients with IBD[94]. The biomarker, assessed as mRNA expression in the mucosa of patients with IBD before therapy, was recently found to be particularly predictive of the absence of response to anti-TNF in terms of mucosal healing at 6 months. The area under the curve for infliximab and adalimumab was 0.90 and 0.94, respectively, with $P < 0.001$[95].

The *NOD2* gene, which encodes a protein involved in inducing the immune response and connected to the TNF-inflammatory pathway, is linked to both a more aggressive course of the disease and susceptibility to CD[96,97]. According to particular research, *NOD2* mutations are linked to a poorer response to anti-TNF therapy[98-100]. In patients with CD receiving TNF antagonist treatment, polymorphisms in the *ATG16L1* gene have been linked to improved response rates and prolonged benefits[84]. In actual therapeutic practice, the genetic variants that confer vulnerability to ADA development could be quite helpful in identifying individuals who could benefit from biological therapy. Few studies revealed certain genetic polymorphisms[101-105] and gene variants[106-110] associated with various responses to biological therapy in IBD.

An overview of the currently known genetic factors that influence the response to biological therapy for patients with IBD is presented in Table 1[28,41,53,56,58,84,86-91,98-110].

Table 1 Genetic factors that influence the response to biological therapy for patients with inflammatory bowel disease

Genetic markers	Patients	Clinical consequences	Ref.
Polymorphisms in TLR2, rs11938228, TLR4, TLR9, TNFRSF1A, IFNG, IL-6, and IL-1B (rs4848306, NOD-like receptor thermal protein domain associated protein 3, Janus kinase 2)	IBD	Clinical response in to anti-TNF	Bek *et al*[53], 2016; Salvador-Martín *et al*[87], 2019; Steenholdt *et al*[101], 2012; Medrano *et al*[102], 2013; Bank *et al*[88], 2014
Polymorphisms in TNF-α promoter (-308 A/G and -857 C/T)	IBD and spondylarthritis	Clinical response to anti-TNF	Tong *et al*[86], 2013; Song *et al* [103], 2015
Polymorphisms implicated in NF-kB pathway: TLR2, TLR4, TLR9, LY96 (MD-2), CD14, mitogen-activated protein kinase 14 (NIK), TNF-α, TNFRSF1A, TNFAIP3 (A20), IL-1B, IL-1RN, IL-6, IL-17A, IFNG	IBD	Clinical response to anti-TNF (adalimumab)	Bank *et al*[88], 2014; Song *et al* [103], 2015; Bek *et al*[53], 2016
Polymorphisms in IL-23R	UC	Early response to infliximab	Jürgens *et al*[56], 2010
HLA-DQA1*05	CD	Development of ADA against infliximab and adalimumab	Sazonovs *et al*[89], 2020; Salvador-Martín *et al*[87], 2023
HLA-DRB1	IBD	Development of ADA against infliximab	Billiet *et al*[90], 2015
Polymorphisms in FcγRIIIa	CD	Development of ADA against infliximab	Louis *et al*[91], 2004
Polymorphisms in NOD2	CD	Clinical response to anti-TNF	Niess *et al*[98], 2012
Polymorphisms in NOD2	CD	Loss of response to anti-TNF	Juanola *et al*[99], 2015
Polymorphisms in NOD2	CD	Lower anti-TNF trough levels	Schäffler *et al*[100], 2018
Polymorphisms in ATG16L1 (C11orf30; rs7927894 CC, CCNY; rs12777960 CC) (rs10210302)	IBD and CD	Clinical response to adalimumab	Koder *et al*[84], 2015; Zapata-Cobo *et al*[28], 2023
Polymorphisms in FAS, FASL, and CASP9 (apoptotic pharmacogenetic index)	CD	Clinical response to infliximab and adalimumab	Hlavaty *et al*[104], 2007; Koder *et al* [84], 2015
Multiple polymorphisms (combined clinical-genetic model)	CD and UC	Short-term and long-term to clinical response anti-TNF	Barber *et al*[58], 2016; Burke *et al* [105], 2018
Polymorphisms in TNFSF4/18, perilipin 2, rs762787, rs9572250, rs144256942, rs523781	IBD	Clinical response to anti-TNF	Wang *et al*[106], 2019
PHACTR3 (rs6100556)	UC and CD	Response to anti-TNF in children	Zapata-Cobo *et al*[28], 2023
CNTN5	CD		Thomas *et al*[107], 2014
FCGR3A	CD and UC	Antibody-dependent immune responses	Curci *et al*[41], 2021
PTGER4 (rs10512734)	CD	Response to adalimumab	Koder *et al*[84], 2015
IL-27	CD	Response to adalimumab	Koder *et al*[84], 2015
NR12	CD	Response to adalimumab	Koder *et al*[84], 2015
FASL (rs763110)	CD	Clinical response in patients with CD treated with infliximab	Zapata-Cobo *et al*[28], 2023; Steenholdt *et al*[101], 2012
IRF1-AS1	UC	Response to anti-TNF in children	Zapata-Cobo *et al*[28], 2023
Polymorphisms in IL-1B	IBD	Response to anti-TNF-α	Bank *et al*[88], 2014
Polymorphisms in IL-18	IBD	Response to anti-TNF-α	Bek *et al*[53], 2016
TLR2 (rs1816702 CC and rs3804099 TT)		Clinical response to infliximab	Salvador-Martín *et al*[87], 2019
Polymorphisms in CXCL12	IBD	Response to anti-TNF-α in children	Zapata-Cobo *et al*[28], 2023
Polymorphisms in IL-10	IBD	Response to anti-TNF-α in children	Salvador-Martín *et al*[108], 2020; Salvador-Martín *et al*[109], 2023
Polymorphisms in IL-17	IBD	Response to anti-TNF-α in children	Salvador-Martín *et al*[108], 2020; Salvador-Martín *et al*[109], 2023; Bank *et al*[88], 2014
Polymorphisms in IL-6	IBD	Response to anti-TNF-α in children	Salvador-Martín *et al*[108], 2020

