World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i22.2715

World J Gastroenterol 2011 June 14; 17(22): 2715-2722
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Belén Beltrán, MD, PhD, *Series Editor*

Familial aggregation in inflammatory bowel disease: Is it genes or environment?

Tiago Nunes, Gionata Fiorino, Silvio Danese, Miquel Sans

Tiago Nunes, Miquel Sans, Department of Gastroenterology, Hospital Clinic i Provincial/IDIBAPS, CIBER EHD, 08036 Barcelona, Spain
Gionata Fiorino, Silvio Danese, Division of Gastroenterology, IRCCS Istituto Clinico Humanitas, Rozzano, Milan 20089, Italy
Author contributions: Fiorino G, Danese S, Sans M and Nunes T performed the literature review; Sans M and Nunes T wrote the manuscript.
Supported by Grants from Ministerio de Ciencia e Innovación (SAF2008/03676) and Fundació Miarnau to Sans M
Correspondence to: Miquel Sans, MD, PhD, Department of Gastroenterology, Hospital Clínic i Provincial/IDIBAPS, CIBER EHD, 170 Villarroel, 08036 Barcelona, Spain. msans@clinic.ub.es
Telephone: +34-93-2275418 Fax: +34-93-2279387
Received: June 28, 2010 Revised: September 18, 2010
Accepted: September 25, 2010
Published online: June 14, 2011

Abstract

Inflammatory bowel disease (IBD) develops in genetically susceptible individuals due to the influence of environmental factors, leading to an abnormal recognition of microbiota antigens by the innate immune system which triggers an exaggerated immune response and subsequent bowel tissue damage. IBD has been more frequently found in families, an observation that could be due to either genetic, environmental or both types of factors present in these families. In addition to expanding our knowledge on IBD pathogenesis, defining the specific contribution to familial IBD of each one of these factors might have also clinical usefulness. We review the available evidence on familial IBD pathogenesis.

Key words: Inflammatory bowel disease; Familial aggregation; Familial clustering; Environmental factors; Genetics; Genome wide association studies

Peer reviewer: Alessandro Fichera, MD, FACS, FASCRS, Assistant Professor, Department of Surgery, University of Chicago, 5841 S. Maryland Ave, MC 5031, Chicago, IL 60637, United States

Nunes T, Fiorino G, Danese S, Sans M. Familial aggregation in IBD: Is it genes or environment? *World J Gastroenterol* 2011; 17(22): 2715-2722 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i22/2715.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i22.2715

INTRODUCTION

Our present understanding of inflammatory bowel disease (IBD) pathogenesis considers ulcerative colitis (UC) and Crohn's disease (CD) as complex conditions that develop in genetically susceptible individuals due to the influence of various environmental factors[1-6]. An abnormal recognition of certain antigens of the bowel microbiota by elements of the innate immunity is thought to play a key role, leading to an exaggerated immune response, release of pro-inflammatory molecules and, ultimately, bowel tissue damage.

In past decades a greater incidence of IBD cases among UC and CD relatives, referred to as family aggregation or familial IBD, has been clearly demonstrated[7-11]. The reason for such an increased risk is not straightforward, but genes, the environment or a combination of both could, in theory, account for family aggregation, considering their contribution to the development of IBD. A better understanding of the factors leading to familial IBD might result in clinical applications.

FAMILLIAL IBD

Familial aggregation among IBD patients or "familial IBD" is defined by the occurrence of a trait in more fam-

ily members than expected by chance. Multiple population studies have demonstrated that relatives of an IBD patient have a much higher risk of developing the same condition, compared to the general population[7-11]. The magnitude of familial aggregation depends on several factors, including: (1) type of IBD; (2) population studied; and (3) family relationship.

In respect to type of IBD, familial aggregation has been more frequently reported in CD than UC[7,9]. In first degree relatives, the age-adjusted relative risk of developing the same type of IBD ranges from 2-8 for UC and from 5-10 in the case of CD[7-9]. As elegantly demonstrated by Yang *et al*[9], affected relatives can develop both forms of IBD, although the greatest risk is associated with the appearance of the same disease type occurring in the index case. Additionally, CD patients tend to have a much higher frequency of relatives affected with UC when compared to UC patients having relatives affected with CD[7].

In respect to different populations, it has been shown that Jewish families present more than twice the number of multiple affected families when compared to the non-Jewish population[9]. However, we cannot rule out the possibility that differences amongst other geographical populations are due to their study design.

Finally, frequency of familial IBD also varies according to the degree and type of kinship. The prevalence of IBD in second-degree relatives appears to be lower than in first-degree relatives, especially in those with discordant disease[7]. In addition, although only a few studies have estimated the age-adjusted risk of IBD in relatives, it seems that the risk of IBD in offspring is higher than in parents and similar, or even slightly higher, than in siblings[8,9,11]. A potential source of bias could result from underreported cases in second-degree relatives and older generations, which might have influenced these differences.

In addition to an increased risk of developing the disease, first-degree relatives of IBD patients also have an increased likelihood of sharing the same phenotype[8,12]. This seems to be partly true in CD owing to the striking clinical concordance in families, in respect to disease location and behavior. On the contrary, literature is scarce and presents mixed results for CD severity and complications[8,9,13-16]. In UC families, the phenotype concordance data is less consistent, but a high concordance rate related to colonic extent and extra-intestinal manifestations has been reported[12,14].

