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Review Article

The Genetics of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is considered as genetic disease due to observation of familial clustering of cases, genetic anticipation between generations and phenotypic concordance of some clinical features within families. Current knowledge of genes/loci associated IBD was largely developed by genome wide association studies which is common disease-common variant analysis strategy. With heterogeneity character and disease incidence of 4.75/100,000/year for Crohn's disease and 2.06/100,000/year for ulcerative colitis in pediatric population, targeted resequencing and whole exome sequencing for the identification of rare pathogenic variants in known or novel genes are becoming more applicable for IBD genetic studies. According to chromosomal locus of genetic susceptibility, IBD was classified into 28 subtypes. According to functions and pathogenesis, genes involved in IBD can be classified into three groups including inflammation, immune regulation, and cellular adhesion/epithelial barrier integration. Genes regulate cell cycle, dysplasia or adhesion may be associated with cancer development in patients with long-standing IBD. Identification of casual genes/variants will be significant for diagnosis, treatment, prevention, cancer surveillance and improved health care for IBD patients.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Genetics

Conflict of interest: None.

Introduction

Inflammatory bowel disease (IBD) is a group of disorders that can be classified as Crohn's disease (CD) and ulcerative colitis (UC). It is thought that the disease results from deregulation of homeostasis of gastrointestinal tract which is caused by inappropriate immune response to intestinal microbes. Although CD and UC have different pathophysiological entities, their clinical presentations (such as abdominal pain, nausea, vomiting, diarrhea and constipation) are similar and non-specific. Diagnosis can be made by symptoms, laboratory tests, radiology, endoscopic examination and pathological findings. Differential diagnosis includes infectious colitis, acute self-limited colitis, diverticulitis, pseudomembranous colitis, irritable bowel syndrome, celiac disease, medication, allergy and cancer. Despite of advance in technology, an accurate diagnosis cannot be achieved in 10% of IBD patients. Affected individuals with colonic disease that cannot be specified are classified as indeterminate colitis. In pediatric series, the prevalence of indeterminate colitis ranges from 5-30%, suggesting variation in classification criteria and uncertainty in diagnosis [1,2].

CD could affect any portion of the gastrointestinal tract with endoscopic features of patchy, skipped "cobblestone" lesions in mucosa. Granulomas and giant cells are common observations while lympho-histiocytic infiltrate is predominant in pathology. The disease is transmural with often complications of strictures and fistulas. UC patients have inflammation involves the rectum but may affect part of the colon or the entire colon. Diffuse continuous erythema and granularity can be seen by endoscopic examination. Inflammation is usually limited to mucosa and submucosa. Neutrophilic infiltrate with crypt abscess is predominant when lesion is examined under microscope [3-5]. Clinical characters of CD and UC are listed in table 1.

IBD is considered as genetic disorder and genetic factors play important role in disease predisposition. Many genes or loci were identified to be implicated in inflammation, immune regulation, cellular adhesion and epithelial barrier integration in intestine homeostasis. Classification of genetic profiles of IBD patients will be important for diagnosis, treatment and cancer prevention.

Genetic Factors in Inflammatory Bowel Disease Etiology

The pathogenesis of IBD is complex and is incompletely understood. Observations of familial clustering of cases [6-7], genetic anticipation [8-10] and phenotypic concordance [11] of

Table 1. Comparison of Clinical Features of Crohn's Disease and Ulcerative Colitis