Gene protein tyrosine phosphatase non-receptor type 2 (rs7234029 AG + GG, CASP9)	IBD	Non-response to anti-TNF and ustekinumab	Hoffmann *et al*[110], 2021

ADA: Anti-drug antibodies; ATG16L1: Autophagy-related 16-like 1; CASP9: Caspase-9; CCNY: Cyclin Y; CD: Crohn's disease; CD14: Cluster of differentiation 14; CNTN5; Contactin 5; CXCL12: C-X-C motif chemokine ligand 12; FASL: Fas ligand; FCGR3A: Fc gamma receptor 3A: FcγRIIIa: Immunoglobulin G Fc receptor IIIa; HLA: Human leukocyte antigen; IBD: Inflammatory bowel disease; IFNG: Interferon gamma; IL: Interleukin; IL-1RN: Interleukin 1 receptor antagonist; IRF1-AS1; Interferon regulatory factor 1 antisense RNA 1; LY96: Lymphocyte antigen 96; NF-kB: Nuclear factor kappa B; NOD: Nucleotide-binding oligomerization domain-containing protein; NR12: Hemopoietin receptor gene; PHACTR3: Phosphatase and actin regulator 3; PTGER4: Prostaglandin E receptor 4; TLR: Toll-like receptor; TNF: Tumor necrosis factor; TNFAIP3: Tumor necrosis factor alpha-induced protein 3; TNFR: Tumor necrosis factor receptor; TNFRSF1A: TNF receptor superfamily member 1A; UC: Ulcerative colitis.

FUTURE DIRECTIONS IN GENETIC RESEARCH FOR IBD THERAPY

Genomics and precision medicine advancements are revolutionizing the approach to treating IBD. Integrating multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, allows for a comprehensive understanding of the complex genetic and molecular mechanisms underlying IBD. By analyzing this vast array of data, researchers can identify specific genetic markers and pathways associated with the disease, leading to more personalized and effective treatment strategies.

Artificial intelligence (AI) is crucial in predicting patient response to biological therapies. Machine learning algorithms can process and analyze large datasets to uncover patterns and predict outcomes based on genetic and clinical information. This predictive capability can significantly enhance clinical decision-making, allowing for selecting the most suitable biological therapy for each patient, thereby improving treatment efficacy and reducing the risk of adverse reactions[111,112].

The potential for novel therapeutic targets based on genetic insights is immense. Emerging therapies, such as those targeting specific genetic pathways implicated in IBD, are showing promise. For example, therapies designed to modulate the immune response or repair intestinal barrier function are developing based on genetic findings. The future landscape of IBD treatment will likely see a shift towards these targeted therapies, which offer the potential for improved patient outcomes and a reduction in the burden of disease. Continued research in this field is essential to fully realizing the benefits of precision medicine in IBD therapy.

CONCLUSION

In summary, understanding the genetic factors that influence the response and failure of biological therapy in IBD is crucial for advancing treatment approaches. Key genetic factors, such as specific gene polymorphisms, mutations, and epigenetic modifications, play significant roles in determining how patients respond to biological therapies. Identifying these genetic markers enables a more precise prediction of treatment outcomes, paving the way for personalized medicine. Integrating multi-omics data and the application of AI in this field are poised to revolutionize IBD treatment. These advancements will allow for the development of novel therapeutic targets and the optimization of existing treatments, ultimately improving patient outcomes. As we move towards a future where treatment plans are tailored to the individual genetic makeup of patients, the potential for reducing the burden of IBD and enhancing the quality of life for patients is immense. However, the implications for personalized medicine are profound. By leveraging genetic insights, healthcare providers can offer more targeted and effective therapies, minimizing adverse effects and maximizing therapeutic benefits. Continued research and technological advancements will be essential to fully harness the potential of precision medicine in IBD treatment, transforming the clinical management of this complex disease.

FOOTNOTES

Author contributions: Peruhova M, Stoyanova D, and Miteva D were involved in conceptualizing the study and writing the manuscript; Peruhova M and Velikova T created the table; Kitanova M, Mirchev M, and Velikova T wrote additional sections of the manuscript; Velikova T was responsible for the critical revision of the manuscript for relevant intellectual content; All authors approved the final version of the manuscript prior to submission.

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