The possibility that IBD develops at an earlier age in offspring than in their parents, a phenomenon known as anticipation, has been controversial[17-21]. Although different studies have reported such differences in age of onset, it seems that multiple biases could account for these findings. Whether familial IBD is a different clinical entity was the subject of debate. However, in the largest population-based study including 654 sporadic and familial IBD patients, a positive familial IBD history did not significantly influence clinical course or risk of developing IBD-related complications[22].

ROLE OF GENES IN FAMILIAL IBD

Evidences supporting the role of genetic factors in IBD pathogenesis

The fact that IBD is a genetically mediated disease was initially derived from the physician's perception of a higher prevalence of UC and CD cases among the relatives of IBD patients. This hypothesis was initially supported by case report studies showing clustering in IBD families and was subsequently confirmed by several population-based studies[3-7]. In one of these studies, Yang *et al*[9] described a risk of developing UC and CD among first degree relatives of IBD patients of 1.6% and 5.2%, respectively. The risk of developing IBD also varies according to the ethnic origin of individuals, a fact that is likely to be linked to their genetic background. In that regard, the prevalence of IBD among the Jewish population is 2 to 4 times higher than in any other ethnic group, being greater in Ashkenazi than in Sephardic or Oriental Jewish, with no influence from their geographical location[9,11].

Another source of evidence underlying the key role of genetic factors in IBD steams from twin studies. In these studies the greatest IBD concordance rate was found in monozygotic twins, ranging from 20% to 50% in CD and from 14% to 19% in UC twins, whereas in dizygotic twins concordance rates dropped to 0%-7% in both CD and UC twins[23-26]. The degree of monozygotic-dizygotic twin concordance found in CD point towards a genetically mediated condition with a non-Mendelian inheritance pattern. Of note, the concordance rates observed in CD are greater than these found in type 1 diabetes, asthma or schizophrenia, all of them diseases with a well-established genetic background.

Genes involved in CD pathogenesis

Several genome linkage studies identified a number of CD susceptibility regions in chromosomes 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19 and X[27-34]. After subsequent confirmation, regions on chromosomes 16, 12, 6, 14, 5, 19 were named IBD1 to IBD7, respectively[35]. Of these 7 original loci, only IBD1 (chromosome 16q12) was replicated in all studies, whereas another three loci, IBD2 (chromosome 12), IBD3 (chromosome 6) and IBD4 (chromosome 14) were replicated in some of the studies[36]. Later on, several CD susceptibility genes, such as NOD2, NOD1, toll-like receptors (TRLs) genes, and novel organic cation transporter (OCTN) genes were identified using either a candidate gene approach or positional cloning techniques[37].

The first and most relevant CD susceptibility gene described to date is NOD2. The carriage of one or more of the three main NOD2 variants (Arg702Trp, Gly908Arg and Leu1007incC) is found in 25%-45% of CD Caucasian patients and in only 15%-20% of healthy subjects[38]. A clear gene-dose effect has been described for NOD2 in CD patients. While the risk of developing CD is increased by 2-3-fold in subjects carrying one NOD2 variant allele, it reaches a 20-40-fold increase in subjects with two or more NOD2 variant alleles. In addition to increasing CD

susceptibility, the *NOD2* gene variants can also influence CD behaviour, phenotypes and need of surgery[39]. Similarly, the carriage of NOD2 variants has also been linked to a slight increase in familial CD risk[40]. In spite of being the most powerful CD susceptibility gene found to date, it must be underlined that the *NOD2* gene only accounts for a small proportion of the genetic inheritance of CD in Caucasians. Moreover, *NOD2* gene variants are infrequent in some geographic areas, such as Scotland, Ireland and Scandinavia, or even completely absent in subjects with an Asian and African-American genetic background[37]. In these cases other genes must account for the genetic predisposition to develop CD. This is in keeping with the highly polygenic nature of this disease.

In the last 3 years, the field of IBD genetics has experienced a dramatic transformation. Completion of the human genome project and development of tools capable of simultaneously studying a great number of genes has resulted in a much higher number of genes influencing CD and UC susceptibility than expected. Several genome-wide association studies (GWAS) have been undertaken in CD patients and healthy controls[41-45] and a meta-analysis has been recently published[46]. In this meta-analysis more than 30 independent loci are found to be convincingly associated with CD, providing an extraordinary insight into CD pathogenesis. Interestingly, most CD susceptibility genes are involved in either recognition of bowel microbiota antigens by the innate immunity, the IL-17/IL-23 pathway or autophagy, suggesting that these molecular mechanisms play a key role in CD pathogenesis.

Several studies have evaluated the frequency of CD-related mutations in affected families[47-49]. Jess *et al*[47] studied NOD2 mutation frequency in a population of Danish twins with IBD. In this study, a high prevalence of NOD2 mutation was observed in both CD twins and their healthy siblings. A Swedish study on monozygotic twin pairs reported a NOD2 frequency in both concordant CD siblings of only 22%, although the prevalence of NOD2 was indeed higher in concordant than in discordant twin pairs[48]. Joossens *et al*[49] investigated the prevalence of genetic markers (NOD2, NOD1, TLR4, CARD8) in multiplex and single-case families, healthy relatives and controls. The authors found a significant correlation between the number of genetic mutations per family and an increasing number of first-degree relatives with CD. However, these results could not discriminate between single-case and multiplex families.

