

New Global Map of Crohn's Disease: Genetic, Environmental, and Socioeconomic Correlations

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Abstract: Seventy-five years after the initial characterization of Crohn's disease (CD), much remains obscure about its etiology. The authors sought to evaluate the incidence trends of the last 25 years worldwide, and the existence of potential correlations with genetic, environmental, and socioeconomic factors that could be etiologically implicated in the pathogenesis of CD. Relevant medical literature for individual countries on the incidence of CD, on the incidence of associated genetic mutations, and on the incidence of suggested etiologic infectious agents such as *Mycobacterium avium paratuberculosis* were retrieved from published medical literature, reports from relevant international congresses, and through official reports from national health authorities. Increasing trends have been observed almost worldwide, with a broad north-south gradient still prevailing in Europe. Distinct regions of New Zealand, Canada, Scotland, France, the Netherlands, and Scandinavia represent the highest incidence areas. Industrialized status and affluence are the common denominators between endemic areas, but are too broad as terms to strongly indicate any particular etiological role. The increasing trends observed in Asia still account for a low prevalence of the disease and may represent increased detection and diagnostic ability of local health systems. Genetic associations are variably reproduced worldwide, in a manner inconsistent with a strong etiologic relationship. Data on paratuberculosis incidence are scarce, and the existing ones are ambivalent regarding an even indirect correlation between CD and an infectious trigger.

(*Inflamm Bowel Dis* 2007;00:000-000)

Key Words: Crohn's disease, epidemiology, incidence, etiology, genetics, NOD2, paratuberculosis, affluence

Crohn's disease (CD) was first recognized as a distinct entity 75 years ago, and although significant progress has been achieved in demystifying aspects of its molecular

pathogenesis, diagnosis, and treatment, its etiological origins remain scarce; at present, CD is considered a result of multifactorial interplay between genetic, immune-related, environmental, and infectious triggers that coalesce into evolution of clinical disease. The correlation with *NOD2* variants has been acknowledged.¹ The continuing study of both local and systematic immune response alterations in CD patients has greatly augmented new therapeutic options, although this immune dysregulation may actually be an epiphenomenon and not an actual trigger. Attempts at implicating certain infectious agents in the etiology of CD have been resurfacing, implicating among others obscure pathogens such as *Mycobacterium avium paratuberculosis* (MAP)²; once again, observations of a possible etiological significance have been counter-challenged by other studies.

Epidemiologic studies are of paramount importance in investigating disease etiology: A burst of scientific literature on CD incidence recently observed has mostly supported the idea of a disease of the developed world, with a typical north-south European gradient.³ The reasoning behind this incidence has been inconsistent; most studies have been localized, often retrospective, and thus subject to inadequate data collection, usually covering limited time periods. Yet, the major existing cohort studies indicate a significant CD incidence rise in the second half of the 20th century. The rationale behind this increase remains speculative, however.

The authors sought to review clinical studies on the evolution of CD incidence in the last 15 years and correlate them with epidemiologic studies of potential etiologic factors for CD. The latter effort at present can only be applied to genetic background; studies on MAP incidence, as will be discussed, are too scarce, and studying other potential environmental triggers possesses certain difficulties that will also be discussed.

MATERIALS AND METHODS

Data on the incidence and prevalence for each country from 1990 onward were sought from the relevant medical literature, abstracts presented at international congresses (including Digestive Disease Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization meetings), reports from official national health authorities, and international organizations with an interest in gastroenterology or inflammatory bowel disease in particular. Medical literature was searched through Medline and Scopus using

Received for publication October 16, 2007; Accepted November 1, 2007.
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DOI 10.1002/ibd.20352
Published online in Wiley InterScience (www.interscience.wiley.com).

“Crohn’s disease” / “Inflammatory bowel disease,” “incidence” / “prevalence,” and individual country names as keywords. Retrieved articles’ references were reviewed to identify further relevant literature reports.

Serial data on incidence were evaluated for the presence of epidemiological trends during the period of the last 15 years. Annual incidence, when not directly provided by the sources, was calculated using individual national population data as indicated in the text.

Studies focusing on the epidemiology of genetic alterations related to CD were retrieved using Medline and Scopus. Keywords used were “Crohn’s disease” / “Inflammatory bowel disease” and “genetics/mutations/variants” or individual gene names (i.e., *NOD2*). Retrieved articles’ references were reviewed to identify further relevant literature reports.

Studies on MAP were identified using Medline and Scopus and keywords “Mycobacterium avium paratuberculosis / paratuberculosis / Johne’s disease” and “incidence / epidemiology.” Published literature on CD and MAP was also evaluated for retrieval of any relevant data. Data from official international organizations such as the Office International des Epizooties (OIE) were also assessed for information on MAP epidemiology.

