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doi:10.3748/wjg.15.788

World J Gastroenterol 2009 February 21; 15(7): 788-803
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Epidemiology and gene markers of ulcerative colitis in the Chinese

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Author contributions: Yun J, Xu CT and Pan BR collected data for retrospective audit; Xu CT collected and wrote the paper; Yun J and Xu CT revised the paper.
Supported by The Science Foundation of Health Bureau of Shaanxi Province, China, No. 04D26
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Received: December 4, 2008 Revised: December 25, 2008
Accepted: January 2, 2009
Published online: February 21, 2009

Abstract

Inflammatory bowel disease (IBD) includes two similar yet distinct conditions called ulcerative colitis (UC) and Crohn's disease (CD). These diseases affect the digestive system and cause the inflammation of intestinal tissue, form sores and bleed easily. Most children with IBD are diagnosed in late childhood and adolescence. However, both UC and CD have been reported as early as in infancy. Most information pertaining to the epidemiology of IBD is based upon adult studies. Symptoms include abdominal pain, cramping, fatigue and diarrhea. Genetic factors play a significant role in determining IBD susceptibility. Epidemiological data support a genetic contribution to the pathogenesis of IBD. Recently, numerous new genes have been identified as being involved in the genetic susceptibility to IBD: *TNF-308A*, *CARD15* (*NOD2*), *MIF-173*, N-acetyltransferase 2 (*NAT2*), *NKG2D* (natural killer cell 2D), *STAT6* (signal transducer and activator of transcription 6), *CTLA-4* (cytotoxic T lymphocyte antigen-4), *MICA-MICB* (major histocompatibility complex A and B), *HLA-DRB1*, *HLA class-Ⅱ*, *IL-18*, *IL-4*, *MICA-A5*, *CD14*, *TLR4*, *Fas-670*, *p53* and *NF-κB*. The characterization of these novel genes has the potential to identify therapeutic agents and aid clinical assessment of phenotype and prognosis in patients with IBD (UC and CD).

Key words: Genetic; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Epidemiology; Susceptibility; Gene

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Yun J, Xu CT, Pan BR. Epidemiology and gene markers of ulcerative colitis in the Chinese. *World J Gastroenterol* 2009; 15(7): 788-803 Available from: URL: http://www.wjgnet.com/1007-9327/15/788.asp DOI: http://dx.doi.org/10.3748/wjg.15.788

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the two primary types of inflammatory bowel disease (IBD). These two diseases have many similarities and sometimes are difficult to distinguish from each other. However, there are several differences. UC is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders. Inflammation usually occurs in the rectum and lower part of the colon, but it may affect the entire colon. UC rarely affects the small intestine except for the end section, called the terminal ileum. UC may also be called colitis or proctitis. Inflammation frequently makes the colon empty, causing diarrhea. Ulcers formed in places where the inflammation has killed the colon cells cause, bleeding and pus discharge. UC is an IBD that causes inflammation in the small intestine and colon. UC is difficult to diagnose because its symptoms are similar to other intestinal disorders and another type of IBD called CD. CD differs from UC because it causes deeper inflammation within the intestinal wall. CD usually occurs in the small intestine, although it can also occur in the mouth, esophagus, stomach, duodenum, large intestine, appendix, and anus. UC may occur in people of any age, but most often it starts between the ages of 15 and 30 years, or less frequently between 50 and 70. Children and adolescents sometimes develop the disease. UC affects men and women equally and appears to occur in some families. Clinical and epidemiological data do not support a simple Mendelian model of inheritance for IBD. CD and UC are considered to be complex

polygenic diseases. UC is a chronic disease in which the large intestine becomes inflamed and ulcerated (pitted or eroded), leading to flare-ups (bouts or attacks) of bloody diarrhea, abdominal cramps, and fever. The long-term risk of colon cancer is increased[1-3].

To make a diagnosis of IBD, physicians must first exclude other possible causes of inflammation. For example, infection with parasites or bacteria may also cause inflammation. Therefore, several tests should be performed. Stool samples are analyzed for evidence of a bacterial or parasitic infection (e.g. acquired during travel), including a type of bacterial infection (*Clostridium difficile* infection) that can result from antibiotic use, and sexually transmitted diseases of the rectum, such as gonorrhea, herpes virus infection, and chlamydia infection. Tissue samples (biopsies) may be taken from the lining of the rectum during sigmoidoscopy (an examination of the sigmoid colon using a viewing tube) and examined microscopically for evidence of other causes of colon inflammation (colitis). Other possible causes of similar abdominal symptoms that should be excluded are ischemic colitis, which occurs more often in people older than 50 years; certain gynecological disorders; celiac disease; and irritable bowel syndrome[1].

In traditional Chinese medicine (TCM), UC is a systemic disease that affects many parts of the body, although patients mainly manifest with intestinal symptoms. In TCM principles, the problem is closely associated with organ dysfunction, in particular the *pi* (spleen), that causes a failure to self-regulate the intestinal environment. TCM specialists generally agree that constitutional weakness, invasion of exogenous pathogens, an unbalanced diet and emotional factors all contribute to the development of the problem.

Genetic changes of patients with UC have been demonstrated. What are the changes in Chinese UC patients? There are gene diversification analyses of Chinese patients with UC in the recent literature.

ETIOLOGY AND EPIDEMIOLOGY

Etiology

The etiology of UC is unknown. The consensus is, so far, that it is a response to environmental triggers (infection, drugs or other agents) in genetically susceptible individuals. The genetic component is not as strong in UC as in CD. However, 10%-20% of patients with UC have at least one family member with IBD[1,2]. There are marked differences between ethnic groups and some (such as Ashkenazi Jews) have a particularly high incidence. Non-steroidal anti-inflammatory drugs may cause an episode of acute active disease in some patients with IBD. UC primarily affects young adults, but it can occur at any age from 5 to 80 years and women tend to be more commonly affected than men. It is a worldwide disorder, and the high-incidence areas include the United Kingdom, the United States, northern Europe and Australia. Low-incidence areas include Asia, Japan, and South America. The causes of UC remain unknown. The major theories are associated with infection, allergy to food component, genetics, environmental factors, and immune response to bacteria or other antigens[1].

Typical symptoms during flare-ups include abdominal cramps, an urge to move the bowels, and diarrhea (typically bloody). The diagnosis is based on an examination of the sigmoid colon using a flexible viewing tube (sigmoidoscopy) or an examination of the large intestine using a flexible viewing tube (colonoscopy). People who have had UC for a long time may develop colon cancer. Treatment is aimed at controlling the inflammation, reducing symptoms, and replacing any lost fluids and nutrients. UC may start at any age but usually begins between the ages of 15 and 30 years. A small group of people have their first attack between the ages of 50 and 70 years. UC usually does not affect the full thickness of the wall of the large intestine and hardly ever affects the small intestine. The disease usually begins in the rectum or the rectum and the sigmoid colon (the lower end of the large intestine) but may eventually spread along part or all of the large intestine. UC, which is confined to the rectum, is a very common and relatively benign form. In some people, most of the large intestine is affected early.

Epidemiology

UC affects about one in 1000 people in the Western world. Peak incidence is between the ages of 10 and 40 years. UC may affect people of any age and 15% of people are over the age of 60 years at diagnosis[1-4]. The incidence of UC in North America is 10-12 cases per 100 000, with a peak incidence of UC occurring between the ages of 15 and 25 years. There is thought to be a bimodal distribution in age of onset, with a second peak in incidence occurring in the sixth decade of life. The disease affects females more than males, with highest incidences in the United States, Canada, the United Kingdom, and Scandinavia. Higher incidences are seen in the northern parts compared to the south in Europe and the United States.

Rising incidence and prevalence of UC have been observed in Asian countries. Lok *et al*[2] conducted a study in an Asian center, aiming to describe the epidemiology and clinical characteristics of UC in the local Chinese population. This is a retrospective analysis of patients with diagnosis of UC in our hospital from June 1990 to December 2006. The diagnosis of UC has to satisfy the internationally accepted criteria. All patients were Chinese residents in a well-defined catchments' area. Clinical and epidemiological data were obtained from medical records and patient interviews. Seventy-three Chinese UC patients were managed in hospital. The hospital-based prevalence has risen by three times over a 10-year period, but no definite rising incidence can be demonstrated. The mean age at diagnosis was 40.6 years and the median duration of disease was 72 mo. In the patient cohort, 38.4% had ulcerative proctitis and 26% had left-sided UC, whereas 35.6% had extensive UC at presentation. The majority presented with mild (39.7%) or moderate (30.2%) disease activity, but 27.4% presented with severe disease. One of the two patients (2.7%) with fulminant disease developed

toxic megacolon. Extra-gastrointestinal manifestations occurred in 13.7%. During the follow-up period, most patients (86.3%) were in disease remission. Four patients (5.5%) underwent colectomy, four (5.5%) died, and two (2.7%) were lost to follow-up. The prevalence but not the incidence of UC is rising in the Chinese population. It usually affects young patients and a substantial proportion of patients presented with severe and fulminant disease. The disease activity of most Chinese patients can be controlled with medical treatment, though a small proportion of patients need surgery or have a fatal outcome[2-4].

