Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.2456

World J Gastroenterol 2009 May 28; 15(20): 2456-2462
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Walter Fries, MD, *Series Editor*

Enteropathic spondyloarthropathy: A common genetic background with inflammatory bowel disease?

Elisabetta Colombo, Anna Latiano, Orazio Palmieri, Fabrizio Bossa, Angelo Andriulli, Vito Annese

Elisabetta Colombo, Fabrizio Bossa, Angelo Andriulli, Unit of Gastroenterology, Department of Medical Sciences, IRCCS-CSS Hospital, 1-71013 San Giovanni Rotondo, Italy
Anna Latiano, Orazio Palmieri, Angelo Andriulli, Vito Annese, Laboratory of Genetic Research, Department of Medical Sciences, IRCCS-CSS Hospital, 1-71013 San Giovanni Rotondo, Italy
Vito Annese, Unit of Digestive Endoscopy, Department of Medical Sciences, IRCCS-CSS Hospital, 1-71013 San Giovanni Rotondo, Italy
Author contributions: Colombo E, Latiano A, Andriulli A and Annese V wrote the paper; Palmieri O and Bossa F collected the literature, designed the tables, and listed the references.
Correspondence to: Vito Annese, MD, Unit of Digestive Endoscopy, Department of Medical Sciences, IRCCS-CSS Hospital, 1-71013 San Giovanni Rotondo, Italy. v.annese@operapadrepio.it
Telephone: +39-882-410784 Fax: +39-882-410784
Received: February 2, 2009 Revised: April 30, 2009
Accepted: May 7, 2009
Published online: May 28, 2009

Abstract

The association between spondyloarthropathy and inflammatory bowel disease (IBD) is largely established, although prevalence is variable because of different population selection and diagnostic methodologies. Most studies indicate that as many as 10%-15% of cases of IBD are complicated by ankylosing spondylitis (AS) or other forms of spondylarthritis (SpA). Of note, ileal inflammation resembling IBD has been reported in up to two thirds of cases of SpA, and it has been suggested that the presence of ileitis is associated with the chronicity of articular complications. Although this observation is of interest to unravel the pathophysiology of the disease, systematic screening of patients with SpA by ileocolonoscopy is not indicated in the absence of gut symptoms, as only a small proportion of patients with subclinical gut inflammation will develop overt IBD over time. The existence of familial clustering of both IBD and AS, the coexistence of both conditions in a patient, the evidence of an increased risk ratio among first- and second-degree relatives of affected AS or IBD patients and finally, the increased cross-risk ratios between AS and IBD, strongly suggest a shared genetic background. So far, however, IL23R is the only identified susceptibility gene shared by both IBD and AS. Although functional studies are still needed to better understand its pathogenic role, great effort is being spent therapeutically targeting this pathway that may prove effective for both disorders.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Ankylosing spondlitis; Sacroiliitis; Spondyloarthropathy

Peer reviewers: Nick P Thompson, MD, Department of Medicine, Freeman Hospital, Newcastle Upon Tyne, NE7 7DN, Unite Kingdom; Christian D Stone, MD, MPH, Director, Inflammatory Bowel Disease Program, Assistant Professor of Medicine, Division of Gastroenterology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8124, Saint Louis, MO 63110, United States

Colombo E, Latiano A, Palmieri O, Bossa F, Andriulli A, Annese V. Enteropathic spondyloarthropathy: A common genetic background with inflammatory bowel disease? *World J Gastroenterol* 2009; 15(20): 2456-2462 Available from: URL: http://www.wjgnet.com/1007-9327/15/2456.asp DOI: http://dx.doi.org/10.3748/wjg.15.2456

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory bowel diseases (IBDs) of unknown etiology that affect up to 1 in 250 of the adult population, with up to 25% of patients being diagnosed during childhood or adolescence[1]. Key features of UC include diffuse mucosal inflammation that extends proximally from the rectum. In CD, conversely, any site in the gastrointestinal tract may be affected with transmural inflammation, which is typically patchy and segmental[2]. Joint complications are the most common extra-intestinal manifestations of IBD, and were recognized as far back as the 1920s. Both axial and peripheral joint complications are recognized. This review mainly focuses on the so-called enteropathic spondyloarthropathy, and more specifically, on the possible pathogenic link which may lie in a common genetic background with IBD.

ANKYLOSING SPONDYLITIS (AS)

AS is a seronegative inflammatory arthropathy that affects

the vertebral column, and is characterized by sacroiliitis and progressive ankylosis (fusion) of the vertebral facet joints. It is defined classically by the modified New York Criteria[3], which include: low back pain for more than 3 mo; relieved by exercise and not improved by rest; limited spinal movement in two planes; and decreased chest expansion. If any of these clinical features is present in association with bilateral grade 2-4 or unilateral grade 3-4 sacroiliitis, then a definitive diagnosis can be made. However, there is some overlap with the more general term of sponyloarthropathy (SpA), as defined by the European Study Group on Spondyloarthropathy[4]. This involves a combination of inflammatory low back pain and a number of other factors including associated conditions, such as IBD or enteric infection, post-dysenteric reactive arthritis, psoriatic arthritis, and post-urethritis arthritis. The prevalence of AS in the general population is 0.25%-1%[5,6], but it is increased in IBD patients to 1%-6%, depending on the study population and the method of investigation[7,8]. In a recent population-based study in Italy[9], the prevalence of AS was 0.37%, while IBD-associated arthritis accounted for 0.09%. However, the clinical spectrum might be broader than that so far defined. In a population-based inception cohort of IBD patients evaluated in Italy and Netherlands, 18% satisfied the European criteria for SpA, 3.1% satisfied the modified New York criteria for AS, however, 14.4% patients developed one or more SpA-related manifestations, without fulfilling any of the classification criteria[10].

