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Genetic factors that predict response and failure of biologic therapy in Inflammatory Bowel Disease

Genetics of IBD biologics failure

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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 IBD patients 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 IBD patients.

Key Words: Inflammatory Bowel Disease; Genetic Predictors; IBD Treatment; Biologic Therapy; biologic therapy Response; Genetic Markers in IBD; IBD Treatment Failure; PharmacogenoThemics; Biologic Therapy Efficacy; Genetic Variability.

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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.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that comprises two entities, namely 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 both for Europe and North America, as well as for the newly industrialized countries of Asia, Africa, and South America. The highest incidence of 505 UC cases and 322 CD cases per 100,000 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-ASA, 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 (Treg) cells, type 2 macrophages, CD4+ T-helper (Th)-17 cells, CD8+ T cells, and natural killer (NK) 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. In contrast, advanced techniques like capsule endoscopy and biomarkers (*i.e.*, fecal, serum, genetic, *etc.*) 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 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 the patients with UC at week 52, respectively. In CD, the same treatment goals are encountered in 76% and 48% of the cases, respectively[8]. For ustekinumab, an anti-IL-12/23 antibody, clinical response and remission at 1 year were seen in 76.8% and 50.6% of the patients with UC[9]. For CD, the percentage of clinical

remission at week 44 is approximately 50%[10]. The non-selective JAK inhibitor, tofacitinib, which has been approved only for the treatment of UC, achieved clinical remission in 40.6% of the cases at week 52[11]. In comparison, the clinical and endoscopic remission rates of the selective JAK1 inhibitor upadacitinib are 33% and 15% for UC *vs* 41% and 24% for CD, respectively[12]. In keeping with those mentioned above, there seems to be a wide interindividual variation in the efficacy of biological treatment, which could be genetically determined. A recent systematic review published in 2024 by Plaza *et al*. showed that single nucleotide polymorphisms may be associated with a different treatment response towards anti-TNF, anti-integrins and anti-IL 12/23 inhibitors[13]. Therefore, a more individualized approach towards every IBD patient

In this review paper, we aimed to 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 keywords 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 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 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 (NAT2) 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 (TNFRSF1A and TNFRSF1B) can affect the binding and efficacy of anti-TNF therapies like infliximab and adalimumab. Specific polymorphisms are associated with better or worse responses to these treatments[18].

Variations in the IL-23 Receptor (IL23R) gene influence responses to biologics targeting the IL-23 pathway, such as ustekinumab. Specific IL23R genotypes are linked to improved treatment responses[19].

When we discuss the implications for treatment outcomes, we should focus on the 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 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, over 240 nonoverlapping genetic loci have been identified as significant risk factors in IBD[21-23]. Among them statistically significant genes are *ATG16 L1*, *CDH1*, HLAs, *HNF4a*, *IL10*, *IL10RA*, *IL10RB*, *IL23R*, *LRRK2*, *NOD2*, *PTPN2*, *TNFSF15*, *IRGM*, *CARD9*, *RNF186*, *etc.* linked to innate and adaptive immunity, autophagy, epithelial barrier, innate mucosal defense, regulatory T cells, oxidative stress, interleukin-10 and interleukin-23 signaling, cell apoptosis, etc.[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 the 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. As it is known, the IBD-causing alleles are rich in non-synonymous mutations in their coding region, modulating the protein structure and function and thus affecting the drug binding affinity or downstream signaling pathways. Furthermore, 80–90% of IDB loci are non-synonymous variants due to mutations in their noncoding regions exerting pathogenic effects by modulating the gene expression[25].

Intensive 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 but the drug interactions, development of resistance, drug quality, *etc.* For example, changes in physiological conditions, such as pH 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 the drug-metabolizing enzymes, the 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 - increased body weight, low serum albumin, and even disease status and medications[30]. Biologics have been used to treat IBD for a long time ago, but guidelines regarding their optimal use are still being researched and developed. Over the past few decades, IBD-related costs have increased significantly 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]. Evidence shows that 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 in the 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 of the IBD patients either do not respond or have a loss of response against the treatment over time. The data show that genetic factors are responsible for this inability. Genetic profiling techniques and GWAS have enabled the identification of genetic variants that could influence the treatment response and development of adverse effects[24].