RESULTS

Global Incidence

The current global status of CD incidence is depicted in Table 1 and Figure 1. Some important parameters that should be further addressed regarding the geographical distribution of the disease follows.

In the US it is estimated that there are 400,000–600,000 patients with CD,⁵³ but national incidence rates have not been reliably reported, and the only notable example of long-term surveillance for CD incidence evolution is the Olmsted County, Minnesota, database,⁵² encompassing registries from the 1930s onward. Whether Minnesota can reliably represent the genetic, environmental, and social background of the US in general, so as to extrapolate conclusions, remains a question. Studies on pediatric CD in the US have been scarce: In Wisconsin the annual incidence of 4.5/10⁵ is double that of pediatric ulcerative colitis (UC),⁵⁴ while the incidence in children of Afro-American origin in Georgia was much higher (7.1/10⁵/year).⁵⁵

In Canada the incidence of the disease in the province of Manitoba is characteristically lower in Indian aboriginals; this discrepancy raises questions about its background, i.e., is it related to a different genetic profile or to the lower hygiene standards of this population (although in the latter case one would expect the opposite effect on CD incidence)? Nevertheless, even in this population a recent increase has been noted, especially in the 30–40 age group. Older reports from the 1980s from Quebec and Ontario exhibited significantly low rates: an incidence of 0.7/10⁵ and prevalence of 33/10⁵ (reflecting a low incidence), respectively.^{56,57} If these data are

compatible with the current status, then CD in Canada, Nova Scotia excluded, would exhibit a west–east gradient, which is indeed unique.

The disease seems to be scarce in Latin America: Apart from the studies mentioned in Table 1, a study from a region of Panama and a region of Argentina showed a practically nonexistent disease in the 1987–1993 period.⁵⁸

The development and continuing evolution of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD) has significantly augmented our understanding of the epidemiologic dynamics of CD and IBD in general. The landmark report on the north–south Europe gradient of CD incidence (7 versus 3.9/10⁵), Alps being the north–south border, has allowed for a better understanding of the potential genetic and environmental factors involved in the evolution of CD.

Significantly important observations may arise from Sweden and are related to a birth cohort phenomenon that is localized in the 1946–1950 or 1945–1954 period, according to different studies.^{59,60}

Of interest are the limited studies from the Baltic former Soviet republics, which one would expect to follow the latitude rule and have a high CD incidence. The only study from this area, from Estonia, showed a low incidence compared to Scandinavia. The acknowledged different infant microflora between Sweden and Estonia⁶¹ may offer general etiologic implications for the disease.

The United Kingdom would theoretically serve as a more localized typical model of the north–south gradient, with a potentially higher incidence in Scotland compared to England and Wales. The older studies from Aberdeen may highlight an increased incidence in the north, but newer data are lacking. The increased incidence of pediatric CD recently reported (doubling in the 1990s, reaching a median annual rate of 4.4/10⁵) may be extrapolated to an increased incidence of CD in general. Comparing the regional UK data, a north–south gradient seems to exist, although typical study limitations (to be discussed below) exist: a typical example is the increased incidence reported from Newcastle, which neighbors Scotland. Other English studies have focused on the racial trends of CD incidence, showing lower prevalence in Southeast Asian residents compared to Europeans or West Indians compared to Caucasians.⁶² The Wales data are of interest mainly in a potential etiologic context: Studies have shown that the increase of CD incidence in the Cardiff region was mainly located in districts bordering the Taff river, where MAP was repeatedly isolated, and thus theoretically implicated through aerosol-mediated infection in CD pathogenesis.⁶³ The incidence is not rising in the Cardiff region overall, however, since the peak was reached in the 1980s.

Incidence trends during the last 15 years are of interest in countries previously under Communist regimes due to the dramatic alteration in lifestyle that has occurred and its potential etiologic implications. Apart from the studies in Table

TABLE 1. Incidence Rates and Trends for Crohn's Disease Worldwide in the Last 15 Years