The traditional method of radiological assessment is by plain radiology of the sacroiliac joints. Magnetic resonance imaging has demonstrated a higher sensitivity[59], although in the absence of symptoms, its significance is sometimes unclear. Idiopathic AS is more common in male subjects, with an M:F ratio of 3:1, whereas in IBD, the M:F ratio is closer to 1:1. The main lesion of AS is sacroiliitis and this is associated with inflammatory low back pain. The symptoms are characterized by an insidious onset over several months, morning stiffness, and exacerbation of pain by rest. The evolution of AS is usually independent of the bowel disease, and more often runs a more benign clinical course than idiopathic AS[11].

ISOLATED SACROILIITIS

Isolated sacroiliitis may occur in association with IBD, without evidence of progressive spinal disease. Although some patients complain of low back pain, in many cases, they may be asymptomatic, therefore, prevalence is dependent largely upon the investigation. Radiographic surveys suggest a prevalence of 18%[7], but higher prevalence is estimated by means of scintigraphy, with radioisotope uptake found in up to 52% of patients with CD and 42% with UC[12]. However, given the large degree of inter- and intra-observer error, and the lack of follow-up information about possible progression to AS, the significance of these findings is unclear. In the majority of patients, it seems a non-progressive condition. In clinical practice, diagnosis is usually made by plain abdominal radiography, but more often it is detected incidentally.

PERIPHERAL ARTHRITIS

Articular manifestations have been reported in association with IBD for many years, but only in the late 1950s was arthritis proven to be inflammatory, and quite distinct from classical rheumatoid arthritis (RA), to be seronegative. Articular manifestations occur in 5%-20% of IBD patients, and more recently, a new classification proposes two distinct clinical forms with specific genetic associations[13].

Type I peripheral arthropathy, defined as acute, self-limiting inflammation that affects fewer than five joint, and is associated with IBD relapse and the presence of other extra-intestinal manifestations. More often, large weight-bearing joints are affected, particularly knees, wrists and ankles. The median duration of illness is 5 wk, however, 10%-20% of patients will develop persistent symptoms. One third of patients will report one episode over time.

Type Ⅱ arthritis is a symmetrical, seronegative, small-joint arthropathy, unrelated to disease activity. The onset may occur at any time during the course of IBD or before, and in CD, it is reported more commonly in colonic disease. It usually runs a more chronic course with a median duration of 3 years. The small joints of the hands are more commonly affected.

ROLE OF INTESTINAL INFLAMMATION

The role of intestinal inflammation and luminal factors in SpA is an area of debate. In a large series of ileocolonoscopy examinations with biopsies in patients with SpA[14,15], inflammatory lesions were found in two thirds of patients, with a similar proportion in those with AS and RA. Moreover, the clinical course of articular disease was independent of the presence of gut inflammation, and a minority of patients (3.7%) developed overt IBD. In another study[16], 123 patients with SpA at initial endoscopy were reassessed clinically, and follow-up endoscopy performed in 49 patients. Articular remission rates were independent of initial gut inflammation and associated with endoscopic and histological remission. In addition, initial chronic gut inflammation implies a high risk of evolution of AS. Nevertheless, a potential confounding factor of these studies is that most patients are treated with non-steroidal anti-inflammatory drugs (NSAIDs) which may promote enteropathy that is hardly distinguishable from primary inflammatory lesions of the gut. Furthermore, in a follow-up study[17] of some patients still taking NSAIDs, no inflammatory gut lesions were found in those in clinical remission from articular symptoms, while in contrast, half of the patients with articular inflammation had persistent inflammatory gut lesions, and one quarter developed overt IBD. This suggests that intestinal inflammation is important in idiopathic as well IBD-associated AS, possibly by determining an increased antigenic load across the inflamed gut mucosa.

Post-enteric reactive arthritis is associated with Gram-negative enterobacteria such as *Salmonella, Escherichia coli, Yersinia* and *Campylobacter*; in these circumstances, bacterial antigens have been isolated in the affected joints. These conditions are clinically very similar to type Ⅰ IBD arthritis, and it therefore seems likely that bacterial antigens may be important in the initiation of the inflammatory process. Furthermore, stronger support on the role of bacteria in initiating arthritis in the presence of gut inflammation has been gained from a study of HLA-B*27 transgenic animal models. These knock-out animals spontaneously develop colitis and axial and peripheral arthritis when reared under normal conditions[18,19]. Interestingly, when they are kept in a germ-free environment, gut and joint inflammation is prevented[19]. Furthermore, different bacteria induce gut and joint inflammation with different efficiency, with *Bacteroides vulgatus* being the most efficient and *E. coli* is ineffective[20]. Thus, it appears likely that similarly to IBD, bacteria are important in the pathogenesis of SpA, with an interaction with the immune system. The link between bacteria, gut/joint inflammation and the immune response, might result from a (common) genetic predisposition.