Jin *et al*[3] explored the indications for colonoscopic examination and the distribution of diagnostic diseases. From January 2000 to December 2004, 5960 patients received colonoscopic examination in a colorectal center. The indications for colonoscopic examination and the distribution of its diagnostic diseases were analyzed. There were 3096 males and 2594 females, and the mean age was 52 ± 15 years. The reasons for colonoscopy included hemafecia (26.9%), atypical abdominal pain (25.8%), diarrhea or increased frequency of stools (11.1%), anal tenesmus or discomfort (7.6%), constipation (7.0%), mucous or bloody purulent stools (3.0%), intra-rectal mass or abdominal mass on physical examination (0.9%), re-examination after colonoscopic polypectomy (10.9%), re-examination after operation for colorectal cancer (1.5%), and simple health examination (2.2%). Colonoscopy reached the cecum in 97.7% of the cases, and at least one disease was found in 2283 cases (40.1%). Among them, colorectal cancer accounted for 10.3%, colorectal polyps 19.6%, UC 4.3%, and CD 0.5%. The indications for colonoscopy are too strict to screen for early stage colorectal cancer. Colonoscopy should be performed in patients with symptoms such as bloody stools, diarrhea, abdominal pain, constipation, or with colorectal polyps, after operation for colorectal cancer, or as members of a hereditary colorectal cancer family[3]. Cigarette smoking, alcohol use, appendectomy, and family history of IBD have all been shown to be associated with IBD, but there was no report of risk factors for IBD in a Chinese population, in which the incidence of IBD has increased during the past decade. Jiang *et al*[4] conducted a case-control study to examine associations between previously reported environmental risk factors and development of UC in Wuhan city, central China. A total of 177 patients with UC and 177 age-matched and sex-matched controls were prospectively studied in Wuhan city from January 2004 to December 2004. An age-matched and sex-matched case-control study was conducted to assess the role of smoking, alcohol use, appendectomy, and other potential risk factors in the development of UC, by a detailed questionnaire. Smoking was a protective factor and ex-smoking is a risk factor for UC (compared with non-smokers, smokers: $P = 0.0001$; ex-smokers: $P = 0.008$). Positive family history of IBD was a risk factor ($P = 0.025$), whereas appendectomy was a protective factor ($P = 0.028$) for UC. There were no significant associations between UC and other factors examined. Although the incidence of UC in Chinese is relatively lower than that in whites, the same risk factors for UC that were reported in white populations were associated with Chinese UC patients. Specifically, smoking was a protective factor for UC and ex-smoking was associated with an increase risk of UC in a Chinese population. Family history of IBD was shown to be a risk for UC, whereas appendectomy was associated with a low risk for UC[2,4].

Investigative papers about IBD in Chinese medical journals from 1989 to 2003 were reviewed to understand the progress of basic IBD research in China, by Bai *et al*[5]. The basic science investigative papers about IBD from 1989 to 2003 in Chinese periodicals (VIP and CMCC) were reviewed and analyzed; the key words used were as follows: IBD, UC, CD, basic science investigation, and literature review. There were 3454 articles about IBD published in Chinese medical journals from 1989 to 2003, and during these 15 years, 508 papers focused on basic scientific investigations. There were 463 papers investigating the pathogenesis of IBD, 287 papers on immunological mechanisms, and 176 papers about other mechanisms. There were 142 papers investigating the mechanisms of TCM in IBD from 1989 to 2003, which included 117 papers related to animal experiments and 25 papers related to clinical studies. There have been relatively few investigative scientific papers on IBD published in Chinese medical journals. However, the study of IBD has been emphasized in China. Research on the immunological mechanisms of IBD has been predominant. Furthermore, a large number of the research papers are about the mechanisms and effects of TCM in IBD.

IBD had been uncommon in China until about 1990, but since then, more and more cases have been seen in clinical settings. The prevalence and phenotype of IBD in the Chinese population is not well known. One study investigated the trend in prevalence of UC and CD in Wuhan city, central China, and evaluated the clinical features, extraintestinal manifestations, and the treatment of IBD in the last 14 years. Three hundred and eighty-nine patients with UC and 63 with CD were retrospectively collected from five central hospitals in Wuhan city, in which high-quality endoscopic and histological diagnoses were available from 1990 to 2003. UC and CD were diagnosed based on clinical, laboratory, radiological, endoscopic and histological examinations according to the internationally accepted Lennard-Jones criteria. The trend toward prevalence of UC and CD increased between 1990 and 2003 in Wuhan city. There was no change in the sex and age distribution comparing the two periods of 1990-1996 and 1997-2003, both in UC and CD. However, the number of individuals with higher education and a professional occupation from 1997 to 2003 was significantly higher than that during the period from 1990 to 1996 in patients with UC ($P \leqslant 0.004$). The mean age of patients with CD was significantly younger than that of UC at the time of diagnosis ($P < 0.0001$). The ratio of male to female patients was 1.53:1 in UC and 2.32:1 in CD, respectively.

The mean duration of onset of the disease to diagnosis was 1.4 years in UC and 1.1 years in CD. The extra-intestinal manifestations of UC and CD were 5.7% and 19%, and complications of UC and CD were 6.4% and 50.8%, respectively. Only 3% of UC patients required surgery, whereas 27% of CD patients underwent surgical procedures ($P < 0.001$). The prevalence of IBD has increased in Wuhan city, central China, but is not as high as in Western countries. The disease in Wuhan city has often been associated with young adult professional males with a high level of education. The clinical presentation of UC was often mild and had few extra-intestinal manifestations[4-6].

GENE MARKERS OF ULCERATIVE COLITIS IN THE CHINESE

Genetic factors play a significant role in determining IBD susceptibility. Many genes play a vital role in the development of IBD, including *TNF-308A*, *CARD15 (NOD2)*, *MIF-173*, *N-acetyltransferase 2 (NAT2)*, *NKG2D (natural killer cell 2D)*, *STAT6 (signal transducer and activator of transcription 6)*, *CTLA-4 (cytotoxic T lymphocyte antigen-4)*, *MICA-MICB (major histocompatibility complex A and B)*, *HLA-DRB1*, *HLA class-Ⅱ*, *IL-18* (*interleukin-18*), *IL-4*, *MICA-A5*, *CD14*, *TLR4*, *Fas-670*, *p53* and *NF-κB*.

TNF-308A

Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine that plays an important role in mediating inflammation and has been implicated in the pathogenesis of IBD. The regulation of TNF expression is genetically determined. The TNF gene lies on the short arm of chromosome 6 (6p21), 250 kb from the center of human leucocyte antigen-B (HLA-B), between HLA-B and DR, and within HLA Ⅱ. Recent studies have evaluated the role of TNF promoter polymorphisms in IBD but data are inconsistent. To date, few studies have reported the association of TNF promoter polymorphisms with susceptibility to UC in the Chinese Han ethnic population. Trans-racial mapping in an ethnically distinct but homogenous population may help clarify these associations. There is an association between TNF promoter polymorphisms and the susceptibility to UC in the Chinese Han ethnic population by genotyping for 6 common TNF promoter polymorphisms[6-9].

In a large sample study, a strong association between UC patients and the TNF-308A polymorphism was found in Japanese subjects[7]. No conclusive data on this association in European patients exist, however. This may reflect that the associations of TNF promoter polymorphisms with susceptibility to UC do vary among ethnic groups. Some scientists have supposed that TNF polymorphism is increased in IBD patients, even more than NOD2, and plays a more important role in the Asian population. IBD in the Asian population has unique epidemiological and clinical characteristics. For example, UC has a higher morbidity than CD in Asia. In an eastern China hospital between 1994 and 2003, 379 patients were diagnosed to have IBD. Of 379 patients, 317 had UC (83.6%) and this study shows similar characteristics of IBD to that in the West. However, there are some differences with respect to low severity and less extra-intestinal manifestations[8]. The ethnic and geographic differences may give important clues to the etiology of IBD. In the final analysis, genetic background plays a key role. To date, few studies have reported the association of TNF promoter polymorphisms with susceptibility to UC in the Chinese Han ethnic population. A number of studies have reported a high population attributed risk percentage of TNF promoter single nucleotide polymorphisms (SNPs), which reflects the higher mutant-type frequency in UC.

The importance of TNFα and the TNF receptor gene polymorphisms in the etiopathogenesis of IBD has not been elucidated. DNA from peripheral blood samples was obtained from 124 patients with CD, 106 patients with UC, and 111 unrelated healthy controls. Two SNPs of the *TNFα* gene, TNF (-308 G/A and -238 G/A), an SNP of the TNF receptor superfamily member 1A gene, TNFRSF1A (also known as TNFR1), at codon 12 in exon 1 (CCA/CCG), and two SNPs of the 1B gene, TNFRSF1B (also known as TNFR2), (1466 A/G and 1493 C/T) were examined. There was a difference in the carrier frequency for haplotype AG (-308 A, -238 G) between UC patients and the controls ($P < 0.01$). There was also a significant difference in carrier frequency for haplotype AT (1466 A, 1493 T) of the *TNFRSF1B* gene between CD patients and the controls ($P < 0.01$), and in those who were poor responders to treatment, which consisted of nutritional therapy, medical therapy and surgical therapy ($P < 0.001$). The authors suggest that one of the genes responsible for UC may be the *TNF* gene, or an adjacent gene, and that *TNFRSF1B* gene polymorphisms contribute greatly to the increased onset risk of CD and to the disease behavior[7].