Genes involved in UC pathogenesis

Two studies aimed at describing the influence in UC of the well-established CD susceptibility genes reported very interesting findings[50,51]. It became clear there is a genetic overlap between the two forms of IBD, with some genes involved in the development of both CD and UC (3p21.31, NKX2-3, CCNY). On the contrary, other genes have been only associated with UC, but not CD (ECM1 HERC2, STAT3 and PTPN2). In that regard, a very recently published UC GWAS meta-analysis has demonstrated that roughly half of the known CD susceptibility gene loci are shared by UC[52]. In addition, more than 20 exclusive UC loci have been recognized to date including, among others, IL10, ARPC2 and ECM1[52-55]. To summarize our present understanding, we believe that some genetic factors influence the global predisposition to develop IBD, whereas other genes are related to the risk of developing either UC or CD, specifically. Such genetic overlap between UC and CD probably contributes to the existence of a 5% of non-classifiable or indeterminate colitis among the IBD population. Similarly, it also contributes to the fact that first degree relatives of CD or UC patients not only have an increased risk of developing the same type of IBD, but also the other form of IBD, although with a lower frequency in the latter case.

EVIDENCE SUPPORTING AN ENVIRONMENTAL AETIOLOGY IN FAMILIAL IBD

Evidences supporting the role of environmental factors in IBD pathogenesis

The remarkable increase in the IBD incidence in the last few decades cannot be explained by changes in the genetic background of a certain population. Instead, it clearly points towards the existence of potent environmental factors playing a key role in IBD pathogenesis. Several studies performed in Europe that have evaluated IBD prevalence in immigrant populations from low IBD risk areas found that immigrants present a similar or higher risk of developing IBD when compared to the indigenous population[56-58]. These results suggest that differences in prevalence are probably associated with lifestyle and environmental factors, and not with a specific genetic background. It is remarkable though that only very few studies have addressed environmental etiologic factors in respect to familial IBD.

Eating habits, pets and previous infections

One of the largest controlled studies addressing the impact of environmental factors on familial IBD was conducted in Belgium by Van Kruiningen *et al*[59] who investigated 21 families with 3 or more first-degree relatives affected with CD. Subjects were interviewed using an extensive questionnaire on potential environmental factors. In this study affected families and controls presented some remarkable differences in eating habits, domestic factors and medical history. IBD patients ate fewer oats, rye and bran, consumed more unpasteurized cheese and drank more well water, compared to controls. Additionally, an increased frequency of smoking habit, appendectomy and fecal-oral transmitted infections was found in a subject who later developed CD. In respect to domestic habits, affected families also presented a lower daily contact with pets during childhood. Taken together, these results point towards a role of certain gastro-intestinal infections as triggering events contributing to the development of IBD, whereas

the contact with pets during childhood seem to have a protective role favoring the immune system modulation.

Another familial aggregation study by the same Belgian group reported on a large Moroccan family with multiple CD cases[60]. Potential environmental, genetic and serological markers were studied in all family members. No differences in CD susceptibility genes or serological antibodies described in Caucasian populations were found between CD patients and healthy subjects. The study of environmental factors revealed the consumption of a large amount of unpasteurized milk in all family members, which was an environmental factor previously associated with occurrence of familial CD[59].

Another questionnaire-based study on environmental factors in a large monozygotic and dizygotic twin population included more than 300 twin pairs who were discordant for IBD diagnosis[61]. Twins with UC and CD reported recurrent gastrointestinal infections more frequently than their healthy siblings. These findings are in keeping with an increased frequency of fecal-oral transmitted infections reported in multiplex CD families[59] and suggest that past gastrointestinal infections might influence the risk of IBD.

Appendectomy

Appendectomy is associated with a lower risk of developing UC, although the exact mechanisms of this protective role are still not elucidated[62]. While controversial, it seems that the effect of appendectomy requires a certain degree of inflammation (appendicitis or lymphadenitis) and also applies to subjects undergoing appendectomy before the age of 20 years[63]. However, in a recently published study evaluating the usefulness of appendectomy as a therapeutic strategy for distal UC, 40% of patients experienced a complete symptoms resolution after elective appendectomy[64]. Conversely to UC, appendectomy seems to be associated with an increased risk of developing CD, although the studies addressing this issue yield conflicting results[65-70]. These discrepancies might be due to the inclusion of appendectomies performed at CD diagnosis or to methodological differences. More recently, data from large Swedish and Danish cohorts and a meta-analysis have demonstrated that the risk of developing CD is markedly increased only during a short period following appendectomy, disappearing after 5 years[71,72]. This behavior suggests that the association of appendectomy with CD might be a diagnostic bias, instead of a true risk factor.

Tobacco

Smoking habit, particularly cigarette smoking, is the most indisputable example of the influence of the environment on IBD[73,74]. Smoking has striking opposite effects on CD and UC, supporting the notion that distinct mechanisms underlie the pathogenesis of each form of IBD[74]. Subjects who have never smoked and former smokers are at a higher risk of developing UC, whereas present smokers have an increased risk of CD. In addition to the impact on disease susceptibility, smoking habit also modifies the clinical course of disease, increasing the risk of experiencing a relapse and the need for surgery[75-78]. Moreover, it has been demonstrated that tobacco discontinuation improves CD course[79]. Tuvlin *et al*[80] conducted a survey on tobacco use in UC and CD patients in familial IBD. In this study, smokers had double the risk of CD and former smokers had double the risk of UC, in younger age groups. A Danish case-report study on 2 monozygotic female twins with ileo-colonic CD and their non-affected brother and parents showed that though the healthy father. brother and twins all presented a NOD2 variant related to CD, only the affected twins were smokers, had undergone appendectomy and were on oral contraceptive use[81]. To further evaluate the influence of smoking habit in familial IBD, Bridger *et al*[82] analyzed 658 IBD patients, including 339 affected sibling pairs of whom 89 were discordant for smoking when diagnosed. Siblings who were discordant for smoking and IBD type almost always show CD in the smoker and UC in the non-smoker patient. The authors also suggest that the protective effect of tobacco on UC is due to a shift towards development of CD, in subjects prone to undergo bowel inflammation, rather than true protection of from the development of UC.