Country ^{Reference}	Incidence (Cases/ 10 ⁵)	Trend	Comments
Belgium ^{4,5}	4.1-4.5	Minimally rising	Incidence significantly higher in Moroccan Brussels immigrants (6.4/10 ⁵)
Brazil (Janeiro) ⁶	Low	Rising	Cases of 1995-1999 almost double compared to 1980-1984
Canada ^{7,8}			Female predominance (inverse in paediatric disease), roughly equal urban: rural distribution
• Alberta	16.5	Rising	
• British Columbia	8.8		
• Manitoba	15.4	Steady	
• Nova Scotia	20.2		
• Saskatchewan	13.5		
Chile ⁹	Low	Rising	Cases of 1996-2002 more than double compared to 1990-1995
China ¹⁰	0.3		
Croatia (Rijeka) ¹¹	6.5	Rising	Urban male predominance
Denmark ¹²	8.6	Rising	Double incidence compared to 1981-1992 ¹³ data, but similar to 1977
Estonia ¹⁴	1.4	Rising	
France (N) ¹⁵	6.4	Rising	Amiens (NE) incidence 9/10 ⁵ ; ¹⁶ Bretagne (N) lower; ¹⁷ Puy-de-Dome (mid-S) similar to north ¹⁸
Germany ^{19,20}	5.2	Moderately rising	
Greece			Crete: predominance of young urban males
• Epirus (NW) ²¹	0.9	Rising	
• Crete (S) ²²	3		
Hungary (W) ²³	4.68	Rising	Six-fold increase compared to 1977
Iceland ²⁴	5.5	Rising	
Ireland ¹⁶	6		
Israel ²⁵	4.2-5		Incidence similar between Ashkenazi and Sephardic Jews, natural history may differ; incidence extremely low in Arab population ²⁶
Italy ²⁷	2.3		No N-S gradient
Japan ^{28,29}	0.5-1.2	Rising	
Lebanon ³⁰	1.4		
Netherlands ³¹ (Maastricht)	6.9	Rising	In the original EC-IBD study the incidence reported from Maastricht was 9/10 ⁵
New Zealand ³² (Canterbury)	16.5		disease extremely rare in Maoris
Norway (SE) ³³	5.8		
Poland ³⁴	Low		
Portugal (N) ¹⁶	4.2		
Puerto Rico ³⁵	1.9	Rising	Young males predominate; females are on average older
Saudi Arabia ³⁶	1.66	Rising	
Slovakia ³⁷	Low		
Spain			No N-S gradient
• Aragon (NE) ³⁸	3.9	Rising	
• Asturias (NW) ³⁹	6.1	Rising	
• Central ⁴⁰	1.6	Rising	
• Granada (S) ⁴¹	0.9		
• Huelva (SW) ⁴²	6.6	Steady	
• Mallorca (SE) ⁴³	5.8		
• Motril (S) ⁴³	6.5		
• Pablona (N) ⁴⁴	2.5	Steady	
• Sabadell (NE) ⁴³	5.2		
• Vigo (NW) ⁴³	5		
Sweden ⁴⁵	8.9	Fluctuating	
United Kingdom			England: varying incidence according to different studies Scotland: young urban female predominance; increasing rates of paediatric disease also ⁵⁰⁻⁵¹
• England & Wales ⁴⁶⁻⁴⁸	5.9-11.1		
• Scotland ⁴⁹	11.7 (1985-7)		
US (Minnesota) ⁵²	7	Steady	Recent inversion to male predominance; young urban patients

EC-IBD: European collaborative study on inflammatory bowel disease; N: north, NE: northeast, NW: northwest, S: south, SE: southeast, SW: southwest.

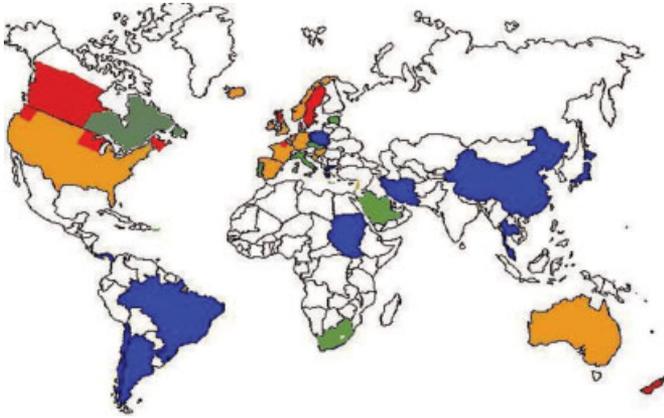


FIGURE 1. The global map of Crohn's disease: red refers to annual incidence above $7/10^5$, orange to incidence $4-7/10^5$, green to incidence $1-4/10^5$, blue to incidence $<1/10^5$. Absence of color indicates absence of data.

1, which show contradicting results (increase in Hungary, low incidence in Poland and Slovakia), a recent report from the Czech Republic on pediatric CD for the years 1990–2001 showed an increase in the annual incidence from 0.25 to $1.26/10^5$, the increasing rate reaching a plateau in 1997–1998 and remaining stable thereafter.⁶⁴

The incidence rates in southern Europe were invariably low in the EC-IBD study: The numerous studies from Spain and the limited Italian data have failed to reproduce a regional north–south gradient. The significance of the definite gradient observed in Greece, on the other hand, may be hampered by the absence of adequate data on the rest of mainland Greece; thus, one cannot specify whether Crete serves as a unique, genetically or physically, triggering environment for CD compared to the rest of Greece, or whether northwest Greece is an anomaly of the Greek rule, possibly due to socioeconomic factors (large percentage of rural population, bottom in the list of European Union affluence indexes). Of the rest of the Balkan countries the increased incidence reported from Croatia is of some importance, since it arises from Rijeka, an industrial region.