Numerous studies from Europe and North America have provided a wealth of information regarding the epidemiological and clinical characteristics of IBD in Caucasians. Previous studies in mainland China have been limited by small patient numbers or by lack of detailed information about clinical subgroups of the disease. Cao *et al*[8] have assessed the demographic and clinical characteristics of IBD in Chinese patients. In the Sir Run Shaw Hospital between 1994 and 2003, 379 patients were diagnosed as having IBD. Demographic and clinical data were collected and analyzed. Of 379 patients, 317 had UC (83.6%, 168 male, 149 female, a male:female ratio of 1.13:1, age range at diagnosis 14-79 years, mean age 44 years) and 62 had CD (16.4%, 39 male and 23 female, a male:female ratio of 1.70:1, age range at diagnosis 13-70 years, mean age 33 years). In UC, 11.4% of patients had proctitis, 25.2% had proctosigmoiditis, 18.6% had disease in the splenic flexure and 44.8% had extensive colitis. Nine patients with UC (2.8%) had arthritis, and three (0.9%) had iritis or conjunctivitis. Of the 62 CD patients, 16 (25.8%) had diseases restricted to the terminal ileum, 15 (24.2%) had colonic diseases,

20 (32.3%) had ileocolonic disease and 11 (17.7%) had disease involving the upper gastrointestinal tract. This study showed similar characteristics of IBD to that in the West, but there are some differences with respect to severity and extra-intestinal manifestations. The ethnic and geographic differences may give important clues to the etiology of IBD[8].

Cao *et al*[9] reported the association with TNF-308A polymorphisms in Chinese patients with UC, suggesting that *TNF* gene may be a susceptibility gene for UC. The production of TNFα is elevated in TNF-308A carriers, resulting in excessive inflammation and onset of UC. The clinical application is to apply this new genetic information in the clinical setting to allow more rational therapies, selecting effective therapies (e.g. anti-TNF antibody) for refractory patients with UC, based on the genetic background. Further studies will be required to determine the functional effects of TNF-308A. Hereafter, authors can study gene knock-out mice, estimate the expression of TNFα in mutant cells using Northern and Western blotting, and investigate TNFα secretion by mutant-type cells after stimulation with LPS, compared with wide-type. We can also carry out a cohort study on correlation of TNFα expression level with *TNF-308A* genes and efficacy of anti-TNF antibody in UC patients based on the genetic background, in order to ascertain whether TNF-308A is responsible for UC[9].

Recent studies have evaluated the role of TNF promoter polymorphisms in IBD, but the data are inconsistent. Trans-racial mapping in an ethnically distinct but homogenous population may help clarify these associations. Cao *et al*[9] investigated the association between TNF promoter polymorphisms and susceptibility to UC in the Chinese Han ethnic population. They studied 110 unrelated UC patients and 292 healthy controls from Zhejiang Province, China. Genotyping for six common TNF promoter polymorphisms (TNF -1031T/C, -863C/A, -857C/T, -380G/A, -308G/A, -238G/A) was carried out by polymerase chain reaction sequence-specific primers (PCR-SSP). TNF -857T was increased in patients but without statistical significance ($P = 0.06$). Haplotype analysis revealed six haplotypes including two (H5 and H3), which contained TNF-308A. Of note, the rare haplotype H3 has not previously been identified in Caucasian populations. Homozygosis for the haplotype H4 comprising the common alleles at each TNF promoter single-nucleotide polymorphism (SNP) was negatively associated with disease ($P < 0.05$). The association with TNF-308A polymorphisms in Chinese patients with UC was reported by Cao *et al*[9]. The functional study in Chinese Han ethnic population is now required.

Progressive venous stenosis mediated, in part, by inflammatory cytokines is a major cause of synthetic hemodialysis graft failure. A TNFα gene polymorphism (G to A, position -308) has been shown to increase plasma cytokine levels and severity of diseases with an underlying inflammatory component. The TNFα-308 G/A and the TNFβ NcO1 polymorphisms have both been described to be associated with survival in sepsis or septic shock of various origins. That the TNFB2/TNFB2 genotype of the TNF-β NcO1 polymorphism is significantly associated with an increased risk for development of severe sepsis in severely injured blunt trauma patients was recently reported[9]. Up to now, neither functional consequences associated with these polymorphisms in inflammation nor the relationship of the TNFα -308 G/A polymorphism to the development of severe sepsis and its significance compared with the TNFβ NcO1 polymorphism have been determined for trauma patients.

The TNFα-308 allele may be related to susceptibility to UC. The *TNFα-308* gene polymorphism is not involved in pathogenesis of CD. No correlation was found between the TNFβ+252 polymorphism and IBD. Polymorphisms of the TNFα-308 and TNFβ+252 loci do not correlate with age, gender, disease activity or lesion site[8-10]. PCR and restriction fragment length polymorphism (RFLP) techniques were used to analyze gene polymorphisms in the *TNFα* and *TNFβ* genes in 131 patients with IBD[10]. The genotype frequency and allelic frequency of TNFα-308 in patients with UC were 15.5% and 8.7%, respectively, significantly higher than the control population ($P < 0.001$). There was no significant difference between patients with CD and the normal population with regard to the genotype frequency and allelic frequency of TNFα-308, and neither were there any differences with regard to TNFβ+252 in patients with IBD (UC and CD) and the normal population. The TNFα-308 polymorphism and the TNFβ+252 loci did not correlate with age, gender, disease activity or lesion site for IBD patients.

CARD15 (NOD2)

A lot of research has been undertaken on the genetic susceptibility of IBD. Genome-wide linkage studies focused on more than 10 chromosomal regions and fine-mapping of these regions have identified a number of genes, including *CARD15 (NOD2)*, *DLG5*, *OCTN1* and *2*, *TLR4* and *CARD4 (NOD1)*. With the recent completion of the human genome project, whole genome association studies (WGAS) have become possible and additional genes (*IL23R, IRGM, PTGER4, ATG16L1*) for CD and UC have been identified. At present, the *CARD15* gene is still the best understood susceptibility gene, explaining around 20% of the genetic predisposition to CD. Prediction of disease phenotype and response to the main therapies has for many years been a goal for physicians treating IBD patients. We now can accumulate some evidence, proving that genetic factors indeed influence both the clinical course of IBD patients and their likelihood of responding to certain therapies. Henckaerts *et al*[11] expected an exponential increase in the efforts devoted to research in this area. The optimal prediction of both disease behavior and response to therapy might result from combinations of clinical, biochemical, serological and genetic factors.

An insertion mutation at nucleotide 3020 (3020insC) in the caspase recruitment domain gene (*CARD15*),

originally reported as NOD2, is strongly associated with CD. The C-insertion mutation at nucleotide 3020 (3020inC) in the leucine-rich repeat (LRR) region results in a frameshift in the tenth LRR followed by a premature stop codon. This truncation mutation is responsible for the inability to activate nuclear factor (NF)-κB in response to bacterial lipopolysaccharide (LPS). The authors aimed to genotype *NOD2/CARD15* gene 3020insC frameshift mutation in Chinese patients with IBD. Guo *et al*[12] genotyped an insertion polymorphism affecting the leucine-rich region of the protein product by the allele-specific PCR in 74 unrelated patients with UC of Han nationality in Hubei Province of China, 15 patients with CD, and 172 healthy individuals. No significant differences were found in the genotype and allele frequencies of the C-insertion mutation of *NOD2* gene among patients with CD and UC and healthy controls. *NOD2* gene 3020insC frame-shift mutation is not a major contributor to the susceptibility to both UC and CD in Chinese Han patients[12].

The SNPs distribution of NOD2/CARD15 (R702W, G908R), OCTN1 1672C/T and OCTN2-207G/C in Chinese patients with IBD was investigated[13]. A total of 151 patients with UC, 61 patients with CD and 200 unrelated healthy controls were genotyped. Genotyping was performed by PCR-SSP or by RFLP analysis. Among the subjects in their study groups, including patients with CD, UC and healthy controls, none had OCTN and CARD15 variants, and very rarely, an IBD family history was found in their patients with the percentage of 0 (0/61 CD) and 1.3% (2/151 UC). The results indicate that although OCTN or CARD15 variation is associated with susceptibility to IBD in Western populations, these might be rare and may not be associated with susceptibility to IBD in Chinese patients[13].

The common variants in NOD2/CARD15 found in Caucasians with CD are not associated with CD in the Chinese Han population[14]. The three previously described SNPs associated with the development of CD in Caucasians are not found in Chinese patients with CD. None of the patients with CD had heterozygous or homozygous SNP variants. Similarly, none of the UC or dyspeptic controls had these SNPs[15].

Nucleotide oligomerization domain (NOD2) and human leukocyte antigen (*HLA*) genes are the most extensively studied genetic regions (IBD1 and IBD3 respectively) in IBD. Mutations of the *NOD2* gene are associated with CD and several *HLA* genes are associated with UC and CD. Toll like receptors (TLRs) play an important role in the innate immune response against infections by mediating recognition of pathogen-associated microbial patterns. Studying SNPs in molecules involved in bacterial recognition seems to be essential to define genetic backgrounds at risk of IBD. Recently, numerous new genes have been identified to be involved in the genetic susceptibility to IBD, such as NOD1/caspase-activation recruitment domains 4 (CARD4), chemokine ligand 20 (CCL20), IL-11, and IL-18. The characterization of these novel genes will lead to the identification of therapeutic agents and clinical assessment of phenotype and prognosis in patients with IBD[16].