Oral contraceptive and non-steroidal anti-inflammatory drugs

Several studies have addressed the potential contribution of contraceptive pills to the development of IBD. It has been demonstrated that the risk of IBD in women taking oral contraceptives is greater that in controls, although there is no direct evidence for a causal relationship[83-85]. Data from two meta-analysis suggest a modest association between the use of oral contraceptives and development of IBD, with a pooled relative risk adjusted for smoking habit of 1.46 for CD and 1.26 for UC[86,87]. The most recent meta-analysis also suggests that the risk disappears once the medication is discontinued[87]. Other frequently used types of drug that have also been associated with IBD are non-steroidal anti-inflammatory drugs (NSAIDs)[88-95]. Due to their inhibitory action on protective prostaglandins, these drugs could enhance intestinal permeability facilitating disease activity. A growing body of evidence suggests a true association between NSAIDs and IBD activity, although the existence of multiple confounding factors makes it difficult to establish a formal relationship[96]. These confounding factors include selection of inadequate control groups, publication bias and intestinal tissue damage due not only to IBD activity but also to NSAIDs. Unfortunately, there are no studies evaluating the role of oral contraceptives and NSAIDs in familial IBD.

IBD as an infectious disease

Van Kruiningen *et al*[97] analyzed the pedigrees and time course of IBD development in a group of patients with familial IBD. They found that first-borns and subsequently born siblings were more frequently affected[87,97]. In addition, they described a statistically significant CD clustering that would indicate an infectious etiology supported by

which family members were affected and time to develop symptomatic disease. Another study by Van Kruiningen *et al*[98] assessed 2 French families with multiple CD cases, in an attempt to identify the suspected infectious cause. However, *Campylobacter*, *Yersinia*, *mycobacteria*, *mycoplasma*, *torovirus*, *coronavirus, Brucella*, *Influenza* and animal enteropathogenic infections were all ruled out and no pathogen could be identified. Even though an abnormal recognition of antigens of the intestinal microbiota by innate immunity is thought to play a key role in IBD pathogenesis, there are no studies addressing specifically the interaction between bowel microbiota and familial IBD.

Intestinal permeability

An abnormal gut barrier function, with an increased intestinal permeability, could contribute to CD pathogenesis[99]. It that regard, it has been demonstrated that small intestinal permeability is increased not only in patients with CD but also in their healthy relatives[100,101]. Peeters *et al*[100] reported that 25% of healthy first-degree relatives of CD patients had an increased small intestinal permeability. The mechanisms responsible for these disturbances in bowel permeability are not fully elucidated and its pathogenesis is a much debated topic. In their study in familial and sporadic CD, Peeters *et al*[100] reported no specific genetic pattern accounting for the abnormal permeability found in patients and relatives. In addition, there were no significant differences between families with multiple members affected and families with only one individual affected. Interestingly, almost half of the spouses presented increased intestinal permeability, which clearly suggests that this abnormality is due to environmental and not to genetic mechanisms. In keeping with this finding, Fries *et al*[102] studied the prevalence of intestinal permeability and some CD genetic markers (including NOD2 main variants) in 23 families of CD patients. Authors found no association between increased intestinal permeability and genetic markers in their population. In contrast, other studies have found an association between an abnormal bowel permeability and the presence of NOD2 variations[101,103].

CONCLUSION

IBD is a complex polygenic disorder modulated by a series of environmental factors, some of which are likely yet to be determined. In spite of the significant progress done in the study of both the genetic and environmental factors associated, the exact contribution of each one of the many factors involved is still largely unknown. From a practical point of view, at present no specific recommendations to IBD families, in respect to genetic or environmental counselling, are available. Large, prospective, population-based studies following IBD patients and their healthy relatives will be necessary to untie the knots in this tangled web of genetic and environmental factors.