GENETIC PREDISPOSITION TO SPONDYLOARTHROPATHY

Idiopathic AS is strongly associated with possession of HLA-B*27, with a 94% prevalence in northern European patients, compared with 10% of healthy controls[21,22]. This association is considerably weaker in IBD-associated AS, ranging between 50% and 80% of patients[23-25]. Conversely, 50% of HLA-B*27-positive IBD patients have AS, compared with 1%-10% of B*27-positive individuals in the general population. Putative mechanisms include B*27 presenting peptide from luminal bacteria, or self proteins causing an inflammatory response, or peptides being presented to the immune system by other antigens such as HLA-DR. Central to these theories is the concept of a triggering bacterial antigen, although evidence is lacking. Patients with isolated sacroiliitis are less likely to be HLA-B*27-positive, and HLA-B*27 seems to be a marker of progressive axial disease rather than sacroiliitis, but long-term studies are needed. Other genes in the HLA region have also been implicated including HLA-DR1, TAP and LMP, but none of these findings have been conclusive. Moreover, subsequent studies have demonstrated other HLA associations in IBD arthritis. The association with HLA-DRB1*0103 is solely with type Ⅰ arthritis, which is also associated with HLA-B*27, whereas type Ⅱ is associated with B*44 and MICA[13,26] (Table 1).

A number of studies have demonstrated a striking overlap within patients and family members with rheumatological, dermatological and gastrointestinal diseases. The susceptibility genes of these disorders appear to overlap with each other[27]. In a study that explored the prevalence of secondary disorders in 3287 AS individuals[28], the sub-group of patients with IBD-AS had higher prevalence of iritis (OR = 1.4) or psoriasis (OR = 1.9) than the controls. Moreover, patients with multiple disorders predicted the highest prevalence of co-existing disease (i.e. psoriasis, IBD, iritis, or AS) within family members. These data suggest that susceptibility factors are additive or have a synergistic effect on each other, thus pointing to a shared gene hypothesis.

Table 1 HLA associations in IBD and IBD-associated arthropathy[11]

	HLA antigens investigated	Percentage in IBD + arthropathy affected patients	Percentage in IBD patients without arthropathy
AS	HLA-B*27	60	7
Type Ⅰ arthritis	HLA-B*27	26	7
	HLA-B*35	33	15
	HLA-DRB1*0103	35	3
Type Ⅱ arthritis	HLA-B*44	62	31

GENETIC PREDISPOSITION TO IBD

IBD is widely believed to originate from a dysregulated immune response to luminal bacteria in a genetically susceptible host[2]. The inheritance model is non-Mendelian but complex-polygenic, with several genes involved together with environmental factors. Of the other environmental factors thought to have an impact on disease susceptibility, only smoking and appendectomy have a substantive evidence base[29]. Concordance data in twins (36% for CD and 16% for UC, 4% for both CD and UC for monozygotic and dizygotic twins, respectively) and multiplex IBD families (relative risk to first-degree relative of proband up to 35 for CD and 15 for UC) have provided strong epidemiological evidence for a genetic contribution to IBD susceptibility[30]. These observations have led to the development of genetic investigations with two broad strategies: one has investigated candidate genes, and the other has used hypothesis-free methods of genome-wide scanning.

Overall, candidate gene strategies have not proved to be particularly fruitful in IBD, but one success has been the identification of an association between the major histocompatibility complex (MHC) region and UC susceptibility, initially in Japanese subjects[31] and later in Europeans[32]. The DRB1*0103 allele has been implicated in both severe UC and extra-intestinal (mainly articular) manifestations of IBD. Subsequently, 11 genome-wide scans by non-parametric linkage analysis were performed in the 1990s, and several susceptibility loci were identified in approximately half of the chromosomes[33].

The *NOD2* gene on chromosome 16q12 was the first susceptibility gene for CD to be identified successfully. It was detected by parallel strategies of positional cloning within a region of linkage and positional candidate gene investigation[34,35], and the finding was subsequently widely replicated in Caucasian, but not in Asian populations. NOD2 encodes an intracellular receptor that is expressed predominantly in monocytes and Paneth cells[33]. This has been implicated in the innate immune response to muramyldipeptide (MDP), a component of peptidoglycan

in bacterial cell walls. The CD-associated variants that are clustered in the C-terminal leucine-rich repeat part of the NOD2 protein significantly diminish responsiveness to MDP. On exposure to MDP, oligomerized NOD2 recruits RIP2 (the serine-threonine kinase RICK) and subsequently activates nuclear factor-κB transcription factor *via* NEMO ubiquitination and IκB degradation. This leads to production of cytokines and cryptidins/defensins, hence facilitating clearance of bacteria. In addition, there is evidence of cross-talk between NOD2 and toll-like receptor pathways. However, the precise mechanism by which NOD2 mutations lead to increased intestinal inflammation is unknown, but it may be that reduced ability to clear bacteria by innate immune mechanisms leads to dysregulation of adaptive immune pathways.