MIF-173 gene

The etiology and pathogenesis of IBD is still unclear, but it has become evident that immune and genetic factors are involved in the process of IBD. Some cytokine gene polymorphisms such as TNFα, IL-1β and IL-1RA are known to be commonly associated with IBD. Macrophage migration inhibitory factor (MIF) is an important pro-inflammatory cytokine and plays a critical role in immune and inflammatory responses. MIF is implicated in a large number of immune and inflammatory diseases, including asthma, chronic hepatitis B, allergic neuritis and rheumatoid arthritis. Plasma MIF was reported elevated in patients with UC or CD compared with healthy controls. Anti-MIF antibodies reduced the severity of experimental colitis and limited the up-regulation of Th1-type cytokines. Anti-MIF antibodies are therefore of a potential therapeutic use in IBD. In the T lymphoblast cell line, the reverse situation was found with the MIF-173*C, significantly increasing the MIF expression under basal conditions. These differences in expression are likely to be due to differences in transcription factor interaction with the MIF-173 element. AP-4 transcription factor is a particular candidate[1,17] based on the promoter sequence analysis.

MIF-173 SNP was genotyped by tetra-primer amplification refractory mutation system (ARMS) and RFLP-PCR was also performed in 142 healthy subjects and 98 patients with IBD[17]. There were no discrepancies between the results obtained by tetra-primer ARMS and RFLP-PCR. The frequency of MIF-173 CC genotype was significantly higher in patients with UC (15.5%) than in healthy individuals (5.6%, $P = 0.018$). There was a trend towards a higher frequency of CC genotype among CD patients compared with healthy controls, however, this did not attain statistical significance ($P = 0.245$). MIF-173 CC genotype may be associated with susceptibility to UC. The results showed that the frequency of MIF-173 CC genotype was significantly higher in patients with UC than in healthy individuals. It suggested that MIF-173 CC genotype could be associated with susceptibility to UC. However CC genotype was not related to clinical features in patients with UC in Chinese Han population[17].

NAT2

Polymorphisms of NAT2 (N-acetyltransferase 2) acetylation may influence drug toxicity and efficacy and are associated with differential susceptibility to cancer. Acetylation phenotype may have clinical implications. NAT 2 is an enzyme that catalyzes the acetylation of harmful arylamines and has been implicated in various types of cancer. NAT 2 is primarily expressed in the hepatic system and intestinal epithelium, and is encoded at two polymorphic loci that give the phenotypic characteristics of slow and fast acetylation[18].

Arylamine NATs are xenobiotic-metabolizing enzymes responsible for the acetylation of many aromatic arylamine and heterocyclic amines, thereby playing an important role in both detoxification and activation of numerous drugs and carcinogens. Two closely related isoforms (NAT1 and NAT2) have been described in humans. NAT2 is mainly expressed in liver and gut, whereas NAT1 is found in a wide range of tissues. Inter-individual variations in NAT genes have been shown to be a potential source of pharmacological and/or pathological susceptibility. In addition, there is evidence that non-genetic factors, such as substrate-dependent inhibition, drug interactions or cellular redox conditions may also contribute to NAT activity. The recent findings provided possible mechanisms by which these environmental determinants may affect NAT activity. Interestingly, these data could contribute to the development of selective NAT inhibitors for the treatment of cancer and microbial diseases[18].

The wild type allele (NAT2*4) and three variant alleles (NAT2*5B, NAT2*6A and NAT*7B) of the *NAT2* gene were determined in 101 patients with IBD (84 patients with UC and 17 patients with CD) and 109 healthy controls by the RFLP-PCR method. Sixty-eight patients with IBD treated with SASP were followed up, and their adverse reactions were recorded. Eleven patients (16%) experienced adverse effects from SASP, including nine cases of sulfapyridine (SP) dose-related adverse effects and two cases of hypersensitivity (skin rash). Patients with the slow acetylator genotypes without the NAT2*4 allele experienced adverse effects more frequently (36%) than those with the fast acetylator genotypes with at least one NAT2*4 allele (11%), but the results were not significantly different ($P = 0.051$). However, those with the slow acetylator genotypes experienced more SP dose-related adverse effects than those with the fast acetylator genotypes ($P = 0.019$). The NAT2 gene polymorphism was not associated with susceptibility to IBD in Chinese populations, but the NAT2 slow acetylator genotypes were significantly associated with SP dose-related adverse effects of SASP in the treatment of IBD[19].

NKG2D

NKG2D (natural killer cell 2D) is an important activated cytokine that has been implicated in inflammatory reactions and the immune response. One of the best characterized NK cell receptors is NKG2D, a highly conserved C-type, lectin-like membrane glycoprotein expressed on essentially all NK cells, as well as on γδ-TcR+ T cells and αβ-TcR+ CD8+ T cells, in humans and mice. Recent studies implicating NKG2D in T cell and NK cell-mediated immunity to viruses and tumors, and its potential role in autoimmune diseases and allergenic bone marrow transplantation have been reviewed. NKG2D is a major activation receptor that associates with novel activation motif with DAP10 or ITAM containing KARAP/DAP12 adaptor molecules. A fundamental question is whether NK cell activation initiated *via* the H60-NKG2D interaction overrides the negative inhibition generated by the engagement of MHC class I to Ly49 receptors. Although an altered balance in the signaling strength of activating and inhibiting pathways of NK cells has been previously postulated. Recent findings illustrate that NK cell activation *via* NKG2D receptor can occur despite the normal expression of MHC class I molecules on the target cells[10-12]. By varying the levels of H60 expression and introducing additional MHC class I molecules on the target cells, Cao *et al*[20] demonstrated that the inhibitory Ly49 receptors can down-regulate NKG2D-mediated NK cell functions.

The function and the location of NKG2D gene show that it is an ideal susceptibility gene for UC. Cao *et al*[20] evaluated the NKG2D gene polymorphisms in patients from Zhejiang Province to determine whether the gene is associated with susceptibility to UC in the Chinese Han population. Blood samples were obtained from 110 patients with UC and 292 healthy controls in Zhejiang. Genotyping for two common NKG2D (10676G/, 908A/) polymorphisms was carried out using polymerase chain sequences with specific primers. NKG2D was not associated with disease (908A allele frequency 19.1% in patients *vs* 16.3% in controls, $P > 0.05$). Neither the patients with UC nor healthy controls had 10676G heterozygous or homozygous variants. The common variants in NKG2D are not associated with UC in the Chinese Han population. Research of larger samples and analysis from different layers and DNA sequences will help determine the function of NKG2D in the process of UC[20].

STAT6

STAT6 (signal transducer and activator of transcription 6) is a human gene. The protein encoded by this gene is a member of the STAT family of transcription factors. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators. This protein plays a central role in exerting IL-4-mediated biological responses. IL-4 and IL-13 share many biological activities. To some extent, this is because they both signal *via* a shared receptor, IL-4Rα. Ligation of IL-4Rα results in activation of STAT6 and insulin receptor substrate (IRS) molecules. In T and B cells, IL-4Rα signaling contributes to cell-mediated and humoral aspects of allergic inflammation. It has recently become clear that IL-4 and IL-13 produced in inflamed tissues activate signaling in normally resident cells of the airway.

The *STAT6* gene is located on chromosome 12q13.3-14.1, just within the IBD2 region and is a key transcription factor involved in IL-4- and IL-13-mediated Th2 response. The G2964A polymorphism in the 3' untranslated region of the *STAT6* gene was studied in 84 unrelated Chinese patients with UC and 176 healthy controls by PCR and the amplification created restriction site method. The results were then compared with those from a Dutch study published previously. Significant

differences in genotype and allele frequencies of the STAT6 G2964A polymorphism were not found between patients with UC and healthy controls. Subgroups of the patients with UC classified according to the age at onset, sex and location of disease did not differ significantly in the distribution of this polymorphism. However, the genotypes ($P < 0.0001$) and allele frequencies ($P < 0.0001$) were significantly different between the Chinese and Dutch populations. The STAT6 G2964A polymorphism is not involved in the genetic susceptibility of Chinese patients to UC[21].