REFERENCES

1 **Fiocchi C**. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998; **115**: 182-205
2 **Cortot A**, Pineton de Chambrun G, Vernier-Massouille G, Vigneron B, Gower Rousseau C. [Inflammatory bowel disease: genetic or environmental diseases?]. *Gastroenterol Clin Biol* 2009; **33**: 681-691
3 **Abraham C**, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; **361**: 2066-2078
4 **Lakatos PL**. Environmental factors affecting inflammatory bowel disease: have we made progress? *Dig Dis* 2009; **27**: 215-225
5 **Fiocchi C**. Susceptibility genes and overall pathogenesis of inflammatory bowel disease: where do we stand? *Dig Dis* 2009; **27**: 226-235
6 **Braus NA**, Elliott DE. Advances in the pathogenesis and treatment of IBD. *Clin Immunol* 2009; **132**: 1-9
7 **Orholm M**, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; **324**: 84-88
8 **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
9 **Yang H**, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993; **34**: 517-524
10 **Freeman HJ**. Familial Crohn's disease in single or multiple first-degree relatives. *J Clin Gastroenterol* 2002; **35**: 9-13
11 **Roth MP**, Petersen GM, McElree C, Vadheim CM, Panish JF, Rotter JI. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. *Gastroenterology* 1989; **96**: 1016-1020
12 **Annese V**, Andreoli A, Astegiano M, Campieri M, Caprilli R, Cucchiara S, D'Incà R, Giaccari S, Iaquinto G, Lombardi G, Napolitano G, Pera A, Riegler G, Valpiani D, Andriulli A. Clinical features in familial cases of Crohn's disease and ulcerative colitis in Italy: a GISC study. Italian Study Group for the Disease of Colon and Rectum. *Am J Gastroenterol* 2001; **96**: 2939-2945
13 **Colombel JF**, Grandbastien B, Gower-Rousseau C, Plegat S, Evrard JP, Dupas JL, Gendre JP, Modigliani R, Bélaïche J, Hostein J, Hugot JP, van Kruiningen H, Cortot A. Clinical characteristics of Crohn's disease in 72 families. *Gastroenterology* 1996; **111**: 604-607
14 **Satsangi J**, Grootscholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996; **38**: 738-741
15 **Bayless TM**, Tokayer AZ, Polito JM 2nd, Quaskey SA, Mellits ED, Harris ML. Crohn's disease: concordance for site and clinical type in affected family members--potential hereditary influences. *Gastroenterology* 1996; **111**: 573-579
16 **Polito JM 2nd**, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology* 1996; **111**: 580-586
17 **Heresbach D**, Gulwani-Akolkar B, Lesser M, Akolkar PN, Lin XY, Heresbach-Le Berre N, Bretagne JF, Katz S, Silver J. Anticipation in Crohn's disease may be influenced by gender and ethnicity of the transmitting parent. *Am J Gastroenterol* 1998; **93**: 2368-2372
18 **Grandbastien B**, Peeters M, Franchimont D, Gower-Rousseau C, Speckel D, Rutgeerts P, Belaïche J, Cortot A, Vlietinck R, Colombel JF. Anticipation in familial Crohn's disease. *Gut* 1998; **42**: 170-174
19 **Lee JC**, Bridger S, McGregor C, Macpherson AJ, Jones JE. Why children with inflammatory bowel disease are diagnosed at a younger age than their affected parent. *Gut* 1999; **44**: 808-811
20 **Faybush EM**, Blanchard JF, Rawsthorne P, Bernstein CN. Generational differences in the age at diagnosis with Ibd: genetic anticipation, bias, or temporal effects. *Am J Gastroenterol*