Following fine mapping of the IBD5 linkage region on chromosome 5q31, consistent evidence for association between CD and a haplotype of markers spanning 250 kb has been observed. More recently, the same locus has been associated also with UC[36]. However, because of the strong linkage disequilibrium (LD) across this region, it has been very difficult to identify the causal variant. Peltekova *et al*[37] have reported a two-locus risk haplotype in the region of the organic cation transporter (OCTN) genes and suggested that this accounts for the association. The two-locus haplotype comprises L503F (1672 C-T, missense substitution) and G207C (transversion) in the *SLC22A4* (OCTN1) and *SLC22A5* (OCTN2) genes, respectively. However, there remains significant debate as to whether these transcripts are truly implicated by the genetic evidence, and a number of other immunoactive candidates remain in the frame, including interferon regulatory factor 1 (IRF1) and a number of important cytokine genes (IL-3, IL-4, IL-5 and IL-13) located within the 250-kb risk haplotype.

Progress from the Human Genome Project and HapMap Project, combined with markedly decreasing genotyping costs, has made possible the performance of adequately powered genome-wide association studies (GWAs) in complex genetic disorders such as IBD. Several GWAs[38] and a meta-analysis[39] have already been performed in CD and more recently in UC[40] and pediatric IBD[41]. Genome scans have identified 11 susceptibility genes and loci and highlighted a number of new, previously unsuspected pathways as playing an important role in IBD pathogenesis, including the IL23 pathway in IBD overall and specific aspects of innate immunity (particularly the autophagy genes *ATG16L1* and *IRGM*) in CD. As expected, a number of genes such as IL23r, IL12B, MHC, STAT3, IBD5, MST1, PTPN2, NKX2-3 seem to be shared in the predisposition to both UC and CD (Table 2).

Table 2 Candidates genes and loci in CD and UC

	Genes and loci	Associated with CD	Associated with UC
1p31	IL23R	Yes	Yes
1q21	ECM1	-	Yes
2q37	ATG16L1	Yes	No
3p21	Several included MST1-BSN	Yes	Yes
5p13	Intergenic, PTGR4	Yes	No
5q31	Several included SLC22A5	Yes	Yes
5q33	IRGM	Yes	No
5q33	IL12B	Yes	Yes
6q21	HLA-DQ/DR	Yes	Yes
10q21	ZNF365	Yes	Yes
10q24	NKX2-3	Yes	Yes
16q12	NOD2	Yes	No
17q21	Several included STAT3	Yes	Yes
18p11	PTPN2	Yes	Yes

CD: Crohn's disease; UC: Ulcerative colitis.

COMMON GENETIC LINK BETWEEN IBD AND SPONDYLOARTHROPATHY

IBD and AS show familial clustering and may coexist in a patient. More intriguingly, healthy first-degree relatives of patients with AS (21%-60%) and CD (10%-54%) have increased permeability of the small intestine[42-44]. These changes might be a consequence of subclinical intestinal inflammation, and conform to the profile of an additive trait in both conditions[45,46]. Evidence from studies of twins and other first-degree relatives suggests that the genetic basis is somewhat stronger for IBD than for AS[47-50].

In the pre-GWA era, studies investigating a possible common genetic background in IBD and articular involvement were concentrated mainly on MHC and NOD2. It has been recognized that genes in the HLA region have a greater role for modifying IBD phenotype than in determining overall disease susceptibility. Within UC clinical subgroups, the uncommon DRB1*0103 allele is associated with both extensive and severe disease, with an early need for surgery[51]. Interestingly, the same allele has also been associated with CD colitis, thus suggesting the molecular basis of a colonic IBD phenotype. Furthermore, type I pauciarticular large-joint arthritis is also associated with this allele and other class I alleles (B*27 and B*35) in LD. However, the low frequency of this allele suggests that this association is unlikely to be clinically useful in predicting disease course. In addition, an increased prevalence of extraintestinal manifestations has been reported previously in colonic IBD, increasing the possibility that the association between DRB1*0103 and articular manifestations may merely mirror the association with colonic disease. Finally, recent evidence from GWA scans has at least refined the signal to the 400-kb haplotype block that contains DRB1*0103, and shows that this locus is common to UC and the colonic (but not small bowel) sub-phenotype of CD[52].

Crane *et al*[53] have investigated the hypothesis that the three major variants of the NOD2 gene are involved in AS. A case-controlled study was performed in 229 AS, 197 IBD-associated AS (78 with CD and 119 with UC), and 229 ethnically matched healthy controls. The Gly908Arg variant was associated with UC-associated AS (OR = 4.6, 95% CI = 1.3-16, $P = 0.016$), with a similar non-significant trend in CD-associated AS (OR = 3.9, 95% CI = 0.8-18, $P = 0.08$). In contrast, no association was found between

NOD2 variants and primary AS, or other variants with UC- or CD-associated AS. Moreover, carriage of the Pro268Ser variant was associated with greater disease activity. Similarly, in subsequent studies, variants of NOD2 do not appear to confer susceptibility to AS[54], but rather identify a subgroup of patient with CD-associated AS[55].