CTLA-4

CTLA-4 (cytotoxic T-lymphocyte antigen 4) is a glycoprotein expressed in activated T cells. CTLA-4 is essentially a costimulatory receptor that controls activation of T cells. In contrast to CD28, CTLA-4 delivers negative signals to T cells. *CTLA-4* gene is located on chromosome 2q33 and three *CTLA-4* gene polymorphisms in exon 1 (adenine or guanine at position) and in promoter -318, and a microsatellite (AT)n marker at position 642 of the 3'-untranslated region of exon 3. Recently, several independent studies reported a reduced inhibitory function of CTLA-4 in individuals with certain CTLA-4 genotypes. CTLA-4 consists of four exons that encode leader peptide, ligand-binding domain, transmembrane domain, and cytoplasmic tail, respectively. In humans, there are two isoforms of CTLA-4, which are a full-length isoform (flCTLA-4 transcript) and a soluble isoform (sCTLA-4 transcript) which lacks exon 3 by alternative splicing. Especially, sCTLA-4 is secreted and circulating in human sera. CTLA-4 is a negative regulator of T-cell proliferation and activation, which plays a critical role in the induction of self-tolerance and mediates antigen-specific apoptosis. Type 1 diabetes is a T-cell mediated autoimmune disease, therefore, its onset is partly associated with deficient expression and function of CTLA-4. Recent findings suggest that programmed cell death may also be involved in the pathogenesis of type 2 diabetes. Furthermore, there is evidence favoring a convergence in signaling pathways toward common effectors of beta-cell apoptosis elicited by stimuli implicated in the pathogenesis of type 1 and type 2 diabetes. If CTLA-4 were involved in this process, its association with type 2 diabetes might be conceivable. A functional role of the CTLA-4 A/G polymorphism, encoding a threonine to alanine change within the signal peptide of CTLA-4, has several possible explanations. It may be in linkage disequilibrium with the (AT)n microsatellite in the 3'-untranslated region and could, therefore, affect RNA stability. Equally, it may be in linkage disequilibrium with other disease-causing mutations[22,23]. However, it is also possible that this signal peptide polymorphism determines a subtle alteration in the subcellular localization of mature CTL A-4 protein, or affects the interaction of the nascent peptide with chaperonins, leading to a functionally important difference in the folding of the mature protein.

Eighty-seven patients with UC and 116 healthy controls were genotyped for CTLA-4 promoter -1722 and -1661 polymorphisms by RFLP-PCR in Hubei Province of central China. The frequency of "A/G + G/G" genotype at the -1661 site was significantly higher in UC patients than in healthy controls ($P = 0.002$). The frequency of the G allele at the -1661 site was also significantly higher in UC patients than in the controls ($P = 0.002$). However, the distribution of the genotypes at the -1722 site was not significantly different between the UC patients and the controls. The G allele of CTLA-4 promoter -1661 polymorphism showed a highly significant association with UC in the Han Chinese of central China[22]. One hundred unrelated Chinese patients with UC and 140 healthy controls were studied. The (AT) repeats in the 3' untranslated region of exon 4 of the CTLA-4 gene were amplified by allele-specific PCR. The amplified products were electrophoresed on a 120 g/L polyacrylamide gel, followed by silver staining. Twenty alleles were found in Chinese patients and healthy controls. The 122-bp allele was increased in UC compared with healthy controls ($P = 0.0001$). The frequency of the longer alleles ($\geqslant$ 118 bp) of UC was higher than that in healthy controls ($P = 0.0001$), but was not associated with location and severity of the disease. Furthermore, the longer alleles were not associated with haplotypes of C-318T/A+49G of the *CTLA-4* gene in Chinese patients with UC. The longer alleles of the *CTLA-4* gene microsatellite polymorphism were strongly associated with UC in Chinese patients[23].

Hou *et al*[24] studied 82 unrelated patients with UC and 204 healthy controls in a Chinese Han population. The frequency of the haplotype 2, 3 (-318C+49G/-318T+49A) was 26% in patients with UC and 41% in healthy controls ($P = 0.0147$), but this significance disappeared when Bonferoni correction was applied. No other significant differences in the distribution of allele and genotype frequencies were observed between *C-318T* and *A+49G* gene polymorphisms in UC of the Chinese Han population. The C-318T and A+49G polymorphisms of the *CTLA-4* gene were not associated with UC in Chinese Han patients[24].

CTLA-4 expressed mainly on activated T cells, inhibits T cell activation by combining B7 through competing CD28 and maintains immune system homeostasis. Polymorphisms in the *CTLA-4* gene are known to be associated with several autoimmune diseases, but no studies have related them to IBD. Sixty-eight unrelated Chinese Han patients with IBD (54 UC and 14 CD) and 140 healthy controls were studied. The (AT)n repeat sequence in the 3' untranslated region of exon 4 was amplified by allele-specific PCR. The amplified products were electrophoresed by 120 g/L polyacrylamide gel, followed by silver staining. Eighteen alleles of CTLA-4 microsatellite were found in Chinese patients and healthy individuals. A long allele of 122 bp was apparently increased in patients with UC compared with healthy controls ($P = 0.0002$). *CTLA-4* gene microsatellite polymorphism was strongly associated with UC in Chinese Han patients in Hubei Province[25].

Xia *et al*[26] studied 139 unrelated patients with UC, 163 patients with CD and 174 healthy controls of Dutch

Caucasian origin, as well as 35 patients with UC and 62 healthy controls from the Chinese Han population. No significant differences in the distribution of allele, genotype and haplotype frequencies were observed between *C-318T* and *A+49G* gene polymorphisms and IBD in Dutch Caucasians and UC in the Chinese Han population. Although the haplotypes of the C-318T and A+49G polymorphisms were distributed differently between Dutch Caucasian and Chinese Han populations, there were no differences in the subgroups of patients with CD classified according to age, localization and behavior in the Vienna classification and in those with UC classified according to age at onset, disease extension and presence of colectomy in the Dutch patients. However, the CTLA4-318 genotype CC was more frequent in patients with CD over 40 years of age (93%) than in younger patients (74%, $P = 0.045$). *C-318T* and *A+49G CTLA4* gene polymorphisms and their haplotypes are not associated with IBD in Dutch Caucasian patients and with UC in Chinese patients[26]. CTLA-4 polymorphism is not associated with UC in the Iranian population[27].

MICA-MICB

The 6D4 monoclonal antibody reacts with the human major histocompatibility complex (MHC) class I -related molecules A and B (MICA and MICB). MICA and MICB are related proteins of 83% amino acid similarity, and show homology with classical human leukocyte antigen (HLA) molecules. The structure of MICA and MICB is similar to classical HLA class I chains, however they do not bind β2 microglobulin or peptide typical of HLA class I. MICA and MICB are expressed on the cell surface of endothelial cells, fibroblasts, gastric epithelium and PHA-stimulated T cells, and act as a ligand for NKGD2 expressed on the surface of NK cells, γδ T cells and αβ CD8+ T cells. There is evidence suggesting that human cytomegalovirus subverts NK cell detection by inhibiting the function of MICB. Furthermore, MICA and MICB expression has been detected in several epithelial tumors isolated from breast, lung, ovary, prostate, colon and kidney. The MIC genes, which were described independently by two groups of investigators in 1994, encode proteins that are remotely similar to the HLA class I gene products. However, the MIC proteins do not associate with β2-microglobulin and have a groove that is too narrow to accommodate peptides for presentation to T cells.

MICA and MICB are stress-inducible cell surface antigens recognized by immunocytes bearing the receptor NKG2D, including intestinal epithelial Vδ1 γ/δ T cells, which may play a role in immunological reaction in intestinal mucosa. Lu *et al*[28] investigated the association of the microsatellite polymorphisms in the intron 1 of MICB and the MICA-MICB haplotype with the susceptibility to UC in the Chinese population. The microsatellite polymorphisms of MICB were genotyped in unrelated 127 Chinese patients with UC and 193 ethnically matched healthy controls by a semiautomatic fluorescently labeled PCR method. All the subjects were of Chinese Han ethnicity. The frequency of MICB-CA18 was significantly higher in UC patients compared with the healthy controls ($P = 0.0016$) and was increased in the female patients compared with the female healthy controls ($P = 0.0006$). Thus, MICB-CA18 is positively associated with UC patients in the Chinese population[28].

HLA class Ⅱ gene and HLA-DRB1 gene

The HLA region located on chromosome 6p encodes the highly polymorphic, classical class I and Ⅱ genes essential for normal lymphocyte function; it also encodes a further 224 genes. Many early studies investigating this region were limited by small sample size, poor statistical methodology, population stratification and variable disease definition. Although more recent studies have improved study design, investigators are still challenged by the complex patterns of linkage disequilibrium across this gene-dense region, and by the disease heterogeneity characteristic of all genetically complex disorders. Evidence is accumulating that both genetic and environmental factors contribute to UC. The most consistent genetic associations have been shown for the MHC locus HLA class Ⅱ alleles, but the IL-1 families of genes and the multidrug resistance gene MDR1 have also been implicated as genetic susceptibility factors for the development of disease. There is a relationship between UC and bacterial flora, with an increased number of adherent *Bacteroides spp.* and Enterobacteriaceae present in inflamed bowel segments[29].

DRB1 genotype is now thought to act mostly on disease phenotype. The presence of a double dose of RA-associated genes is associated with severe disease with cartilage destruction and increased frequency of extra-articular manifestations. IL-1 is the dominant cartilage-destructive cytokine and its impact on cartilage destruction can be reduced by regulatory cytokines such as IL-4 and IL-10. Increased frequency of particular polymorphism of *IL-1* and *IL-10* genes has been recently identified in the simultaneous presence of susceptible *DRB1* genes, and a specific polymorphism of exon 5 of the *IL-1β* gene is suggested to be predictive of erosive arthritis. Thus, the influence of DRB1 genotype on RA phenotype could be related to genetically controlled patterns of production of cytokines involved in cartilage erosion.