2002; **97**: 636-640
21 **Hampe J**, Heymann K, Kruis W, Raedler A, Fölsch UR, Schreiber S. Anticipation in inflammatory bowel disease: a phenomenon caused by an accumulation of confounders. *Am J Med Genet* 2000; **92**: 178-183
22 **Henriksen M**, Jahnsen J, Lygren I, Vatn MH, Moum B. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. *Am J Gastroenterol* 2007; **102**: 1955-1963
23 **Halfvarson J**, Bodin L, Tysk C, Lindberg E, Järnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003; **124**: 1767-1773
24 **Orholm M**, Binder V, Sørensen 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
25 **Thompson NP**, Driscoll R, Pounder RE, Wakefield AJ. Genetics versus environment in inflammatory bowel disease: results of a British twin study. *BMJ* 1996; **312**: 95-96
26 **Spehlmann ME**, Begun AZ, Burghardt J, Lepage P, Raedler A, Schreiber S. Epidemiology of inflammatory bowel disease in a German twin cohort: results of a nationwide study. *Inflamm Bowel Dis* 2008; **14**: 968-976
27 **Cho JH**, Nicolae DL, Gold LH, Fields CT, LaBuda MC, Rohal PM, Pickles MR, Qin L, Fu Y, Mann JS, Kirschner BS, Jabs EW, Weber J, Hanauer SB, Bayless TM, Brant SR. Identification of novel susceptibility loci for inflammatory bowel disease on chromosomes 1p, 3q, and 4q: evidence for epistasis between 1p and IBD1. *Proc Natl Acad Sci USA* 1998; **95**: 7502-7507
28 **Barmada MM**, Brant SR, Nicolae DL, Achkar JP, Panhuysen CI, Bayless TM, Cho JH, Duerr RH. A genome scan in 260 inflammatory bowel disease-affected relative pairs. *Inflamm Bowel Dis* 2004; **10**: 513-520
29 **Vermeire S**, Rutgeerts P, Van Steen K, Joossens S, Claessens G, Pierik M, Peeters M, Vlietinck R. Genome wide scan in a Flemish inflammatory bowel disease population: support for the IBD4 locus, population heterogeneity, and epistasis. *Gut* 2004; **53**: 980-986
30 **Paavola P**, Heliö T, Kiuru M, Halme L, Turunen U, Terwilliger J, Karvonen AL, Julkunen R, Niemelä S, Nurmi H, Färkkilä M, Kontula K. Genetic analysis in Finnish families with inflammatory bowel disease supports linkage to chromosome 3p21. *Eur J Hum Genet* 2001; **9**: 328-334
31 **Rioux JD**, Daly MJ, Green T, Stone V, Lander ES, Hudson TJ, Steinhart AH, Bull S, Cohen Z, Greenberg G, Griffiths A, McLeod R, Silverberg M, Williams CN, Siminovitch KA. Absence of linkage between inflammatory bowel disease and selected loci on chromosomes 3, 7, 12, and 16. *Gastroenterology* 1998; **115**: 1062-1065
32 **Williams CN**, Kocher K, Lander ES, Daly MJ, Rioux JD. Using a genome-wide scan and meta-analysis to identify a novel IBD locus and confirm previously identified IBD loci. *Inflamm Bowel Dis* 2002; **8**: 375-381
33 **Duerr RH**, Barmada MM, Zhang L, Pfützer R, Weeks DE. High-density genome scan in Crohn disease shows confirmed linkage to chromosome 14q11-12. *Am J Hum Genet* 2000; **66**: 1857-1862
34 **Ma Y**, Ohmen JD, Li Z, Bentley LG, McElree C, Pressman S, Targan SR, Fischel-Ghodsian N, Rotter JI, Yang H. A genome-wide search identifies potential new susceptibility loci for Crohn's disease. *Inflamm Bowel Dis* 1999; **5**: 271-278
35 **Zheng CQ**, Hu GZ, Zeng ZS, Lin LJ, Gu GG. Progress in searching for susceptibility gene for inflammatory bowel disease by positional cloning. *World J Gastroenterol* 2003; **9**: 1646-1656
36 **Tamboli CP**, Cortot A, Colombel JF. What are the major arguments in favour of the genetic susceptibility for inflammatory bowel disease? *Eur J Gastroenterol Hepatol* 2003; **15**: 587-592
37 **Henckaerts L**, Figueroa C, Vermeire S, Sans M. The role of genetics in inflammatory bowel disease. *Curr Drug Targets* 2008; **9**: 361-368
38 **Roussomoustakaki M**, Koutroubakis I, Vardas EM, Dimoulios P, Kouroumalis EA, Baritaki S, Koutsoudakis G, Krambovitis E. NOD2 insertion mutation in a Cretan Crohn's disease population. *Gastroenterology* 2003; **124**: 272-273; author reply 273-274
39 **Annese V**, Lombardi G, Perri F, D'Incà R, Ardizzone S, Riegler G, Giaccari S, Vecchi M, Castiglione F, Gionchetti P, Cocchiara E, Vigneri S, Latiano A, Palmieri O, Andriulli A. Variants of CARD15 are associated with an aggressive clinical course of Crohn's disease--an IG-IBD study. *Am J Gastroenterol* 2005; **100**: 84-92
40 **Heliö T**, Halme L, Lappalainen M, Fodstad H, Paavola-Sakki P, Turunen U, Färkkilä M, Krusius T, Kontula K. CARD15/NOD2 gene variants are associated with familially occurring and complicated forms of Crohn's disease. *Gut* 2003; **52**: 558-562
41 **Rioux JD**, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, Shugart YY, Griffiths AM, Targan SR, Ippoliti AF, Bernard EJ, Mei L, Nicolae DL, Regueiro M, Schumm LP, Steinhart AH, Rotter JI, Duerr RH, Cho JH, Daly MJ, Brant SR. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* 2007; **39**: 596-604
42 **Hampe J**, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J, Günther S, Prescott NJ, Onnie CM, Häsler R, Sipos B, Fölsch UR, Lengauer T, Platzer M, Mathew CG, Krawczak M, Schreiber S. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet* 2007; **39**: 207-211
43 **Duerr RH**, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; **314**: 1461-1463
44 **Libioulle C**, Louis E, Hansoul S, Sandor C, Farnir F, Franchimont D, Vermeire S, Dewit O, de Vos M, Dixon A, Demarche B, Gut I, Heath S, Foglio M, Liang L, Laukens D, Mni M, Zelenika D, Van Gossum A, Rutgeerts P, Belaiche J, Lathrop M, Georges M. Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. *PLoS Genet* 2007; **3**: e58
45 **Parkes M**, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, Fisher SA, Roberts RG, Nimmo ER, Cummings FR, Soars D, Drummond H, Lees CW, Khawaja SA, Bagnall R, Burke DA, Todhunter CE, Ahmad T, Onnie CM, McArdle W, Strachan D, Bethel G, Bryan C, Lewis CM, Deloukas P, Forbes A, Sanderson J, Jewell DP, Satsangi J, Mansfield JC, Cardon L, Mathew CG. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet* 2007; **39**: 830-832
46 **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

47 **Jess T**, Riis L, Jespersgaard C, Hougs L, Andersen PS, Orholm MK, Binder V, Munkholm P. Disease concordance, zygosity, and NOD2/CARD15 status: follow-up of a population-based cohort of Danish twins with inflammatory bowel disease. *Am J Gastroenterol* 2005; **100**: 2486-2492

48 **Halfvarson J**, Bresso F, D'Amato M, Järnerot G, Pettersson S, Tysk C. CARD15/NOD2 polymorphisms do not explain concordance of Crohn's disease in Swedish monozygotic twins. *Dig Liver Dis* 2005; **37**: 768-772

49 **Joossens M**, Van Steen K, Branche J, Sendid B, Rutgeerts P, Vasseur F, Poulain D, Broly F, Colombel JF, Vermeire S, Chamaillard M. Familial aggregation and antimicrobial response dose-dependently affect the risk for Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 58-67

50 **Anderson CA**, Massey DC, Barrett JC, Prescott NJ, Tremelling M, Fisher SA, Gwilliam R, Jacob J, Nimmo ER, Drummond H, Lees CW, Onnie CM, Hanson C, Blaszczyk K, Ravindrarajah R, Hunt S, Varma D, Hammond N, Lewis G, Attlesey H, Watkins N, Ouwehand W, Strachan D, McArdle W, Lewis CM, Lobo A, Sanderson J, Jewell DP, Deloukas P, Mansfield JC, Mathew CG, Satsangi J, Parkes M. Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology* 2009; **136**: 523-529.e3