Feature	Crohn's disease (CD)	Ulcerative colitis (UC)
Location	Affect any portion of the gastrointestinal tract, most commonly the ileum and colon	Inflammation involves the rectum and may affect part of the colon or the entire colon
Clinical presentations	Diarrhea, abdominal pain, bloody stool, weight loss, growth failure, anemia	Diarrhea, abdominal pain, bloody stool, weight loss, growth failure, anemia
Endoscopic features	Deep fissuring ulcers and ''cobble stoned'' mucosa	Diffuse continuous inflammation extending from the rectum proximately, diffuse erythema, friability, granularity, and loss of vascular pattern in the colon.
Pathology	Transmural inflammation. Discontinuous, patchy disease with skip lesions. May involve entire gastrointestinal tract. Granulomas and giant cells are seen in the majority of patients. Strictures and fistulas are common. Predominantly lympho-histiocytic infiltrate.	Inflammation limited to mucosa and superficial submucosa. Contiguous disease, no skip lesions. Perianal fistulas and ulcers are rare, no granulomas and giant cells. Predominantly neutrophilic infiltrate with crypt abscesses.
Serology	Anti-neutrophil cytoplasmic antibody (pANCA) is identified in 20% of CD patients; Anti-Saccharomyces cerevisiae antibody (ASCA) is present in 40-80% of CD patients	pANCA in 75%
Genetic test	NOD2 mutations are presented in about 25% of CD patients	
Treatment	Aminosalicylates and antibiotics (for mild mucosal disease), nutritional therapy (including elemental or polymeric formulas), corticosteroids (for moderate disease), and infliximab (for corticosteroid-resistant or fistulizing disease). Aminosalicylates, 6-mercaptopurine, azathioprine, methotrexate, and infliximab can be used as maintenance therapies.	Aminosalicylates (for mild disease), corticosteroids (for moderate disease), and cyclosporine (for severe disease). Aminosalicylates, 6-mercaptopurine, and azathioprine for maintenance therapies.
Surgery as treatment	Disease likely to recur	Results in cure of illness
Risk with tobacco	Increased in smokers and tend to have more severe disease	Former smokers and nonsmokers are at greater risk
Cancer development	Rare	Common

some clinical features of the disease in familial cases indicated IBD is a genetic disease. Inheritance of IBD can be autosomal dominant [12-13], autosomal recessive [14-15], polygenic or multifactorial [16]. It is suggested that recessive gene with incomplete penetrance confer susceptibility to CD [17]. Polygenic inheritance can be responsible for individuals who inherited few susceptibility genes and develop IBD [18-19]. Twin studies revealed that rates of concordance are more modest for CD than for UC, indicating genetic factors are likely to play a more prominent role in CD than in UC. Occurrence of CD and UC in the same families also suggested some genetic loci may contribute to both disorders [20-21].

The Role of Genetics in the Diagnosis of Inflammatory Bowel Disease

According to chromosomal locus of genetic susceptibility, IBD was classified into 28 subtypes by Online Mendelian Inheritance in Man (Table 2). Recent studies suggested there are a total of 163 non-overlapping genetic risk loci associated with IBD, including 71 loci for CD, 47 loci for UC, and 110 loci confer susceptibility to both CD and UC [22-25]. Candidate genes have been proposed in some of these regions and new genes have been discovered. These genes are involved in barrier function, epithelial restitution, microbial defense, innate immune regulation, reactive oxygen species generation, autophagy, regulation of adaptive immunity, endoplasmic reticulum stress and metabolic pathways associated with cellular homeostasis in intestinal epithelial cells. Despite of the progress, it is estimated that known genetic associations account for only about 20% of the genetic variance underlying susceptibility to inflammatory bowel disease and the remaining genetic factors have not been identified [3].

Table 2. Inflammatory Bowel Disease Classification According to Susceptible Loci

Inflammatory bowel disease (IBD) subtype	Cytoband	Candidate gene(s)
IBD1	7p15.3	IL6
	16q12.1	NOD2
IBD2	12p13.2-q24.1	Unknown
IBD3	6p21.3	Unknown
IBD4	14q11-q12	Unknown
IBD5	5q31	OCTN1, OCTN2, SLC22A5
IBD6	19p13	Unknown
IBD7	1p36	Unknown
IBD8	16p	Unknown
IBD9	3p26	Unknown
IBD10	2q37.1	ATG16L1
IBD11	7q22	MUC3A
IBD12	3p21	MST1, BSN
IBD13	7q21.1	ABCB1
IBD14	7q32	IRF5
IBD15	10q21	ZNF365
IBD16	9q32	TNFSF15
IBD17	1p31.1	IL23R
IBD18	5p13.1	PTGER4
IBD19	5q33	IRGM, IL12B
IBD20	10q24	NKX2-3
IBD21	18p11	PTPN2
IBD22	17q21	STAT3
IBD23	1q32	IL10
IBD24	20q13	Unknown
IBD25	21q22	IL10RB
IBD26	12q15	Unknown
IBD27	13q13.3	Unknown
IBD28	11q23.3	IL10RA