Recently, the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium have published the first association scan with 14 436 non-synonymous single nucleotide polymorphisms (SNPs) in 922 independent cases of AS, together with autoimmune thyroid disease, multiple sclerosis and breast cancer, against a common control dataset of 1500 healthy individuals[56]. The strongest association in AS was observed in the MHC region, centered around the HLA-B genes, but the association of $P < 10^{-20}$ was observed across about 1.5 Mb, probably reflecting the strong effect of HLA-B27, even over distant SNPs with modest LD. To validate less strong signals obtained at the first scan, a further 471 independent AS cases and 625 new controls were genotyped with additional SNPs. In the combined data set, a strong association ($P = 1.2 \times 10^{-8}$ to 3.4×10^{-10}) with SNPs of the ARTS1 gene (OR = 1.4) and IL23R gene (peak P value of 7.5×10^{-9} at the rs11209032 with an OR of 1.3) was found. The association with IL23R remained strong when considering individuals with AS not having IBD (n = 1066). These genes both represent excellent biological candidates, but more importantly, IL23R has been documented recently in CD and psoriasis[57], which suggests that this gene is a common susceptibility factor for the major seronegative diseases, at least partially explaining their co-occurrence. IL23R is a key factor in the regulation of a newly defined effector T-cell subset, T_H17 cells[33]. They express high levels of the cytokine IL-17 in response to stimulation, in addition to IL-1, IL-6, tumor necrosis factor α, IL-22 and IL-25. In animal models, blocking IL-23 reduces inflammation, which suggests that IL23R variants associated with disease are pro-inflammatory. No functional studies of IL23R variants are available to date, however a promising treatment of CD has been reported with anti-IL-12p40 antibodies, which block IL-12 and IL-23, as these cytokines share the p40 subunit[58].

A different perspective was employed in a study that explored the possible common genetic background of IBD and AS through a genealogical evaluation in Iceland[59]. Icelanders are relatively homogeneous with respect to the environment, cultural aspects and genetic factors; moreover, extensive genealogical records and diseases registries are available. By investigating the genealogical database and registry of subjects with AS (n = 205) and IBD (n = 1352), the risk ratios for relatives for each disease and the cross-risk ratios (AS *vs* IBD and *vice versa*) were estimated. First-, second- and third-degree relatives of patients with AS, had risk ratios of 94, 25 and 3.5, respectively, of developing AS (each $P < 0.0005$), while first-, second- and third-degree relatives of patients with IBD had risk ratios of 4.4, 2.2 and 1.4, respectively (each $P < 0.0001$). More intriguingly, the cross-risk ratio was 3.0 and 2.1 ($P < 0.0001$), respectively, in first- and second-degree relatives, with a comparable effect for UC and CD. This elevated cross-risk ratio between IBD and AS strongly suggests that there is a genetic component shared by these complex diseases, and should stimulate further molecular and functional studies.

CONCLUSION

The clinical association between spondyloarthropathy and IBD is well-established, with studies indicating that as many as 10%-15% of cases of IBD are complicated by AS or other forms of SpA[60]. Ileal inflammation that resembles IBD has been reported in up to two thirds of cases of SpA, and it has been suggested that the presence of ileitis is associated with the chronicity of articular complications. Moreover, evidence that there is familial clustering of IBD and AS, that both conditions may coexist in patients, that there is an increased risk ratio among first- and second-degree relatives of affected AS or IBD patients and finally, that there is an increased cross-risk ratios between AS and IBD, confirm the existence of a shared genetic predisposition. So far, IL23R is the only identified susceptibility gene shared by IBD and AS. Functional studies are still needed to better understand its functional role, but it is hoped that treatment that targets this pathway may prove effective in both disorders.

REFERENCES

1 **Podolsky DK**. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429
2 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434
3 **van der Linden S**, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; **27**: 361-368
4 **Dougados M**, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, Cats A, Dijkmans B, Olivieri I, Pasero G. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; **34**: 1218-1227
5 **Calin A**. Ankylosing spondylitis. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. Oxford textbook of rheumatology. Vol. 2. Oxford: Oxford University Press, 1998: 1058–1070
6 **van der Linden S**, van der Heijde DM. Clinical and epidemiologic aspects of ankylosing spondylitis and spondyloarthropathies. *Curr Opin Rheumatol* 1996; **8**: 269-274
7 **Wright V**, Watkinson G. Sacro-iliitis and ulcerative colitis. *Br Med J* 1965; **2**: 675-680
8 **de Vlam K**, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. *J Rheumatol* 2000; **27**: 2860-2865
9 **De Angelis R**, Salaffi F, Grassi W. Prevalence of spondyloarthropathies in an Italian population sample: a regional community-based study. *Scand J Rheumatol* 2007; **36**: 14-21
10 **Salvarani C**, Vlachonikolis IG, van der Heijde DM, Fornaciari G, Macchioni P, Beltrami M, Olivieri I, Di Gennaro F, Politi P, Stockbrugger RW, Russel MG. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol* 2001; **36**: 1307-1313
11 **Orchard TR**. Extraintestinal manifestations: skin, joint and mucocutaneous manifestations. In: Satsangi J, Sutherland