Numerous voices have raised concern about the increasing appearance of CD in Asia, where the disease was considered a rare entity in the recent past.⁶⁵ Even though the incidence remains low compared to the developed world, when one takes into account that China and India comprise 40% of the world population, the Asian continent may well actually harbor the majority of CD patients worldwide.

Apart from the studies presented in Table 1, isolated, nonepidemiologic reports exist from Qatar⁶⁶ and Kuwait.⁶⁷ A report from Iran shows that UC vastly predominates at a rate of 9:1.⁶⁸ In India, CD was considered nonexistent until 1986, and is still frequently misdiagnosed as enteric tuberculosis, or even amebic colitis.⁶⁹ Although concern about its incidence in India is obvious in the literature, epidemiologic data are inadequate. Patients from Bangladesh have been studied as UK immigrants,

showing a rapid increase in disease incidence in 1997–2001 compared to 1981–1989 ($7.3/10^5$ /year versus $2.3/10^5$ /year), a trend also observed for UC and pediatric CD.⁷⁰ Reports on CD in Thailand indicate a random existence.⁷¹ In Malaysia, a 2001–2003 study including only 34 patients showed an increased prevalence in Indians, compared to Chinese and particularly Malay populations.⁷² Reports from Singapore show a majority of Chinese patients, and a trend toward increased prevalence, although the number of patients reported indicates an extremely low incidence.⁷³

The rarity of the disease in China is striking. A study focusing on Wuhan city for 1990–2003 showed that CD was much less common than UC, predominant in patients with higher education, and tending to increase through the study period (although this increase was more obvious for UC).⁷⁴ The acknowledged increasing trends in CD incidence in Japan have often been attributed to the Westernization of Japanese society, but the rates are still low.

Early Australian reports indicated an incidence similar to that of northern Europe and the US.⁷⁵ A 1971–2001 study on pediatric disease showed an increase in annual rates from 0.13 to $2/10^5$, and a typical urban patient profile.⁷⁶

The New Zealand Canterbury study is of primary importance since it may have escaped many of the pitfalls of other epidemiological reports: 25% of the included patients self-referred, minimizing underestimation of prevalence.

Regarding Africa, in a continent where infectious threats impose a huge burden on mortality and life expectancy is often below the expected age peaks of CD, few things can be noted for CD, at least at present. A report from South Africa showed that the CD incidence in the early 1980s was $2.6/10^5$ ⁷⁷ and a study from Sudan evaluated 12 patients in a period of 12 years⁷⁸; significantly more patients were recently reported from the city of Algiers for the 1993–2003 period.⁷⁹ In a similar vein, of interest are the Belgian reports highlighting an increased CD incidence in Moroccan immigrants, and even a recent cluster of cases.⁸⁰

Genetics

Table 2 reviews the most important studies focusing on the relationship between *NOD2* and CD, while significant studies focusing on other CD-related genetic mutations are summarized in Table 3.

The acknowledged relation of the *NOD2* variants (R702W, G908R, and 1007fs mutations) with CD is represented to varying degrees in Table 2, ranging from a modest relationship to conferring a significant odds ratio. The numerous correlations that have also been or not been outlined in the various studies do not confer significantly different results from a recent meta-analysis¹⁴⁵ that acknowledged their potential for influencing disease development and phenotypic characteristics. Attempting to correlate the relative frequency of *NOD2* variants with disease incidence yields interesting

TABLE 2. Selected Studies on NOD2 Variant Incidence and Correlations in Patients with Crohn's Disease