Genes associated with Crohn's disease

Genes involved in innate immune system response, including nucleotide-binding oligomerization domain protein 2 (NOD2), autophagy 16-like 1 (ATG16L1) and immunity-related GTPase family, M (IRGM) confer CD development. NOD2, also called caspase recruitment domain-containing protein 15 (CARD15), is the first susceptibility gene identified for CD. NOD2 is expressed in epithelial cells, Paneth cells, macrophages, dendritic cells, and endothelial cells in intestine [26]. NOD2 regulates nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. Studies indicated NOD2 mutations could induce defects in pathogen clearance, impaired tolerance to chronic bacterial stimulation and decrease in Paneth cell's α-defensin expression. NOD2 non-synonymous functional variants occur in about 25% CD patients with incomplete penetrance. Missense variant mutation panel R702W, G908R, 1007fs are considered as independent risk factors for CD in Caucasian patients but are absent in Asian and are rare in African-American patients with CD [27-31], indicating IBD may be genetically different per ethnicity. ATG16L1 gene is broadly expressed in intestinal epithelial cells, antigen-presenting cells, CD4+, CD8+ and CD19+ primary human T cells. Both ATG16L1 and IRGM are implicated in autophagy and loss-of-function variants in these two genes could cause reduced pathogen clearance in intestine [32-34].

Genes involved in ulcerative colitis development

Genes regulate mucosa barrier functions confer risk of CD and UC but seems more prominent in pathogenesis of UC. Extracellular matrix protein 1 (ECM1), cadherin 1, type 1 (CDH1), hepatocyte nuclear factor 4, alpha (HNF4α) and laminin B1 (LAMB1) confer risk for UC [35-36]. CDH1, also called E-cadherin, encodes a transmembrane glycoprotein which is the principle component of the adherent junction. HNF4α is a tran-

scription factor expressed in liver, pancreas and intestine. It regulates tight junction of epithelial cells and control para-cellular permeability. LAMB1 encodes glycoprotein component of the basement membrane. Association of these genes with UC were established by single study and more investigations are needed to make further conclusion.

Genes associated with both Crohn's disease and ulcerative colitis

Genes involved in T cell tolerance or adaptive immune systems are susceptible for both CD and UC. Inhibitory cytokine interleukin-10 (IL10) contributes to T cell tolerance in intestine. IL10 confer risk loci for UC and child onset CD while IL10 receptor mutations were identified in patients with severe colitis [37-41]. NK2 homeobox 3 (NKX2-3) is a transcription factor expressed in gut mesoderm during development. It regulates migration and homing of lymphocytes and macrophages [42]. Susceptibility loci were identified in NKX2-3 for both CD and UC patients [43]. Multiple genes in the IL23 pathway, including IL23 receptor (IL23R), IL12B (encodes the p40 subunit of IL12 and IL23), Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) have been shown to be associated with both CD and UC [44]. IL23 is a heterodimeric cytokine consisting of p19 (IL23A) and p40 (IL12B) subunits. IL23 receptor pairs with IL12RB1 to mediate IL23 responsiveness. Studies indicated that IL23 receptor may be associated with IBD, psoriasis, ankylosing spondylitis and seronegative diseases [45-47]. JAK2 is a member of a family of tyrosine kinases involved in cytokine receptor signaling. JAK2 mutations were found in patients with leukemia, thrombocythemia or polycythemia vera [48-50]. STAT3, also called acute phase response factor, acts as an adaptor molecule in signal transduction from the type I interferon receptor. STAT3 mutations could cause autosomal dominant IgE recurrent infection syndrome [51-52].