LR, editors. Inflammatory bowel disease. Churchill Livingstone: Elsevier Limited, 2003: chapt. 43, 669-684
12 **Agnew JE**, Pocock DG, Jewell DP. Sacroiliac joint uptake ratios in inflammatory bowel disease: relationship to back pain and to activity of bowel disease. *Br J Radiol* 1982; **55**: 821-826
13 **Orchard TR**, Thiyagaraja S, Welsh KI, Wordsworth BP, Hill Gaston JS, Jewell DP. Clinical phenotype is related to HLA genotype in the peripheral arthropathies of inflammatory bowel disease. *Gastroenterology* 2000; **118**: 274-278
14 **Mielants H**, Veys EM, De Vos M, Cuvelier C, Goemaere S, De Clercq L, Schatteman L, Elewaut D. The evolution of spondyloarthropathies in relation to gut histology. I. Clinical aspects. *J Rheumatol* 1995; **22**: 2266-2272
15 **Mielants H**, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, Schatteman L, Elewaut D. The evolution of spondyloarthropathies in relation to gut histology. II. Histological aspects. *J Rheumatol* 1995; **22**: 2273-2278
16 **De Vos M**, Mielants H, Cuvelier C, Elewaut A, Veys E. Long-term evolution of gut inflammation in patients with spondyloarthropathy. *Gastroenterology* 1996; **110**: 1696-1703
17 **Mielants H**, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, Schatteman L, Gyselbrecht L, Elewaut D. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. *J Rheumatol* 1995; **22**: 2279-2284
18 **Rath HC**, Herfarth HH, Ikeda JS, Grenther WB, Hamm TE Jr, Balish E, Taurog JD, Hammer RE, Wilson KH, Sartor RB. Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27/human beta2 microglobulin transgenic rats. *J Clin Invest* 1996; **98**: 945-953
19 **Taurog JD**, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernandez-Sueiro JL, Balish E, Hammer RE. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; **180**: 2359-2364
20 **Rath H**, Schulta M, Grenther W. Colitis, gastritis and antibacterial lymphocyte responses in HLA-B27 transgenic rats monoinoculated with Bacteroides vulgatus or Escherichia coli. *Gastroenterology* 1997; **112**: A1068
21 **Brewerton DA**, Hart FD, Nicholls A, Caffrey M, James DC, Sturrock RD. Ankylosing spondylitis and HL-A 27. *Lancet* 1973; **1**: 904-907
22 **Brown MA**, Pile KD, Kennedy LG, Calin A, Darke C, Bell J, Wordsworth BP, Cornelis F. HLA class I associations of ankylosing spondylitis in the white population in the United Kingdom. *Ann Rheum Dis* 1996; **55**: 268-270
23 **Brewerton DA**, Caffrey M, Nicholls A, Walters D, James DC. HL-A 27 and arthropathies associated with ulcerative colitis and psoriasis. *Lancet* 1974; **1**: 956-958
24 **Dekker-Saeys BJ**, Meuwissen SG, Van Den Berg-Loonen EM, De Haas WH, Meijers KA, Tytgat GN. Ankylosing spondylitis and inflammatory bowel disease. III. Clinical characteristics and results of histocompatibility typing (HLA B27) in 50 patients with both ankylosing spondylitis and inflammatory bowel disease. *Ann Rheum Dis* 1978; **37**: 36-41
25 **Mallas EG**, Mackintosh P, Asquith P, Cooke WT. Histocompatibility antigens in inflammatory bowel disease. Their clinical significance and their association with arthropathy with special reference to HLA-B27 (W27). *Gut* 1976; **17**: 906-910
26 **Orchard TR**, Dhar A, Simmons JD, Vaughan R, Welsh KI, Jewell DP. MHC class I chain-like gene A (MICA) and its associations with inflammatory bowel disease and peripheral arthropathy. *Clin Exp Immunol* 2001; **126**: 437-440
27 **Schreiber S**, Rosenstiel P, Albrecht M, Hampe J, Krawczak M. Genetics of Crohn disease, an archetypal inflammatory barrier disease. *Nat Rev Genet* 2005; **6**: 376-388
28 **Brophy S**, Pavy S, Lewis P, Taylor G, Bradbury L, Robertson D, Lovell C, Calin A. Inflammatory eye, skin, and bowel disease in spondyloarthritis: genetic, phenotypic, and environmental factors. *J Rheumatol* 2001; **28**: 2667-2673
29 **Loftus EV Jr**. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517
30 **Russell RK**, Satsangi J. IBD: a family affair. *Best Pract Res Clin Gastroenterol* 2004; **18**: 525-539
31 **Asakura H**, Tsuchiya M, Aiso S, Watanabe M, Kobayashi K, Hibi T, Ando K, Takata H, Sekiguchi S. Association of the human lymphocyte-DR2 antigen with Japanese ulcerative colitis. *Gastroenterology* 1982; **82**: 413-418
32 **Satsangi J**, Welsh KI, Bunce M, Julier C, Farrant JM, Bell JI, Jewell DP. Contribution of genes of the major histocompatibility complex to susceptibility and disease phenotype in inflammatory bowel disease. *Lancet* 1996; **347**: 1212-1217
33 **Cho JH**, Weaver CT. The genetics of inflammatory bowel disease. *Gastroenterology* 2007; **133**: 1327-1339
34 **Hugot JP**, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001; **411**: 599-603
35 **Ogura Y**, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001; **411**: 603-606
36 **Rioux JD**, Daly MJ, Silverberg MS, Lindblad K, Steinhart H, Cohen Z, Delmonte T, Kocher K, Miller K, Guschwan S, Kulbokas EJ, O'Leary S, Winchester E, Dewar K, Green T, Stone V, Chow C, Cohen A, Langelier D, Lapointe G, Gaudet D, Faith J, Branco N, Bull SB, McLeod RS, Griffiths AM, Bitton A, Greenberg GR, Lander ES, Siminovitch KA, Hudson TJ. Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. *Nat Genet* 2001; **29**: 223-228
37 **Peltekova VD**, Wintle RF, Rubin LA, Amos CI, Huang Q, Gu X, Newman B, Van Oene M, Cescon D, Greenberg G, Griffiths AM, St George-Hyslop PH, Siminovitch KA. Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet* 2004; **36**: 471-475
38 **Mathew CG**. New links to the pathogenesis of Crohn disease provided by genome-wide association scans. *Nat Rev Genet* 2008; **9**: 9-14
39 **Barrett JC**, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008; **40**: 955-962
40 **Franke A**, Balschun T, Karlsen TH, Sventoraityte J, Nikolaus S, Mayr G, Domingues FS, Albrecht M, Nothnagel M, Ellinghaus D, Sina C, Onnie CM, Weersma RK, Stokkers PC, Wijmenga C, Gazouli M, Strachan D, McArdle WL, Vermeire S, Rutgeerts P, Rosenstiel P, Krawczak M, Vatn MH, Mathew CG, Schreiber S. Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility. *Nat Genet* 2008; **40**: 1319-1323
41 **Kugathasan S**, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, Cucchiara S, Kim CE, Frackelton