A study revealed genetic associations with primary non-response[40]. They found that SNPs in loci *DENND1B* (rs2488397) and *AHR* (rs1077773) were 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 *PRDM1* (rs62421049), chr21q22.2 (rs2836866), *CD28* (rs3116494), *SMAD3* (rs17293632) and *IFIH1* (rs1990760) were associated[40].

Usually, SNPs with long-term responses are associated with responsiveness for infliximab or adalimumab therapy in patients with IBD. However, evaluation of the impact of some of them, such as rs396991-GG (*FCGR3A*), rs6100556-TT (*PHATCR3*), rs2241880-AA, rs10210302-CC, and rs2241880-GG (*ATG16 L1*), showed a reduced clinical response at the end of the therapy in pediatric IBD patients (pIDB)[27,41].

In some cases, the presence of certain variants in the genotype of IDB patients may worsen the drug treatment. In their research, Zapata-Cobo *et al*. (2023) demonstrate that specific SNPs such as rs6908425 (*CDKAL1*), rs2241880 (*ATG16 L1*), rs2188962 (*IRF1-AS1*), and rs6100556 (*PHACTR3*) are associated with long-term worse response to anti-TNF drugs in IBD children[28].

SNPs with short-term responses do not show a response to drug treatment. For example, rs976881-AA+GA (*TNFRSF1B*), related to the TNF-α pathway, and rs1813443-CC and rs1568885-TT (*CNTN5*) from the immunoglobulin superfamily, are associated with non-response to infliximab and rs4645983-GG (*CASP9*) – 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, SNP rs1061624-AA+GA in TNFRSF1B in Spanish patients with CD is related to beneficial long-term response to infliximab, while, in Italian ones, it is linked to a short-term non-response[27].

BIOMARKERS FOR PREDICTING BIOLOGICAL THERAPY RESPONSE

OVERVIEW OF BIOMARKERS IN IBD

The IOIBD STRIDE-II recommendations from 2021 confirm 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 the accumulating clinical evidence, serum and fecal biomarkers are endorsed 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 CRP are the two most widely used classical biomarkers in IBD. A meta-analysis 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 (AUC) of 0.84 for FC in reflecting endoscopic disease activity in CD[43]. The evidence suggests that a reduction in FC and a 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 6 studies indicated that patients with elevated FC had a 53% to 83% probability of relapse during the subsequent 2 to 3 months[45]. Different studies confirm FC as a predictor of relapse at the time of anti-tumor necrosis factor (TNF) discontinuation predicted subsequent relapse at cutoff values 50 to 150 mg/g[46].

Whereas FC has high sensitivity and lower specificity in identifying mucosal inflammation, CRP has the opposite characteristics: 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 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 at 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, and none have proved reliable in being alone as a 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. Understanding precisely 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 have 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 response to biological treatment in IBD patients. A favorable clinical response may be observed, *e.g.*, with polymorphisms in genes such as FCGR3A, TNFRSF1A, IL6, IL1B, *etc.*, and conversely, variants of TLR2 and TLR9 show a negative correlation[53].

Some genetic variants in the TNFRSF1B and NFkB genes can affect TNF-αlpha production or the binding of TNF-αlpha blockers to the TNF-αlpha receptor. These, in turn, may influence the primary response to anti-TNF therapy in CD[54] or UC patients[55].

Polymorphisms in the IL23 receptor are associated with response in UC patients, and a polymorphism in the NOD2/CARD15 gene is associated with CD patients[56]. These data and the genetic variants described above are related to predicting positive, negative or no response to biological treatment in patients with IBD[54-59].