CD and UC have a combined prevalence of 200 to 300 per 100,000 in the United States [53]. In pediatric population, the incidence of CD is 4.75/100,000/year and UC is 2.06/100,000/year [54]. Most of the susceptible genes/loci reported were identified by genome wide association studies. Recently, targeted sequencing of candidate genes on CD patients using next generation sequencing technology followed by genotyping independent IBD case-control series identified rare variants in NOD2 in both CD and UC patients. A splice site variant in caspase recruitment domain-containing protein 9 (CARD9), rare variants in interleukin 18 receptor accessory protein (IL-18RAP), cullin 2 (CUL2), chromosome 1 open reading frame 106 (C1ORF106), protein tyrosine phosphatase, non-receptor type 22, lymphoid (PTPN22), and mucin 19 (MUC19) were also found in IBD patients [55]. These indicated that rare functional variants may have significant impact on IBD. A summary of candidate genes for CD and UC as well as their roles in disease development are listed in table 3.

Genetic testing for inflammatory bowel disease

Variants identified in specific genes described above are considered as genetic predispositions for IBD. Currently, genetic testing for high-risk alleles is not used in clinical practice for making diagnosis. Genetic studies on very early onset IBD (0-10 year old) patients are especially helpful in the identification of monogenic cause for the disease because the effect of environmental modifiers is minimal. It is suggested that genetic analysis can identify the cause of the disorder and may play a role in identifying patient's likelihood of developing complications over time [56-57]. Therefore genetic testing may aid physician in making appropriate treatment decisions.

Treatment Regimen and Potential Application of Personalized Medicine for Ibd Patients

The goal of management for IBD patients is induction and maintenance of remission. Medication resistance and adverse effects could be significant in IBD management due to the lifelong illness. Application of personalized therapy is promising in reducing family burden and improving quality of life for these patients.

As the first evaluated treatment regimen for IBD, corticosteroids continue to be favored by some clinicians [58]. A 30 day short course is usually applied for the induction of remission. The outcome of the first steroid treatment course showed prolonged steroid response in 44%, steroid dependency in 36%, and steroid resistant in 20% of the CD patients [59]. Study on pediatric IBD cohort indicated that most subjects initially responded to corticosteroids. However, after 1 year, 58% of pediatric patients with CD and 43% of pediatric patients with UC either were steroid dependent or required surgery [60]. The findings emphasized the need for early steroid-sparing medications in IBD therapy.

5-aminosalicylic acid (5-ASA) is an antibacterial/anti-inflammation drug most commonly used to treat mild or moderate active IBD. It is superior to corticosteroids in patients with colonic disease for maintain remission [61]. Tolerance to the drug is dose-related and corresponds to genetically-determined hepatic acetylation of sulfapyridine [62]. The choice of 5-ASA application is influenced by tolerance, dose schedule and cost. Identify variants associated with 5-ASA metabolism may be helpful for dosage adjustment and determine medication regimen for patients. It is reported that metronidazole is effective in treating perianal disease in patients with CD [63]. But long term exposure may cause adverse effect such as peripheral neuropathy. Other antibiotic therapy has been used on an empirical basis to reduce corticosteroids exposure and the application may not alter the long-term course of the disease.

Table 3. Genes Associated with Inflammatory Bowel Disease

Gene	Gene Name	Function	Inheritance	Note
ARPC2	Actin related protein 2/3 complex, subunit 2	Phagocytosis		
ATG16L1	ATG16 autophagy related 16-like 1 (S. cerevisiae)	Autophagy		Confer risk of CD
C1ORF106	Chromosome 1 open reading frame 106	Uncharacterized protein		
CARD9	Caspase recruitment domain family, member 9	Apoptosis, immune	AR	
CDH1	Cadherin 1, type 1, E-cadherin (epithelial)	Adhesion, mucosal barrier	AD	Confer risk of UC
CUL2	Cullin 2	Cell cycle		
E-cadherin	E-cadherin	Adhesion		Genetic correlation between cancer and UC
ECM1	Extracellular matrix protein 1	Mucosal barrier	AR	Confer risk of UC
GNA12	Guanine nucleotide binding protein (G protein) alpha 12	Mucosal barrier		Confer development of UC
HERC2	Homologous to the E6-AP carboxyl terminus (HECT) and regulator of chromosome condensation 1-protein like domain (RLD) domain containing E3 ubiquitin protein ligase 2	Ubiquitin mediated proteolysis	AR	
HNF4A	Hepatocyte nuclear factor 4, alpha	Mucosal barrier	AD	Confer risk of UC
ICAM1	Intercellular adhesion molecule 1	Adhesion	AR	
ICOSLG	Inducible T-cell co-stimulator ligand	Cell adhesion, immune		
IL10	Interleukin 10	Inflammation		Perhaps the most amenable to therapeutic intervention to UC
IL10R	Interleukin 10 receptor	Inflammation	AR	
IL12B	Interleukin 12B	Inflammation		
IL18	Interleukin 18 (interferon-gamma-inducing factor)	Inflammation		
IL18RAP	Interleukin 18 receptor accessory protein	Inflammation		
IL1R2	Interleukin 1 receptor, type II	Inflammation		