Country/ year ^{Reference}	Relation to Crohn's	Localization/ age correlations	Comments
Europe 2002 ⁸¹	+	Related to ileal-specific disease	Increased frequency in familial cases
Belgium, France 2002 ⁸²	+	-	Not related to infliximab response
US 2002 ⁸³	- (heterozygotes) + (compound heterozygotes and homozygotes)	Related to early-onset in familial cases only	Ashkenazi Jew population; G908R most prevalent in familial cases
Germany- Korea 2003 ⁸⁴	+	(Germany)-(Korea)	Complete absence of variants in Korea
Australia 2003 ⁸⁵	+	-	Overall frequency though is low
China 2003 ⁸⁶	-	-	Complete absence of variants
Canada 2004 ⁸⁷	+	Related to ileal disease when associated with specific HLA DRB1 variants	-
Israel 2004 ⁸⁸	+	-	Heterozygosity 47.4% in Ashkenazi versus 27.6% in Sephardic Jewish patients
Italy 2004 ⁸⁹	+	(L1007fs)- (G908R, R702W)	Related to distal ileal fibrostenotic disease
UK and Ireland 2004 ⁹⁰	+	(G908R, L1007fs)	Related to ileal disease, penetrating disease, early-onset
Hungary 2004 ⁹¹	+	(R702W)	Relation to ileal disease
Greece 2004 ⁹²	+	Related to early-onset, ileal/ ileocolonic disease	Inverse relation to extra-intestinal manifestations (arthritis, PSC)
Greece 2005 ⁹³	+	-	Variants in <u>81.7%</u> of CD patients
China 2005 ⁹⁴	-	-	Possible synergistic action with TLR4
US (Wisconsin) 2005 ⁹⁵	+	(Caucasian)-(African-American and Hispanic)	Complete absence of variants
Netherlands 2005 ⁹⁶	+	(R702W, L1007fs)	Paediatric population
Israel 2005 ⁹⁷	-	-	-
Denmark- Portugal 2005 ⁹⁸	+	(Denmark)-(Portugal)	Israeli Arab population; total variant rate significantly lower to Israeli Jewish
UK (Scotland) 2005 ⁹⁹	+	(L1007fs)	High mutation incidence in Portuguese controls
Italy 2005 ¹⁰⁰	+	(NOD2-L1007fs)	Early-onset population
US (Kentucky) 2005 ¹⁰¹	+	Gastroduodenal disease (homozygosity for L1007fs, or two allelic variants)Ileal (G908R)Early-onset (L1007fs)	Familial cases
Turkey (Istanbul) 2006 ¹⁰²	+	(G908R)	Controls exhibited 0% incidence of G908R (OR 36.8)
Sweden 2006 ¹⁰³	+	(R702W, G908R)	inverse for colonic
Turkey (Ankara) 2006 ¹⁰⁴	-	-	-
Croatia 2006 ¹⁰⁵	+	(R702W)	Early-onset; surgery
Spain 2006 ¹⁰⁶	+	(R702W)	stricturing; early-onset
Italy (South) 2006 ¹⁰⁷	+	(all)	-
US (Manitoba) 2007 ¹⁰⁸	+	-	OR 3.7 for heterozygotes, 40 for homozygotes/compound heterozygotes
Europe 2007 ¹⁰⁹	+	-	No correlation to CD incidence: <u>inverse</u> North to South scale: overall 12.1 in Scandinavia, versus 32.8 for rest of Europe
Netherlands 2007 ¹¹⁰	+	(G908R, L1007fs)	stricturing and penetrating disease (particularly L)

CD: Crohn's disease, HLA: human leucocyte antigen, NOD: nucleotide-binding oligomerization domain, OR: odds ratio, PSC: primary sclerosing cholangitis, TLR: Toll-like receptor.

TABLE 3. Selected Studies on Correlation of Crohn's Disease with Genetic Variants Other than NOD2

Country/Year	Genes Studied	Relation to Crohn's	Localization/ Age Correlations	Comments
UK 2001 ¹¹¹	IL4, IL4R	+ (IL4)- (IL4R)	-	Coexistence of IL4 and IL4R also marginally related
China-Netherlands 2002 ¹¹²	CTLA4	+ (Chinese) - (Dutch)	More common in older patients	
Japan 2003 ¹¹³	IL18	+	-	A specific polymorphism related, especially in females
Germany 2004 ¹¹⁴	DLG5	+	-	Synergy with NOD2
UK and Ireland 2004 ⁹⁰	TLR4	-	-	
Greece 2005 ⁹³	TLR4	+		Possible synergistic action with NOD2
Spain 2006 ¹¹⁵	OCTN1, OCTN2	+	Relation to fistulizing disease when NOD2-	Homozygous mutants related to lack of response to infliximab
UK 2005 ¹¹⁶	DLG5	-	-	
Greece 2005 ¹¹⁷	OCTN1, OCTN2, DLG5	+(OCTN1, OCTN2)-(DLG5)	TC haplotype related to ileitis/ ileocolitis and tendency for fibrostenotic disease	DLG5 polymorphism completely absent
Netherlands 2005 ⁹⁶	TLR4	+	-	
Spain 2005 ¹¹⁸	IL10	+(IL10G microsatellite and -1082G SNP)	-	
India 2005 ¹¹⁹	IL-1receptor-a	+(allele2)		
Germany 2005 ¹²⁰	TLR4	+	Stricture disease Penetrating disease in TLR4-/NOD2+	Relation to stricturing disease particularly in NOD2- patients
Japan 2005 ¹²¹	TNFSF15	+	-	Also included two European cohorts
China 2005 ¹²²	TNF- α , TNF- β	-	-	TNF- α related to UC
Italy 2005 ¹⁰⁰	TLR4	-	-	TLR4 mutations statistically significantly increased in relatives but not in patients!
Canada 2005 ¹²³	DLG5	+	none	Modest relation, clearer for UC; not observed in Ashkenazi Jews; no interaction with NOD2/OCTN
UK 2006 ¹²⁴	TNF- α , DLG5	+(TNF- α)-(DLG5)	-	No interaction with NOD2 mutations
Israel 2006 ¹²⁵	TNF- α	-	-	
Turkey (Ankara) 2006 ¹⁰⁴	ICAM1	-	-	
UK 2006 ¹²⁶	NOD1	-	-	
UK 2006 ¹²⁷	TUCAN	+	Non-colonic disease	Association more significant in NOD2- negative patients
Australia 2006 ¹²⁸	Angiotensinogen-6, TGF β	+	stricturing disease (TGF β)	
US ¹²⁹	IL23 receptor	+		Different variants predispose to or strongly protect against Crohn; possibly the most interest candidate for further therapeutic targeting
US (Wisconsin)2007 ¹³⁰	DLG5	Inverse in female	-	paediatric CD patients; R30Q variant