EC, Annaiah K, Glessner JT, Santa E, Willson T, Eckert AW, Bonkowski E, Shaner JL, Smith RM, Otieno FG, Peterson N, Abrams DJ, Chiavacci RM, Grundmeier R, Mamula P, Tomer G, Piccoli DA, Monos DS, Annese V, Denson LA, Grant SF, Hakonarson H. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet* 2008; **40**: 1211-1215

42 **Vaile JH**, Meddings JB, Yacyshyn BR, Russell AS, Maksymowych WP. Bowel permeability and CD45RO expression on circulating CD20+ B cells in patients with ankylosing spondylitis and their relatives. *J Rheumatol* 1999; **26**: 128-135

43 **May GR**, Sutherland LR, Meddings JB. Is small intestinal permeability really increased in relatives of patients with Crohn's disease? *Gastroenterology* 1993; **104**: 1627-1632

44 **Teahon K**, Smethurst P, Levi AJ, Menzies IS, Bjarnason I. Intestinal permeability in patients with Crohn's disease and their first degree relatives. *Gut* 1992; **33**: 320-323

45 **Thjodleifsson B**, Sigthorsson G, Cariglia N, Reynisdottir I, Gudbjartsson DF, Kristjansson K, Meddings JB, Gudnason V, Wandall JH, Andersen LP, Sherwood R, Kjeld M, Oddsson E, Gudjonsson H, Bjarnason I. Subclinical intestinal inflammation: an inherited abnormality in Crohn's disease relatives? *Gastroenterology* 2003; **124**: 1728-1737

46 **Bjarnason I**, Helgason KO, Geirsson AJ, Sigthorsson G, Reynisdottir I, Gudbjartsson D, Einarsdottir AS, Sherwood R, Kristjansson K, Kjartansson O, Thjodleifsson B. Subclinical intestinal inflammation and sacroiliac changes in relatives of patients with ankylosing spondylitis. *Gastroenterology* 2003; **125**: 1598-1605

47 **Lee JC**, Lennard-Jones JE. Inflammatory bowel disease in 67 families each with three or more affected first-degree relatives. *Gastroenterology* 1996; **111**: 587-596

48 **Peeters M**, Nevens H, Baert F, Hiele M, de Meyer AM, Vlietinck R, Rutgeerts P. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996; **111**: 597-603

49 **Orholm M**, Binder V, Sorensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. *Scand J Gastroenterol* 2000; **35**: 1075-1081

50 **Halfvarson J**, Bodin L, Tysk C, Lindberg E, Jarnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003; **124**: 1767-1773

51 **Ahmad T**, Tamboli CP, Jewell D, Colombel JF. Clinical relevance of advances in genetics and pharmacogenetics of IBD. *Gastroenterology* 2004; **126**: 1533-1549

52 **Fisher SA**, Tremelling M, Anderson CA, Gwilliam R, Bumpstead S, Prescott NJ, Nimmo ER, Massey D, Berzuini C, Johnson C, Barrett JC, Cummings FR, Drummond H, Lees CW, Onnie CM, Hanson CE, Blaszczyk K, Inouye M, Ewels P, Ravindrarajah R, Keniry A, Hunt S, Carter M, Watkins N, Ouwehand W, Lewis CM, Cardon L, Lobo A, Forbes A, Sanderson J, Jewell DP, Mansfield JC, Deloukas P, Mathew CG, Parkes M, Satsangi J. Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease. *Nat Genet* 2008; **40**: 710-712

53 **Crane AM**, Bradbury L, van Heel DA, McGovern DP, Brophy S, Rubin L, Siminovitch KA, Wordsworth BP, Calin A, Brown MA. Role of NOD2 variants in spondylarthritis. *Arthritis Rheum* 2002; **46**: 1629-1633

54 **van der Paardt M**, Crusius JB, de Koning MH, Murillo LS, van de Stadt RJ, Dijkmans BA, Pena AS, van der Horst-Bruinsma IE. CARD15 gene mutations are not associated with ankylosing spondylitis. *Genes Immun* 2003; **4**: 77-78