The pathogenesis of UC and CD is still unknown, but the importance of genetic susceptibility has been clearly shown by epidemiological data from family studies. Linkage studies have identified two susceptibility loci for IBD on chromosomes 12 and 16. Importantly, these linkages have been replicated by independent investigators, and studies of positional candidates within these regions continue, together with fine mapping strategies. Regions of suggestive linkage on chromosomes 1, 3, 4, 6, 7, 10, 22 and X have also been reported in individual studies. Other important candidate genes investigated include the IL-1 receptor antagonist, MUC3 and genes of the HLA system. The apparently conflicting data in different studies from around the world may be explained by ethnic differences,

case mix and genetic heterogeneity. Replicated class Ⅱ HLA associations include HLA DRB1*0103 and DR2 (DRB1*1502) involved in UC susceptibility, and HLA DRB1*03 and DR4 as resistance alleles for CD and UC, respectively. Animal studies have provided insights from targeted mutations and quantitative trait locus analysis. The goals of continuing research include narrowing the regions of linkages and analysis of candidate genes, and the application of newly developed methods using SNPs. Advances in IBD genetics hold the potential to provide knowledge about the disease pathogenesis at the molecular level, with ensuing benefits for clinical practice[29,30].

Antigen presentation by MHC class Ⅱ molecules plays an important role in controlling immunity and autoimmunity. Multiple co-factors including the invariant chain (Ii), HLA-DM and HLA-DO are involved in this process. Chen *et al*[30] found that DO inhibits presentation of endogenous self-antigens and that development-regulated DO expression enables antigen-presenting cells to preferentially present different sources of peptide antigens at different stages of development. Disruption of this regulatory mechanism can result in not only immunodeficiency but also autoimmunity. Clinical tests for any of these potential genetic defects are not yet available. They proposed the use of multi-color flow cytometry in conjunction with intracellular staining to detect expression of Ii, DM and DO in peripheral blood B cells, as a convenient reliable screening test to identify individuals with defects in antigen presentation.

Subgroups of UC patients have been further defined by the presence of anti-neutrophil cytoplasmic antibodies (ANCAs). Lee *et al*[31] attempted to define the *HLA class Ⅱ* genes (DRβ, DQα, DQβ) and their relationship with ANCA in southern Chinese patients with UC. Patients were tested for class Ⅱ genes by RFLP and PCR. The indirect immunofluorescence test was used to detect ANCA in the sera. Ethnically matched normal controls were used for comparison. In ANCA-positive UC patients, there was a strong association with the HLA-DQα1c allele ($P < 0.0001$) when compared with controls. This association was not found in ANCA-negative UC patients ($P = 0.21$). In Chinese UC patients, ANCA positivity is associated with the HLA-DQα1c allele, which is not the case in Caucasian patients[31].

Three human mucin cDNAs (Muc-1, Muc-2 and Muc-3) have recently been cloned and sequenced. The major portion of each mucin consists of sequences repeated in tandem along the protein. Three mucins are distinct due to differences in tandem repeat length, lack of sequence homology and different chromosomal locations of their genes. Since altered mucin glycosylation occurs in cancer, resulting in exposure of core carbohydrate, Yuan[32] postulated that increased exposure or other alteration of core peptide structure might occur in cancerous tissues. Antibodies against Muc-1, Muc-2 and Muc-3 tandem repeats were used for immunohistochemical analysis of normal, non-malignant and cancer tissues. The results indicate that, in normal tissues, only Muc-2 was expressed, while in cancerous tissues, all three mucin core peptides were significantly accumulated. All of the three mucin core peptides were increasingly expressed in adenoma, dysplastic epithelium and active UC (pre-malignant lesions), but not in hyperplastic polyps, ischemic colitis and quiescent UC (non-malignant diseases)[32].

The genetic factors predisposing to UC have remained totally unclear to date. HLA-DRB1 genotyping was carried out in 72 unrelated patients with UC and 314 healthy controls using PCR-SSP[33]. All of the patients and healthy controls are Han people in China. The frequency of DRB1*07 allele was increased in UC patients compared with healthy controls ($P = 0.0229$), but the significance disappeared when Bonferroni correction was applied ($P = 0.2977$). Furthermore, compared with healthy controls, although HLA-DRB1*07, DRB1*16/DRB1*09 and DRB1*07/DRB1*12 genotypes were increased in frequency in the patients with extensive colitis, and the patients without extra-intestinal manifestations (EIMs) carried an increased frequency of HLA-DRB1*07 and DRB1*07/DRB1*12 genotypes, although these differences did not reach statistical significance after Bonferroni correction. HLA-DRB1 alleles showed no strong association with UC, and no HLA-DRB1 alleles or genotypes were strongly associated with clinical subgroups of UC in Chinese patients[33].

IL-18 and IL-4 genes

IL-18 is a pro-inflammatory cytokine. Although IL-18 has been implicated as a mediator of antibacterial defense, detrimental effects of IL-18 during bacterial infections have also been demonstrated. Microglia and astrocytes can produce IL-18. *Streptococcus. pneumoniae* is an important microorganism in meningitis. IL-18 plays an important role in sarcoidosis by inducing IFN-γ. The roles of -137 (G/C), -607 (C/A), and -656 (G/T) SNPs of *IL-18* gene promoter regions were compared between 176 individuals in a control group and 161 patients in an experimental group. The major haplotypes-137G/-607C/-656G had a higher promoter activity under the stimulus of sodium butyrate than another major haplotype, -137G/-607A/-656T. This coincided with the genotype with a high IL-18 concentration in the serum. Smokers had a significantly shorter clinical course than non-smokers. A difference in protein expression based on the disparities of *IL-18* gene promoter activity explains the different clinical picture for sarcoidosis, and suggests the effect of smoking on the disease[34].

IL18 was mapped to 11q22.2-22.3 in 1998. Owing to IL-18's important and novel role in immunomodulation, the gene itself has been subject to scrutiny, with the aim of discovering variants that may affect disease susceptibility and/or progression. Despite being sequenced numerous times in different populations, no non-synonymous variants have been found. However, a number of polymorphisms within the proximal promoter have been verified that may interfere with transcription-factor-binding sites. Many of the subsequent association analyses have centered on these

variants, but have yielded no consistent results, despite numerous different study populations being genotyped. IL18 has recently been resequenced in its entirety, enabling the tagging SNP methodology to be adopted. This approach has yielded interesting results, with genetic variation affecting protein levels, and risk. The review by Thompson *et al*[34] aims to compile and reflect the data of interest published to date, with a focus on the diseases related to aberrant inflammatory control.

Under normal situations, the intestinal mucosa is in a state of 'controlled' inflammation regulated by a delicate balance of proinflammatory (TNFα, IFNγ, IL-1, IL-6, IL-12) and anti-inflammatory cytokines (IL-4, IL-10, IL-11). The mucosal immune system is the central effector of intestinal inflammation and injury, with cytokines playing a central role in modulating inflammation. Cytokines may, therefore, be a logical target for IBD therapy using specific cytokine inhibitors. Biotechnology agents targeted against TNF, leukocyte adhesion, Th1 cell polarization, T-cell activation or NF-κB, and other miscellaneous therapies are being evaluated as potential therapies for IBD. In this context, infliximab is currently the only biological agent approved for the treatment of inflammatory and fistulizing CD. Other anti-TNF biological agents have emerged, including CDP 571, certolizumab pegol (CDP 870), etanercept, onercept and adalimumab. However, ongoing research continues to generate new biological agents targeted at specific pathogenic mechanisms involved in the inflammatory process. Lymphocyte-endothelial interactions mediated by adhesion molecules are important in leukocyte migration and recruitment to sites of inflammation, and selective blockade of these adhesion molecules is a novel and promising strategy to treat UC and CD. Therapeutic agents that inhibit leukocyte trafficking include natalizumab, MLN-02 and alicaforsen (ISIS 2302). More controlled clinical trials are currently being conducted, exploring the safety and efficacy of old and new biological agents and the research certainly will open new and exciting perspectives on the development of therapies for IBD.

Eighty-one UC patients and 114 healthy subjects were enrolled by Peng *et al*[35]. *IL-1β*, *IL-1RA* and *IL-4* gene polymorphisms were analyzed with RFLP-PCR and PCR-SSP, respectively. The gene frequency of allele RP2 of IL-4 in patients with UC was significantly higher than that in healthy subjects ($P = 0.00002$), but the gene frequency of allele RP1 in HS was significantly higher than that in UC patients ($P = 0.00002$). The OR of the genotype RP1.2 and RP2.2 was 2.71 and 9.04 respectively. There was no difference in the gene frequencies of IL-1β and IL-1RA between patients with UC and healthy subjects ($P > 0.05$). When patients with UC were divided into ANCA-positive and -negative groups, there was a significant difference in the gene frequencies of allele RP1 and RP2 of IL-4 between the two groups ($P < 0.05$). There is a correlation between the Chinese UC patients and the gene polymorphisms of intron 3 of IL-4. The gene frequency of allele RP1 in UC patients is lower, but the gene frequency of allele RP2 is significantly higher. The differences in gene frequencies of IL-4 between the UC patients and healthy subjects are mainly found in the ANCA-positive UC patients. The Chinese UC patients are not associated with IL-1β and IL-1RA gene polymorphisms[35].