TABLE 3. (Continued)

Country/Year	Genes Studied	Relation to Crohn's	Localization/ Age Correlations	Comments
Canada 2007 ¹³¹	OCTN1, OCTN2	+	-	Not observed in Ashkenazi Jews; IRF1, PDLIM, and P4HA2 are the potential causal variants
Europe 2007 ¹⁰⁹	TLR4	-	-	
Germany 2007 ¹³²	HLA-G gene (IBD3)	+	ileocecal disease	14-bp deletion
Hungary 2007 ¹³³	CTLA4	-	-	+49G polymorphism
Sweden 2007 ¹³⁴	OCTN1, OCTN2	+	-	Variant allelic frequency for 1, homozygosity for both
Germany 2007 ¹³⁵	IL23 receptor	+	Ileal (rs1004819 variant)	Variants strongly predisposing to or protective for Crohn
UK 2007 ¹³⁶	IL23 receptor	+	None	No phenotype associations presented here; variants predisposing to or protective for Crohn
UK 2007 ¹³⁷	IL23 receptor	+		variants predisposing to or protective for Crohn; potential epistatic interaction with OCTN
Germany 2007 ¹³⁸	ATG16L1	+	-	Confirmed in a UK case-control sample; interaction with NOD2
Canada 2007 ¹³⁹	ATG16L1	+	-	
UK 2007 ¹⁴⁰	ATG16L1	+	Ileal	OR 1.65 for Crohn in general, but 2.2 for ileal disease; no interaction with NOD2
UK 2007 ¹⁴¹	ATG16L1	+	None	No interaction with NOD2
Japan 2007 ¹⁴²	ATG16L1/IL23 receptor	-	-	-
US 2007 ¹⁴³	ATG16L1	+		Paediatric population
New Zealand 2007 ¹⁴⁴	ATG16L1/IL23 receptor	+	None	IL23 receptor was associated with CD only in the absence of NOD2 mutations; IL23 receptor variants either protective or predisposing

ATG16L1: autophagy related 16-like 1, CTLA4: Cytotoxic T-Lymphocyte Antigen 4, DLG: Drosophila discs large, HLA: human leucocyte antigen, IBD: inflammatory bowel disease, ICAM: intercellular adhesion molecule, IL: interleukin, NOD: nucleotide-binding oligomerization domain, OCTN: organic cation transporter, TGF: Transforming growth factor, TLR: Toll-like receptor, TNF: tumour necrosis factor, TUCAN: tumor-upregulated CARD-containing antagonist of caspase-nine.

results: It is tempting to correlate the complete absence of *NOD2* variants in CD patients and a healthy population in East Asia with the significantly low incidence of the disease. In a similar vein, the overall low prevalence of *NOD2* variants in Maoris in general can be considered the underlying cause of disease incidence in this population.¹⁴⁶ On the other hand, a recent 3-continent study showed that disease incidence was not related to *NOD2* incidence in a healthy population.¹⁴⁷ Another recent European study showed that the frequency of *NOD2* variants exhibits an inverse gradient (south to north).¹⁰⁹ Typical examples that follow this route are presented in Table 2: Croatia, possessing a relatively high CD incidence, also exhibits a relatively low, compared to

average, percentage of *NOD2* mutations. Similarly, the overwhelming percentage of *NOD2* variant-positive patients reported from Greece does not correlate with a similarly striking disease incidence. The increased percentage of mutations in Ashkenazi compared to Sephardic Jews does not correlate with the roughly similar disease incidence (but on the other hand the low variant percentage in the Arab Israeli population, compared to Jewish, correlates with the lower disease incidence).