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, ANG1, ANG2, CEACAM1, EMMPRIN, TGFA, MMP1-3, MMP9, IL-6, some apolipoproteins, *etc.* 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 CD and UC patients 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-αlpha therapy, while 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.* investigated different combinations of clinical and microbial data to predict the efficacy of TNF-αlpha treatment[73]. They 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 correlation with responses to therapy[74-76]. The diversity of all these different populations cannot be completely ruled out as misleading in clinical practice, as their amount and types also depend on different

factors. Recently, miRNAs have also been considered potential biomarkers for therapeutic responses in IBD patients[77].

One study found significant changes in the expression of several miRNAs after anti-TNF treatment in pediatric IBD patients[78], but another study did not confirm the correlations[79]. Further studies on miRNAs as possible predictive markers in IBD patients 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 interferon (IFN)-γ 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, gender, genetics, biochemical profile, microbial composition, mucosal conditions, *etc.*, influence therapy response. Namely, this may be why none of these biomarkers have been included in routine clinical practice. For this to happen, future efforts should focus on robust validation of certain biomarkers in large numbers of IBD patients.

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 disturbing fact is that half of the patients who are 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 be only possible with a

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 *et al*. established 240 susceptibility loci for IBD[22]. 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 instance, a study by Jürgens *et al*. demonstrated that therapeutic responses to Infliximab are detected in adult patients with CD who are homozygous for the high-risk IL-23R variant compared to low-risk IL-23R variants. Unfortunately, a few percent of patients have these IL23R variants; thus, using this marker in clinical practice is unreliable[56].

The caspase-9 (CASP9) gene regulates the 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 was established that polymorphism in the CASP9 gene (rs4645983) is related to short-term non-response to Adalimumab[84].

Some data showed that a better response to Infliximab could be identified in CD patients with polymorphism in the Caspase-9 gene and Fas Ligand gen.[85] According to some GWAS, there has been opposing evidence about the relationship between treatment response and polymorphisms in TNF-encoding genes. Two polymorphisms in the TNF promoter were linked to IBD patients' responsiveness to TNF inhibition, according to a 2013 meta-analysis: More often occurring alleles were linked to higher response rates[86].

Better clinical response was found to be positively connected with polymorphisms in the FCGR3A, TLR4, TNFRSF1A, IFNG, IL6, and IL1B genes, while variants of TLR2 and

TLR9 showed a negative correlation[87]. In individuals with IBD receiving anti-TNF medication, polymorphisms in the TNF, NFkB, and other cytokine pathways have been connected to better outcomes. For instance, a study by Bank *et al*. demonstrates that in IBD patients receiving anti-TNF therapy, polymorphisms in the TNF, NFkB, and other cytokine pathways have been connected to better response to treatment[88].

A study by Koder *et al*. investigates single nucleotide polymorphisms (SNP) in genes that regulate the cell division cycle (CCNY; rs12777960 CC), chromatin organization (C11orf30; rs7927894 CC), and synthesis of some proinflammatory cytokines (IL-13; rs1295686 TT). The authors established that these SNP are related to long-term response to Adalimumab[84]. Furthermore, in CD patients receiving anti-TNF therapy, the HLA-DQA1*05 allele, the HLA-DRB1 allele, and polymorphisms at the FCGR3A locus (encoding IgG Fc receptor IIIa) have been linked to a higher risk of ADA production[89-91]. Monoclonal antibodies represent big, complex proteins, they can lead to the synthesis of ADA, which is 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].

The IL-13 receptor alpha 2 (IL13RA2) is another marker that has been previously discovered by gene array investigations in mucosal biopsies of IBD patients[94]. The biomarker, assessed as mRNA expression in the mucosa of IBD patients 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 receiver operating characteristic (AUROC) for infliximab and adalimumab was 0.90 and 0.94, respectively, with a p-value of less than 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 CD patients receiving TNF antagonist treatment, polymorphisms in the ATG16 L1 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 and gene variants associated with various responses to biological therapy in IBD[101-110].

An overview of the currently known genetic factors that influence the response to biological therapy for IBD patients is presented in Table 1.

Table 1. Genetic factors that influence the response to biological therapy for IBD patients

< TABLE 1 >

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 artificial intelligence 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.

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