MICA-A5

The role of MICA protein in the immune response is unknown. Recently, it was shown that this polymorphic molecule is mainly expressed by epithelial cells and interacts with the γδT cells. γδT cells appear to dominate lymphocyte populations isolated from epithelium. T lymphocytes bearing γδ receptors have also been isolated from the female genital tract. Expression of MICA by cervical epithelium and its recognition by γδT cells suggest that it may be important in immune surveillance and direct induction of mucosal immunity[35-37]. IBD arises in part from a genetic predisposition, through the inheritance of a number of contributory genetic polymorphisms. These variant forms of genes may be associated with an abnormal response to normal luminal bacteria. A consistent observation across most populations is that any of three polymorphisms of the caspase-activated recruitment domain (CARD15) gene are more prevalent in IBD patients as compared with unaffected controls. Similar aberrant responses to bacteria are associated with variants in autophagy-related 16-like 1 (ATG16L1) and human defensin (HBD-2, -3 and -4) genes. The defective bacterial signal in turn leads to an excessive immune response, presenting as chronic gut inflammation in susceptible individuals. Inconsistent population reports implicate the MHC, which encodes a number of HLA, antigens MICA or cytokines, such as TNFα. Toll-like receptors encoded by the *TLR4* or *TLR9* genes may also play a role. Recent whole genome scans suggest that a rare variant in the IL-23 receptor (IL23R) gene may actually protect against IBD. Other implicated genes may affect mucosal cell polarity (Drosophila discs large homologue5, DLG5) or mucosal transporter function (sodium dependent organic transporters, SLC22A4 and SLC22A5). A variant in ABCB1 (ATP-binding cassette subfamily B member 1) may be especially associated with increased risk of UC. While pharmacogenetics is increasingly being used to predict and optimize clinical response to therapy, nutrigenetics may have even greater potential. In many cases, IBD can be controlled through prescribing an elemental diet, which appears to act through modulating cytokine response and changing the gut microbiota. More generally, no single group of dietary items is beneficial or detrimental to all patients, and elimination diets have been used to individualize dietary requirements. However, recognizing the nature of the genes involved may suggest a more strategic approach. Pro- or prebiotics will directly influence the microbial flora, while immunonutrition, including omega-3 fatty acids and certain polyphenols, may reduce the symptoms of gut inflammation. The expression of gut transporters may be modulated through various herbal remedies, including green tea polyphenols. Such approaches would

require that the gene of interest is functioning normally, other than its expression being up- or down-regulated. However, new approaches are being developed to overcome the effects of polymorphisms that affect the function of a gene. A combination of human correlation studies with experimental models could provide a rational strategy for optimizing nutrigenetic approaches to IBD[36].

MICA plays a role in regulating protective responses by intestinal epithelial Vδ1 γδT cells and the polymorphisms of MICA were reported to be related to several autoimmune diseases. Henckaerts *et al*[11] investigated the association of the microsatellite polymorphisms of TM region of the *MICA* gene with the susceptibility to UC in the Chinese population. The microsatellite polymorphisms of the MICA gene were genotyped in 86 unrelated Chinese patients with UC and 172 ethnically matched healthy controls by a semiautomatic fluorescently labelled PCR method. All the subjects were of Chinese Han ethnicity. The frequency of MICA-A5.1 homozygous genotype and A5.1 allele was significantly increased in UC patients compared with healthy controls ($P = 0.0009$ and $P = 0.0014$). When adjusting for the effects of gender and age at onset, MICA-A5.1 homozygous genotype and A5.1 allele were also increased in the UC patients. Moreover, MICA-A5.1 allele was significantly increased in frequency in the female UC patients ($P = 0.0095$). Logistic regression analysis also revealed that gender was independently associated with UC patients carrying the MICA-A5.1 allele ($P = 0.046$), although the UC patients with extensive colitis ($P = 0.005$) and those with EIMs ($P = 0.0039$) were more likely to carry the MICA-A5.1 allele. EIMs were associated with extent of disease ($P < 0.0001$) and MICA-A5.1 allele was not associated with UC patients with extensive colitis or with EIMs in the logistic regression analysis. Therefore, the MICA-A5.1 homozygous genotype and A5.1 allele were closely associated with UC and the MICA-A5.1 allele was positively associated with the female UC patients in the Chinese population[37].

CD14 and TLR4 genes

TLR and CD14 are components of the lipopolysaccharide receptor complex. A large volume of has been research undertaken on the genetic susceptibility of IBD. Genome-wide linkage studies pointed towards more than 10 chromosomal regions, and fine-mapping of these regions led to the identification of a number of genes, including *CARD15* (*NOD2*), *DLG5*, *OCTN1* and *2*, *TLR4* and *CARD4* (*NOD1*). With the recent completion of the human genome project, whole genome association studies have now become possible and have identified additional genes (*IL23R*, *IRGM*, *PTGER4*, *ATG16L1*) for CD and UC, which have subsequently been replicated. At present, the CARD15 gene is still the most understood susceptibility gene, explaining around 20% of the genetic predisposition to CD. Prediction of disease phenotype and response to the main therapies has for many years been a goal for physicians treating IBD patients. Only now, we have started to accumulate some evidence proving that genetic factors indeed influence both the clinical course of IBD patients and their likelihood of responding to certain therapies. In the coming years, we expect an exponential increase in the efforts devoted to research in this area. The optimal prediction of both disease behavior and response to therapy might result from complex combinations of clinical, biochemical, serological and genetic factors[38].

RFLP-PCR was used to genotype polymorphisms TLR4 Asp299Gly and CD14 C-260T in 114 patients with UC and 160 healthy controls in the Chinese Han population. Moreover, a comparison was made with 170 healthy Dutch white subjects[39]. No TLR4 Asp299Gly mutation was detected in any patients or healthy controls in the Chinese Han population, which was similar to Japanese subjects, but the mutation occurred in 10% of the Dutch white subjects. There were no significant differences of CD14 genotypes between healthy controls and the patients in Chinese patients with UC.

Fas-670 gene

Fas (Apo-1/CD95) antigen is a 45-kDa type I membrane protein, which is expressed in various tissues and cells. Fas is a member of the TNF superfamily and mediates apoptosis when cross-linked with agonistic anti-Fas antibody or Fas ligand (FasL). Although the best-characterized physiological system involving Fas/FasL-mediated apoptosis is observed in the immune system, a role of Fas/FasL in non-lymphiod tissues has become increasingly evident. Fas-mediated apoptosis is thought to be involved in autoimmune disease and inflammatory disorders. Recent studies have suggested that immune dysregulation and genetic factors play important roles in the pathogenesis of IBD. Defective apoptosis of lamina propria T cells may be a factor in mucosal immune dysregulation and tissue inflammation. One of these polymorphisms is a single nucleotide substitution at the -670 position that alters the *Mva* I restriction enzyme cutting site, creating an RFLP. This polymorphism is situated at the consensus sequence site, the gamma interferon activation site. This site can bind to transcription factors such as STATs, thus exerting an effect on the level of transcription of the Fas protein. Although expression and functional effects of the Fas antigen have been found to be associated with IBD, the relationship between Fas-670 polymorphism and IBD has not been reported yet. In a recent study, Peng *et al*[35] could not find any significant association between Fas-670 polymorphism and IBD, which indicates genetic heterogeneity of the diseases. Since Fas-670 polymorphism does not contribute to IBD, there may be other genes that are involved in the pathogenesis of IBD, and other mechanisms of gene regulation may influence Fas-mediated epithelial apoptosis in IBD.

For the Fas-670 polymorphism, it has been hypothesized that either increased apoptosis of intestinal epithelium or decreased apoptosis of lamina propria lymphocytes may induce inflammation of the gut. Fifty unrelated Chinese patients with IBD (38 patients with UC and 12 with CD) and 124 healthy controls were

genotyped for the Fas-670 polymorphism by RFLP-PCR. The PCR product was digested by *Mva* I restriction enzyme. Distribution of the Fas-670 gene polymorphism was 33% for the AA genotype, 52% for the AG genotype and 15% for the GG genotype in 124 healthy subjects, and 30% for the AA genotype, 42% for the AG genotype and 28% for the GG genotype in patients with IBD. However, there was no significant difference in the genotype (P = 0.1498), allele frequencies (P = 0.3198) and carriage frequencies (P = 0.4133) between healthy controls and IBD patients. Furthermore, no difference was found between left-sided and total colitis (P = 0.8242). Fas-670 polymorphism is not associated with IBD in Chinese patients. In a recent study, Xia *et al*[40] genotyped Fas-670 polymorphism in Chinese patients with IBD and healthy controls, and found that the polymorphism was not associated with UC and CD. The study suggested that Fas-670 polymorphism might not play a role in susceptibility of IBD in Chinese patients.

p53 gene

The *p53* gene like the *Rb* gene is a tumor suppressor gene, i.e. its activity stops the formation of tumors. If a person inherits only one functional copy of the *p53* gene from their parents, they are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. This condition is rare, and is known as Li-Fraumeni syndrome. However, mutations in p53 are found in most tumor types, and so contribute to the complex network of molecular events leading to tumor formation. The *p53* gene has been mapped to chromosome 17. In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (Cdk2). When p21 is combined with Cdk2, the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the stop signal for cell division. Thus cells divide uncontrollably, and form tumors.

p53 protein expression was detected by immunohistochemistry in 70 specimens from 21 cases of UC and 25 colonic mucosa specimens from normal subjects. The specimens of UC were examined for the mutation in exon 5, 6, 7, 8 of *p53* gene with the microdissection-PCR-SSCP/HA-clone-sequencing technique and the alterations in 10 microsatellite loci with the microdissection-PCR-SSLP-clone-sequencing technique[41]. None of 25 normal specimens was p53-positive immunohistochemically, while 4/21 of UC specimens were p53-positive. p53-positive rate in inflammatory mucosa of UC specimens was 0/5, and 1/7, 2/7 and 1/2 in low-grade displasia (LGD), high-grade displasia (HGD) and carcinoma, respectively. The abnormal exons were detected by SSCP and confirmed by sequencing in two out of 21 cases: one was exon 6 in a case with carcinoma and the other was exon 8 in an HGD case; both had positive p53 expression. Two cases were positive in the Bat26 locus by SSLP: one was an LGD case, and the other was a case of carcinoma, which also had abnormal exon 6 of *p53* gene. Another nine microsatellite loci, [TGFβRII (A) (10), IGFIIR (G) (8), IGFIIR (CT) (5), TGFβRII (GT) (3), BAX (G) (8), hMSH3 (A) 8, hMSH6 (C) (8), TCF4 (A) (9) and DPC4 (CA) (17)] were negative in all cases. The *p53* gene mutations and microsatellite instability may be one of the mechanisms for higher risk of carcinogenesis in UC[42].