The studies that have evaluated other genetic predispositions to CD, as is shown in Table 3, preclude any definite conclusions, and are too limited in number and with varying design to allow for further analysis. One should note, however,

that the exciting pathogenetic discoveries led by the implication of interleukin-23 receptor genes and autophagy related 16-like 1 (ATG16L1) genes may open new horizons. Yet these genetic interactions were not replicated in the only study focusing on non-Caucasian patients, arising from Japan.

DISCUSSION

What unites Canterbury in New Zealand, Nova Scotia and Manitoba in Canada, Amiens in France, Maastricht in the Netherlands, Stockholm in Sweden, and Minnesota in the US (apart from the existence of scientists alert enough to reveal the evolving epidemiologic trends)? Unlocking this strange union would subsequently unlock the mystery of Crohn's etiology, still speculated upon 75 years after its baptism.

Differences in the genetic profile may provide a difference indeed; however, of the numerous genetic alterations incriminated, even the ones systematically reproduced, cannot persuasively hold the epicenter of the pathogenetic process of CD. Furthermore, the evolution of CD incidence, at least in certain areas, is a matter of decades, and genetic factors, alterations of which might take centuries to induce a phenotypic difference, cannot account for these changes. These alterations, having potentially taken place in an early stage of human history, can be indeed incriminated for the relative absence of CD in East Asia. Bearing in mind the multifactorial etiologic model the generally accepted the story of Crohn's in China or Korea may actually follow this path: the absence of a specific genetic background seems to halt Crohn's pathogenesis, since there is no background upon which specific exogenous factors may act. The slightly higher incidence in Japan, in this vein, could be explained by the extreme selection pressure generated by social Westernization, with all its consequences.

Environmental factors should obviously then take their toll: but environment is a broad and vague concept. Researchers have long speculated that CD may be an infectious disease, and the most prominent candidate was MAP. Admittedly, there is a striking resemblance between enteric tuberculosis and CD; MAP has been persuasively epidemiologically correlated with CD in Wales and Sardinia,¹⁴⁸ among other areas, while isolated clusters of cases may imply a similar infectious origin.¹⁴⁹ A recent meta-analysis also supported a relationship, despite avoiding characterizing it as etiologic.¹⁵⁰ The epidemiology of MAP, however, cannot be adequately evaluated and compared to that of CD. One indirect attempt failed to elicit any correlation.¹⁵¹ Even if the epidemiology is known and similar (for example, in Canada, where herds in Alberta, a region with high CD incidence, are three times more seropositive than herds in Ontario,¹⁵² a region with probably low incidence), the road to etiologic implication is long. Furthermore, using the same Canadian example, the difference of seroprevalence between Nova Scotia herds and Ontario herds is not that striking. At inter-

national level limited data exist. The pathogen is obviously widespread, but quantification cannot be achieved due to limited studying and reporting. Data from OIE show that MAP is reported from most countries worldwide, but annual cases for 2004 are too few (possibly due to inadequate sampling or reporting).¹⁵³ Sweden has a high CD incidence but low MAP seroprevalence; a recent Korean study¹⁵⁴ showed higher seroprevalence percentages, in a pattern inverse to that of CD incidence. On the other hand, the recent incidence increase in New Zealand should also be mentioned.¹⁵⁵

A different view: Manitoba and Minnesota are neighboring regions; their similarities may cross the US-Canada border and be related to an endemic, hitherto unrecognized pathogen.

The concept of CD as a disease of the rich tells us a few things about etiology. The popular model of immune-mediated disease development is intriguing, but once more vague: It has been suggested that higher incidence rates among those of higher socioeconomic status may be due to a delayed and/or low level of exposure to common infectious agents during childhood because of improved domestic hygiene, resulting in persistent altered immune responses in genetically susceptible hosts. This has been termed the *hygiene hypothesis*. Recently Hugot et al's¹⁵⁶ groundbreaking "cold chain" hypothesis also provided a link with hygiene by incriminating psychrotrophic bacteria, the presence of which is maintained in refrigerated foodstuff. The Westernization of Japanese life and the increasing incidence in certain former Communist countries may be compatible models. In Puerto Rico, attempting to explain the low incidence of the disease in a Hispanic population, researchers raised among others the possibility of a relation with low breastfeeding rates: in this model, maternal antibodies might protect from psychrotrophic bacteria during early life exposure.

Yet whatever the actual effect imposed by environmental triggers in CD incidence, this effect would require a latent period for disease pathogenesis to evolve and clinical presentation and diagnosis to be made. Even if bacteria or diet were implicated, their pathogenetic effect would require protracted exposure over time, and thus the changes in socioeconomic status should actually precede the changes in CD incidence by a period of 5-10 years at least. Although the hygiene hypothesis is based on a similar concept, it would actually require a far longer latent period (otherwise the majority of new patients contributing to an increase in CD incidence would belong to the pediatric population).