IL23R	Interleukin 23 receptor	Inflammation		
IL6	Interleukin 6 (interferon, beta 2)	Inflammation		
IRGM	Immunity-related GTPase family, M	Autophagy		Confer risk of CD
JAK2	Janus kinase 2	Inflammation	AD	
LAMB1	Laminin beta1	Mucosal barrier		Confer risk of UC
MLCK	Myosin light chain kinase 2	Mucosal barrier		
MUC1 ect	Mucin, oligomeric mucus/gel-forming	Mucosal barrier		
NEMO (IKBKG)	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma	Inflammation, apoptosis		
NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells	Inflammation		
NKX2-3	*NK2* transcription factor related, locus 3 (Drosophila)	Development, immune		
NOD1 (CARD4)	Nucleotide-binding oligomerization domain containing 1	Inflammation		
NOD2 (CARD15)	Nucleotide-binding oligomerization domain containing 2	Autophagy, immune	AD	Confer risk of CD
ORMDL3	Orosomucoid (ORM1)-like 3 (S. cerevisiae)	Ceramid metabolic, endoplasmic reticulum		
PRDM1	PR domain containing 1, with ZNF domain	Inflammation		
PSMG1	Proteasome (prosome, macropain) assembly chaperone 1	Proteosome assembly, endoplastic reticulum		
PTGER4	Prostaglandin E receptor 4	Inflammation		
PTPN2	Protein tyrosine phosphatase, non-receptor type 2	Inflammation		
PTPN22	Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)	Immune	AD	
REL	v-rel reticuloendotheliosis viral oncogene homolog (avian)	Inflammation		
SMAD3	Mothers against decapentaplegic, drosophila, homolog of, 3	Cell cycle, cell-cell junction		
SOCS3	Suppressor of cytokine signaling 3	Inflammation		

STAT3	Signal transducer and activator of transcription 3 (acute-phase response factor)	Inflammation	AD
STAT4	Signal transducer and activator of transcription 4	Inflammation	
TNFRSF1B	Tumor necrosis factor receptor superfamily, member 1B	Inflammation	
TNFRSF6B	Tumor necrosis factor receptor superfamily, member 6B	Inflammation	
TNFSF15	Tumor necrosis factor (ligand) superfamily, member 15	Inflammation	
TYK2	Tyrosine kinase 2	Immune	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CD, Crohn's disease; UC, ulcerative colitis