NF-κB

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that acts as a transcription factor. NF-κB is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, and bacterial or viral antigens. NF-κB plays a key role in regulating the immune response to infection. Consistent with this role, incorrect regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF-κB has also been implicated in the processes of synaptic plasticity and memory.

In the healthy gut, the mucosal immune system ensures the balance between pro- and anti-inflammatory mediators, thereby allowing an effective defense against luminal pathogens, but at the same time prevents an overwhelming immune reaction directed against the huge amount of harmless luminal antigens (e.g. components of food or non-pathogenic bacteria). In both entities of IBD (CD and UC), this immunological balance is severely impaired and shifted towards the pro-inflammatory side. The chronic mucosal inflammation in IBD is caused by hyperactivation of effectors immune cells, which produce high levels of pro-inflammatory cytokines like TNFα, IL-6 and IFNγ, resulting in colonic tissue damage. NF-κB was identified as one of the key regulators in this immunological setting. Its activation is markedly induced in IBD patients, and through its ability to promote the expression of various pro-inflammatory genes, it strongly influences the course of mucosal inflammation. Considering the different cell-type specific effects that are mediated by NF-κB, the authors described its complex role in IBD and discussed the existing pharmacological attempts to block the activation of NF-κB to develop new therapeutic strategies in IBD.

A total of 27 cases of UC were investigated. Fifteen cases received sulfasalazine (SASP) treatment or SASP and glucocorticoid treatment, and 12 patients did not receive any medication related to UC[41]. Normal mucosa from nine colon cancer patients served as a control. Ten pieces of intestinal mucosal biopsy specimens were obtained from each patient. The mRNA expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were determined by RT-PCR. The protein levels of ICAM-1 and VCAM-1 were measured by ELISA. NF-κB DNA binding activity was evaluated by electrophoretic mobility shift assay (EMSA). The results showed that NF-κB DNA binding activity, mRNA and protein expression of

ICAM-1 and VCAM-1 were increased significantly in patients with UC compared with normal control ($P < 0.05$). Glucocorticoids and SASP markedly inhibited NF-κB activation and significantly decreased mRNA and protein expression of ICAM-1 and VCAM-1 ($P < 0.05$). Adhesive molecule (ICAM-1 and VCAM-1) gene activation had significant positive correlation with the NF-κB DNA binding activity ($P < 0.05$, $P < 0.05$, respectively). NF-κB is a major and essential factor in regulating the expression of adhesive molecules; it plays an important role in the pathogenesis of UC. SASP and glucocorticoids ameliorate UC *via* inhibition of NF-κB activation and reduction of adhesive molecule expression[42].

Among the 31 patients with UC, 17 patients received SASP or SASP and glucocorticoid treatment, and 14 patients did not receive any medication related to UC. Normal mucosa from 11 colon cancer cases served as a control. Ten pieces of intestinal mucosal biopsy specimens were obtained from each patient. NF-κB DNA binding activity was evaluated with EMSA. Expression of cytokine mRNA was studied RT-PCR. The expression of IL-1β and IL-8 mRNA was increased significantly in patients with UC, as compared with that in the control specimens ($P < 0.05$), and had a significant positive correlation with NF-κB DNA binding activity ($P < 0.05$, $P < 0.05$, respectively). Glucocorticoids and SASP strongly inhibited NF-κB activation and significantly decreased the expression of IL-1β and IL-8 mRNA. NF-κB is a major and essential factor in regulating the expression of cytokine and plays a fundamental role in the pathogenesis of UC. SASP and glucocorticoids decreased cytokine expression *via* inhibition of NF-κB activation[43].Various components of the mucosal immune system are implicated in the immunopathogenesis of UC. Evidence from animal models also suggests that an altered immune response to the commensal microflora of the host plays a central role in the development of UC. Therefore, it is elucidated that the cells and molecules are implicated in the immunopathogenesis of the disease from four aspects: antigens in the intestine, dendritic cells, TLRs and NF-κB in UC[44].

Ten pieces of colon mucosal biopsy specimens were obtained from 31 patients with UC, 17 of whom received SASP or SASP plus glucocorticoid and 14 received no medication. Samples of normal mucosa around the lesion taken from 11 patients with colon cancer were used as controls. NF-κB DNA binding activity was evaluated by EMSA. NF-κB p65 expression was determined by Western blot analysis and immunohistochemical staining with a NF-κB p65 antibody. The type of cells containing activated NF-κB p65 was identified by double immunofluorescence confocal laser scanning microscopy. The expression of NF-κB p65 and NF-κB DNA binding activity was significantly higher in patients with UC than in the controls ($P < 0.05$), and was correlated with the degree of inflammation. The NF-κB expression was significantly stronger in the nuclei than in the cytoplasm in patients with UC without pharmacotherapy. The NF-κB expression in nuclei was significantly stronger in the group without pharmacotherapy than in the group with pharmacotherapy ($P < 0.05$). Only a few NF-κB p65-positive cells were seen in the controls. NF-κB p65 expression was found in all major subsets of mononuclear cells, including macrophages, B lymphocytes, T lymphocytes, and cryptal epithelial cells. The increased activation of NF-κB and increased expression of NF-κB may be involved in the pathogenesis of UC. Glucocorticoids and SASP strongly inhibited NF-κB activation and expression. The inhibition of NF-κB activation may be a central part of the anti-inflammatory action of glucocorticoids and SASP, which might represent an important pharmacological mechanism in the treatment of patients with UC. NF-κB will be an important target for cytokine-based therapy of UC[45].

Table 1 Epidemiology and gene markers of IBD[2-6,48,49]

Epidemiology	Gene markers of IBD
Incidence per 100 000	0.5-2.0 (China); 2-14 (North America)
Prevalence per 100 000	1-23 (China); 26-246 (North America)
Geography	Northern Countries > Southern Countries; Lower (China)
Age of onset (yr)	20-35 (China)
Sex	M > F (China)
Race	Whites > Blacks; Lower (Chinese)
Possible genetic associations (Chinese)	*TNF-308A*, *CARD15* (*NOD2*), *MIF-173*, NAT2, *NKG2D*, *STAT6*, *CTLA-4*, *MICA-MICB*, *HLA-DRB1*, *HLA class Ⅱ*, *IL-18*, *IL-4*, *MICA-A5*, *CD14*, *TLR4*, *Fas-670*, *p53*, *NF-κB*; Chromosome 3, 5, 7, 12, 16 ,19

CONCLUSION

Epidemiology and genetic research in IBD (UC and CD) has provided knowledge about the complexity and heterogeneity of the disease and has started to correlate the interactions between genetic and environmental risk factors in IBD; however, the complex genetic background that allows the development of IBD is not fully understood. Understanding the pathways in which genetic factors influence IBD will uncover pathogenesis of the disease, offer more accurate diagnosis, and ultimately lead to the development of better new drugs and therapies. The most important advance toward understanding this process has been identification of specific genetic associations with IBD, which will shed new light on future research of IBD. Researchers are studying how and why the immune system is activated, how it damages the colon, and the processes involved in healing. Currently, numerous clinical trials on UC are being conducted. Immunomodulators used for treating severe UC include azathioprine/6-MP, methotrexate and cyclosporine. Integrated traditional Chinese and modern medicine is safe and effective in maintaining remission in patients with UC[1,11,46]. There are also complementary and alternative therapies for IBD[47]. Epidemiology and gene markers of IBD are shown in Table 1.

UC and CD are complex polygenic disorders, characterized by several genes, together with environmental factors contributing to the development of IBD. Recent advances in research on genetic susceptibility have allowed the identification of diverse genes at different levels, innate immunity, antigen presentation molecules,epithelial integrity, drug transporters and cell adhesion. The application of genetic testing into clinical practice has become available and all genetic markers may have several clinical implications: prediction of disease phenotype, molecular classification, prevention of complications, and prognosis.

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S- Editor Tian L **L- Editor** Ma JY **E- Editor** Lin YP