51 **Franke A**, Balschun T, Karlsen TH, Hedderich J, May S, Lu T, Schuldt D, Nikolaus S, Rosenstiel P, Krawczak M, Schreiber S. Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis. *Nat Genet* 2008; **40**: 713-715

52 **McGovern DP**, Gardet A, Törkvist L, Goyette P, Essers J, Taylor KD, Neale BM, Ong RT, Lagacé C, Li C, Green T, Stevens CR, Beauchamp C, Fleshner PR, Carlson M, D'Amato M, Halfvarson J, Hibberd ML, Lördal M, Padyukov L, Andriulli A, Colombo E, Latiano A, Palmieri O, Bernard EJ, Deslandres C, Hommes DW, de Jong DJ, Stokkers PC, Weersma RK, Sharma Y, Silverberg MS, Cho JH, Wu J, Roeder K, Brant SR, Schumm LP, Duerr RH, Dubinsky MC, Glazer NL, Haritunians T, Ippoliti A, Melmed GY, Siscovick DS, Vasiliauskas EA, Targan SR, Annese V, Wijmenga C, Pettersson S, Rotter JI, Xavier RJ, Daly MJ, Rioux JD, Seielstad M. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nat Genet* 2010; **42**: 332-337

53 **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

54 **Silverberg MS**, Cho JH, Rioux JD, McGovern DP, Wu J, Annese V, Achkar JP, Goyette P, Scott R, Xu W, Barmada MM, Klei L, Daly MJ, Abraham C, Bayless TM, Bossa F, Griffiths AM, Ippoliti AF, Lahaie RG, Latiano A, Paré P, Proctor DD, Regueiro MD, Steinhart AH, Targan SR, Schumm LP, Kistner EO, Lee AT, Gregersen PK, Rotter JI, Brant SR, Taylor KD, Roeder K, Duerr RH. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 2009; **41**: 216-220

55 **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

56 **Montgomery SM**, Morris DL, Pounder RE, Wakefield AJ. Asian ethnic origin and the risk of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 543-546

57 **Probert CS**, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. *Gut* 1992; **33**: 687-693

58 **Carr I**, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second- generation South Asians in Leicester (1991-1994). *Am J Gastroenterol* 1999; **94**: 2918-2922

59 **Van Kruiningen HJ**, Joossens M, Vermeire S, Joossens S, Debeugny S, Gower-Rousseau C, Cortot A, Colombel JF, Rutgeerts P, Vlietinck R. Environmental factors in familial Crohn's disease in Belgium. *Inflamm Bowel Dis* 2005; **11**: 360-365

60 **Joossens M**, Simoens M, Vermeire S, Bossuyt X, Geboes K, Rutgeerts P. Contribution of genetic and environmental factors in the pathogenesis of Crohn's disease in a large family with multiple cases. *Inflamm Bowel Dis* 2007; **13**: 580-584

61 **Halfvarson J**, Jess T, Magnuson A, Montgomery SM, Orholm M, Tysk C, Binder V, Järnerot G. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish-Danish twin population. *Inflamm Bowel Dis* 2006; **12**: 925-933

62 **Andersson RE**, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. *N Engl J Med* 2001; **344**: 808-814

63 **Frisch M**, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. *BMJ* 2009; **338**: b716

64 **Bolin TD**, Wong S, Crouch R, Engelman JL, Riordan SM. Appendicectomy as a therapy for ulcerative proctitis. *Am J Gastroenterol* 2009; **104**: 2476-2482

65 **Andersson RE**, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. *Gastroenterology* 2003; **124**: 40-46

66 **Frisch M**, Johansen C, Mellemkjaer L, Engels EA, Gridley G, Biggar RJ, Olsen JH. Appendectomy and subsequent risk of inflammatory bowel diseases. *Surgery* 2001; **130**: 36-43

67 **Frisch M**, Gridley G. Appendectomy in adulthood and the risk of inflammatory bowel diseases. *Scand J Gastroenterol* 2002; **37**: 1175-1177

68 **Radford-Smith GL**, Edwards JE, Purdie DM, Pandeya N, Watson M, Martin NG, Green A, Newman B, Florin TH. Protective role of appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. *Gut* 2002; **51**: 808-813

69 **Reif S**, Lavy A, Keter D, Broide E, Niv Y, Halak A, Ron Y, Eliakim R, Odes S, Patz J, Fich A, Villa Y, Arber N, Gilat T. Appendectomy is more frequent but not a risk factor in Crohn's disease while being protective in ulcerative colitis: a comparison of surgical procedures in inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 829-832

70 **Russel MG**, Dorant E, Brummer RJ, van de Kruijs MA, Muris JW, Bergers JM, Goedhard J, Stockbrügger RW. Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. South Limburg Inflammatory Bowel Disease Study Group. *Gastroenterology* 1997; **113**: 377-382

71 **Kaplan GG**, Jackson T, Sands BE, Frisch M, Andersson RE, Korzenik J. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. *Am J Gastroenterol* 2008; **103**: 2925-2931

72 **Kaplan GG**, Pedersen BV, Andersson RE, Sands BE, Korzenik J, Frisch M. The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark. *Gut* 2007; **56**: 1387-1392

73 **Calkins BM**. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989; **34**: 1841-1854