55 **Laukens D**, Peeters H, Marichal D, Vander Cruyssen B, Mielants H, Elewaut D, Demetter P, Cuvelier C, Van Den Berghe M, Rottiers P, Veys EM, Remaut E, Steidler L, De Keyser F, De Vos M. CARD15 gene polymorphisms in patients with spondyloarthropathies identify a specific phenotype previously related to Crohn's disease. *Ann Rheum Dis* 2005; **64**: 930-935

56 **Burton PR**, Clayton DG, Cardon LR, Craddock N, Deloukas P, Duncanson A, Kwiatkowski DP, McCarthy MI, Ouwehand WH, Samani NJ, Todd JA, Donnelly P, Barrett JC, Davison D, Easton D, Evans DM, Leung HT, Marchini JL, Morris AP, Spencer CC, Tobin MD, Attwood AP, Boorman JP, Cant B, Everson U, Hussey JM, Jolley JD, Knight AS, Koch K, Meech E, Nutland S, Prowse CV, Stevens HE, Taylor NC, Walters GR, Walker NM, Watkins NA, Winzer T, Jones RW, McArdle WL, Ring SM, Strachan DP, Pembrey M, Breen G, St Clair D, Caesar S, Gordon-Smith K, Jones L, Fraser C, Green EK, Grozeva D, Hamshere ML, Holmans PA, Jones IR, Kirov G, Moskivina V, Nikolov I, O'Donovan MC, Owen MJ, Collier DA, Elkin A, Farmer A, Williamson R, McGuffin P, Young AH, Ferrier IN, Ball SG, Balmforth AJ, Barrett JH, Bishop TD, Iles MM, Maqbool A, Yuldasheva N, Hall AS, Braund PS, Dixon RJ, Mangino M, Stevens S, Thompson JR, Bredin F, Tremelling M, Parkes M, Drummond H, Lees CW, Nimmo ER, Satsangi J, Fisher SA, Forbes A, Lewis CM, Onnie CM, Prescott NJ, Sanderson J, Matthew CG, Barbour J, Mohiuddin MK, Todhunter CE, Mansfield JC, Ahmad T, Cummings FR, Jewell DP, Webster J, Brown MJ, Lathrop MG, Connell J, Dominiczak A, Marcano CA, Burke B, Dobson R, Gungadoo J, Lee KL, Munroe PB, Newhouse SJ, Onipinla A, Wallace C, Xue M, Caulfield M, Farrall M, Barton A, Bruce IN, Donovan H, Eyre S, Gilbert PD, Hilder SL, Hinks AM, John SL, Potter C, Silman AJ, Symmons DP, Thomson W, Worthington J, Dunger DB, Widmer B, Frayling TM, Freathy RM, Lango H, Perry JR, Shields BM, Weedon MN, Hattersley AT, Hitman GA, Walker M, Elliott KS, Groves CJ, Lindgren CM, Rayner NW, Timpson NJ, Zeggini E, Newport M, Sirugo G, Lyons E, Vannberg F, Hill AV, Bradbury LA, Farrar C, Pointon JJ, Wordsworth P, Brown MA, Franklyn JA, Heward JM, Simmonds MJ, Gough SC, Seal S, Stratton MR, Rahman N, Ban M, Goris A, Sawcer SJ, Compston A, Conway D, Jallow M, Newport M, Sirugo G, Rockett KA, Bumpstead SJ, Chaney A, Downes K, Ghori MJ, Gwilliam R, Hunt SE, Inouye M, Keniry A, King E, McGinnis R, Potter S, Ravindrarajah R, Whittaker P, Widden C, Withers D, Cardin NJ, Davison D, Ferreira T, Pereira-Gale J, Hallgrimsdo'ttir IB, Howie BN, Su Z, Teo YY, Vukcevic D, Bentley D, Brown MA, Compston A, Farrall M, Hall AS, Hattersley AT, Hill AV, Parkes M, Pembrey M, Stratton MR, Mitchell SL, Newby PR, Brand OJ, Carr-Smith J, Pearce SH, McGinnis R, Keniry A, Deloukas P, Reveille JD, Zhou X, Sims AM, Dowling A, Taylor J, Doan T, Davis JC, Savage L, Ward MM, Learch TL, Weisman MH, Brown M. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. *Nat Genet* 2007; **39**: 1329-1337

57 **Cargill M**, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, Matsunami N, Ardlie KG, Civello D, Catanese JJ, Leong DU, Panko JM, McAllister LB, Hansen CB, Papenfuss J, Prescott SM, White TJ, Leppert MF, Krueger GG, Begovich AB. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet* 2007; **80**: 273-290

58 **Mannon PJ**, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present D, Dolin B, Goodman N, Groden C, Hornung RL, Quezado M, Yang Z, Neurath MF, Salfeld J, Veldman GM, Schwertschlag U, Strober W. Anti-interleukin-12 antibody for active Crohn's disease. *N Engl J Med* 2004; **351**: 2069-2079

59 **Thjodleifsson B**, Geirsson AJ, Bjornsson S, Bjarnason I. A common genetic background for inflammatory bowel disease and ankylosing spondylitis: a genealogic study in Iceland. *Arthritis Rheum* 2007; **56**: 2633-2639

60 **Rudwaleit M**, Baeten D. Ankylosing spondylitis and bowel disease. *Best Pract Res Clin Rheumatol* 2006; **20**: 451-471

S- Editor Tian L **L- Editor** Kerr C **E- Editor** Ma WH