Immunomodulators are used for long-term treatment in some patients with CD or UC. Clinical study on a pediatric IBD cohort indicated that a significant portion of CD (47.1%) and UC (30.2%) patients are using immunomodulators [64]. According to Crohn's and Colitis Foundation of America (CCFA), this type of medication can be applied when patients do not respond to aminosalicylates, antibiotics, or corticosteroids; have steroid-dependent disease or frequently require steroids; have experienced side effects with corticosteroid treatment; have perianal disease that does not respond to antibiotics; have fistulas or need to maintain remission. Most commonly used immunomodulators are azathioprine (AZT), 6-mercaptopurine (6-MP), methotrexate (MTX) and cyclosporine. AZT and 6-MP have slow onset of actions. These medications are well tolerated during long-term therapy although complications of reversible pancreatitis and bone marrow suppression may occur in some patients [65-66]. Thiopurine S-methyltransferase (TPMT) metabolize thiopurine drugs-AZT and 6-MP. Pharmacogenetic studies indicated that polymorphisms in the TPMT gene play a significant role in the occurrence of various side effects of thiopurine drugs [67-68]. Low TPMT activity will direct thiopurine metabolism to alternative pathway and the product of the drugs could inhibit bone marrow. It is suggested that TPMT activity should be determined in all patients prior to initiating treatment with thiopurine to minimize the risk of myelotoxicity [69]. MTX became standard therapy for autoimmune diseases because of anti-inflammation activity. It is demonstrated that weekly injection of MTX had significant corticosteroid-sparing effects in CD patients [70]. Side effects such as hepatic, bone marrow and pulmonary toxicity necessitate careful monitoring. The G2677T variant in the multi-drug resistance-1 (MDR1) gene predicted gastrointestinal and unspecified intolerance to azathioprine and methotrexate in IBD patients [71-72]. Cyclosporine is a more potent immunosuppressive drug for the treatment of acute, severe UC or refractory CD [73-74]. Renal dysfunction, neural toxicity and opportunistic infections are side effects that hamper its usage [75]. Immunomodulators weaken or modulate the activity of the immune system. They may be appropriate or more beneficial for treating IBD patients who have genetic mutations that cause overactive immune response. Transforming growth factor (TGF)-β1 inhibits T-cell proliferation and differentiation and reduces macrophage activation and dendritic-cell maturation [76]. In patients with CD, TGF-β intracellular signaling is blocked by high levels of the mothers against decapentaplegic, drosophila homologue of 7 (SMAD7) protein [76]. An oral SMAD7 antisense oligonucleotide called mongersen was developed and had significantly higher rates of remission (72%) in participants with CD who received 160mg of the reagent than those who received placebo (17%) ($P<0.001$) in phase 2 clinical trial. This indicated that mongersen has promising efficacy in treating CD [77].

Biologic therapies, which target specific disease mechanisms, have been proved to be more effective in some IBD patients. It is reported that biologics treatment has been used on 36.4% pediatric patients with CD and 9.3% pediatric patients with UC [63]. Anti- tumor necrosis factor (TNF)-α biological compound can be applied on CD patients because these subjects may have elevated TNF in the mucosa [78]. Anti-p40 monoclonal antibodies have been reported to be effective in CD as p40 is common to both interleukin-23 and interleukin-12 pathways [79]. Nineteen functional SNPs in fourteen genes that alter the NFκB-mediated inflammation response are genetic markers

that could predict individual response to anti-TNF therapy among patients with CD, UC or both CD and UC [80]. There are many other treatments under investigations such as anti-interferon γ (Fontolizumab), infusion of interleukin-10–producing T cells and the administration of interleukin-10–producing bacteria [81-84]. Serious side effects could occur in patients treated with biologics [83]. Increased risk of infection or malignant disorders should be monitored [85-86].

Many treatment options exist for IBD patients. However, medication study is hampered by the absence of well-defined end points of disease activity. Improvement in disease monitoring and therapy will depend on the development of a more refined and integrated understanding of the disease mechanisms. Genetic study will be valuable for the determination of etiology for individual subject so that specific treatment regimen can be applied to improve efficacy of medications.

Conclusions

The understanding of IBD genetics has been advanced by identifying a number of susceptibility gene/loci with the NOD2 gene being the most replicated and understood at present. Further investigation of genetics in IBD will improve understanding of the clinical heterogeneity of the disease. Application of high throughput sequencing will reveal novel genes associated with IBD which can help to stratify disease subtypes, assist diagnosis and improve efficacy of treatment. The integration of clinical presentations, endoscopic examinations, pathology, serology and genetic factors will be essential for genotype-phenotype correlations and to achieve the ultimate goal of better health care for IBD patients. Patients with longstanding IBD, especially patients with UC, may develop colorectal cancer. Genes regulate dysplasia or adhesion may be involved in carcinogenesis. In combination with colonoscopy and biopsy, genetic testing could provide additional information for diagnosis, treatment and cancer surveillance strategy for patients with longstanding IBD.

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