74 **Mahid SS**, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006; **81**: 1462-1471
75 **Breuer-Katschinski BD**, Holländer N, Goebell H. Effect of cigarette smoking on the course of Crohn's disease. *Eur J Gastroenterol Hepatol* 1996; **8**: 225-228
76 **Sutherland LR**, Ramcharan S, Bryant H, Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990; **98**: 1123-1128
77 **Lindberg E**, Järnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and clinical course. *Gut* 1992; **33**: 779-782
78 **Cottone M**, Rosselli M, Orlando A, Oliva L, Puleo A, Cappello M, Traina M, Tonelli F, Pagliaro L. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* 1994; **106**: 643-648
79 **Cosnes J**, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001; **120**: 1093-1099
80 **Tuvlin JA**, Raza SS, Bracamonte S, Julian C, Hanauer SB, Nicolae DL, King AC, Cho JH. Smoking and inflammatory bowel disease: trends in familial and sporadic cohorts. *Inflamm Bowel Dis* 2007; **13**: 573-579
81 **Vind I**, Jespersgaard C, Hougs L, Riis L, Dinesen L, Andersen PS, Locht H, Jess T, Munkholm P. Genetic and environmental factors in monozygotic twins with Crohn's disease and their first-degree relatives: a case report. *Digestion* 2005; **71**: 262-265
82 **Bridger S**, Lee JC, Bjarnason I, Jones JE, Macpherson AJ. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis. *Gut* 2002; **51**: 21-25
83 **Lesko SM**, Kaufman DW, Rosenberg L, Helmrich SP, Miller DR, Stolley PD, Shapiro S. Evidence for an increased risk of Crohn's disease in oral contraceptive users. *Gastroenterology* 1985; **89**: 1046-1049
84 **Sandler RS**, Wurzelmann JI, Lyles CM. Oral contraceptive use and the risk of inflammatory bowel disease. *Epidemiology* 1992; **3**: 374-378
85 **Vessey M**, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *Br Med J* (Clin Res Ed) 1986; **292**: 1101-1103
86 **Godet PG**, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995; **37**: 668-673
87 **Cornish JA**, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol* 2008; **103**: 2394-2400
88 **Gleeson MH**, Davis AJ. Non-steroidal anti-inflammatory drugs, aspirin and newly diagnosed colitis: a case-control study. *Aliment Pharmacol Ther* 2003; **17**: 817-825
89 **Gleeson MH**, Lim SH, Spencer D. Non-steroidal anti-inflammatory drugs, salicylates, and colitis. *Lancet* 1996; **347**: 904-905
90 **Tanner AR**, Raghunath AS. Colonic inflammation and nonsteroidal anti-inflammatory drug administration. An assessment of the frequency of the problem. *Digestion* 1988; **41**: 116-120
91 **Evans JM**, McMahon AD, Murray FE, McDevitt DG, MacDonald TM. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997; **40**: 619-622
92 **Bonner GF**, Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 1946-1948
93 **Gibson GR**, Whitacre EB, Ricotti CA. Colitis induced by nonsteroidal anti-inflammatory drugs. Report of four cases and review of the literature. *Arch Intern Med* 1992; **152**: 625-632
94 **Felder JB**, Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol* 2000; **95**: 1949-1954
95 **Sandborn WJ**, Stenson WF, Brynskov J, Lorenz RG, Steidle GM, Robbins JL, Kent JD, Bloom BJ. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol* 2006; **4**: 203-211
96 **Singh S**, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am J Gastroenterol* 2009; **104**: 1298-1313; quiz 1314
97 **Van Kruiningen HJ**, Joossens M, Vermeire S, Joossens S, Debeugny S, Gower-Rousseau C, Cortot A, Colombel JF, Rutgeerts P, Vlietinck R. Familial Crohn's disease in Belgium: pedigrees, temporal relationships among cases, and family histories. *J Clin Gastroenterol* 2007; **41**: 583-590
98 **Van Kruiningen HJ**, Colombel JF, Cartun RW, Whitlock RH, Koopmans M, Kangro HO, Hoogkamp-Korstanje JA, Lecomte-Houcke M, Devred M, Paris JC. An in-depth study of Crohn's disease in two French families. *Gastroenterology* 1993; **104**: 351-360
99 **Peeters M**, Ghoos Y, Maes B, Hiele M, Geboes K, Vantrappen G, Rutgeerts P. Increased permeability of macroscopically normal small bowel in Crohn's disease. *Dig Dis Sci* 1994; **39**: 2170-2176
100 **Peeters M**, Geypens B, Claus D, Nevens H, Ghoos Y, Verbeke G, Baert F, Vermeire S, Vlietinck R, Rutgeerts P. Clustering of increased small intestinal permeability in families with Crohn's disease. *Gastroenterology* 1997; **113**: 802-807
101 **D'Incà R**, Annese V, di Leo V, Latiano A, Quaino V, Abazia C, Vettorato MG, Sturniolo GC. Increased intestinal permeability and NOD2 variants in familial and sporadic Crohn's disease. *Aliment Pharmacol Ther* 2006; **23**: 1455-1461
102 **Fries W**, Renda MC, Lo Presti MA, Raso A, Orlando A, Oliva L, Giofré MR, Maggio A, Mattaliano A, Macaluso A, Cottone M. Intestinal permeability and genetic determinants in patients, first-degree relatives, and controls in a high-incidence area of Crohn's disease in Southern Italy. *Am J Gastroenterol* 2005; **100**: 2730-2736
103 **Buhner S**, Buning C, Genschel J, Kling K, Herrmann D, Dignass A, Kuechler I, Krueger S, Schmidt HH, Lochs H. Genetic basis for increased intestinal permeability in families with Crohn's disease: role of CARD15 3020insC mutation? *Gut* 2006; **55**: 342-347

S- Editor Sun H **L- Editor** Rutherford A **E- Editor** Zheng XM