Birth cohorts may offer interesting information in this context, yet they have not been adequately utilized. What makes the Swedish population born after World War II more susceptible to Crohn's? One could argue that World War II is not necessarily the important event that characterizes this cohort: However, a more obvious disruption of "environment" as a global war cannot be imagined. What changed so significantly, then, post-WW II?

Whatever the change, affluence can serve as an indirect marker of CD incidence. Acknowledged as a disease of the developed world, a disease of the industrialized north, or an urban disease, the environmental factor seems to be crucial in its development. But again, what is the main component of “environment”? What makes educated or rich people more susceptible? The immune tolerance hypothesis satisfies most of these scenario needs, and the gradual rise in incidence in Southeast Asian immigrants to the Western world further agrees. Once more, though, existing studies fail to provide answers: NW Greece for example, exhibits perhaps the lowest CD incidence in the European Union, and is acclaimed as 1 of the poorest regions of the Union prior to the expansion. Yet in terms of hygiene and health infrastructure its status is more compatible with the Western world than with developing countries. If one is to believe that endemic pathogens protect from future immune attacks that lead to CD, what is the common pathogen between NW Greece and, say, India?

Why Most Studies Fail to Offer More Information

Designing a proper epidemiologic study for CD is difficult: Many studies have focused on hospital registries, thus underestimating benign cases that may not need admission during study periods. Some studies, for example, the New Zealand one, have managed to overcome this obstacle, hence the increased percentage of self-referencing. Another pitfall is that one cannot be certain that the increased incidence observed is not in fact attributed to increased detection due to the enhanced availability of sophisticated endoscopic techniques worldwide. Long-term studies, such as the ones from the UK, Canada, Sweden, or Minnesota, can overrule this objection, but that may just be the case for reports from the developing world or former Communist countries. Furthermore, there is a striking absence of information on population characteristics: affluence in a selected region can be indirectly estimated by gross domestic product, for example, or the percentage of rural/urban population. Selecting such *personal* data may be a violation of privacy, however. Evaluating educational status tells us few things about the environmental influences of childhood (the age where these may actually serve as a disease trigger). Estimating the prevalence of various potential pathogens is a broad task, and one would not know where to start; furthermore, both a pathogen's prevalence and disease incidence may serve as epiphenomena to hygiene status.

Summarizing the lessons learned from these studies, CD is definitely emerging worldwide as a major public health threat. The increasing reports of pediatric disease further underline this threat. Changes in lifestyle, at the regional, national, or international level, seem to play an etiologic role in the increasing incidence of the disease: Whether these factors are pure exogenous triggers or part of an exogenous–endogenous immune chain we still do not know. Seventy-five

years after Crohn's characterization as a unique entity, we are still in the dark.

REFERENCES

- Gaya DR, Russell RK, Nimmo ER, et al. New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet*. 2006;367:1271–1284.
- Greenstein RJ. Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease. *Lancet Infect Dis*. 2003;3:507–514.
- Binder V. Epidemiology of IBD during the twentieth century: an integrated view. *Best Pract Res Clin Gastroenterol*. 2004;18:463–479.
- Latour P, Louis E, Belaiche J. Incidence of inflammatory bowel disease in the area of Liege: a 3 years prospective study (1993-1996). *Acta Gastroenterol Belg*. 1998;61:410–413.
- Van Gossum A, Adler M, De Reuck M, et al. Epidemiology of inflammatory bowel disease in Brussels' area (1992-1993). *Acta Gastroenterol Belg*. 1996;59:7–9.
- Souza MH, Troncon LE, Rodrigues CM, et al. Trends in the occurrence (1980-1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in southeastern Brazil. *Arq Gastroenterol*. 2002. Apr;39:98–105.
- Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol*. 2006;101:1559–1568.
- Bernstein CN, Blanchard JF, Rawsthorne P, et al. Epidemiology of Crohn's disease and ulcerative colitis in a central Canadian province: a population-based study. *Am J Epidemiol*. 1999;149:916–924.
- Figuerola CC, Quera PR, Valenzuela EJ, et al. Inflammatory bowel disease: experience of two Chilean centers. *Rev Med Chil*. 2005;133:1295–1304.
- Zheng J, Zhu X, Hungfu Z, et al. Crohn's disease in mainland China: a systematic analysis of 50 years of research. *Chin J Dig Dis*. 2005;6:175–181.
- Sincic BM, Vucelic B, Persic M, et al. Incidence of inflammatory bowel disease in Primorsko-goranska County, Croatia, 2000-2004: A prospective population-based study. *Scand J Gastroenterol*. 2006;41:437–444.
- Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol*. 2006;101:1274–1282.
- Fonager K, Sorensen HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981-1992. *Int J Epidemiol*. 1997;26:1003–1008.
- Salupere R. Inflammatory bowel disease in Estonia: a prospective epidemiologic study 1993-1998. *World J Gastroenterol*. 2001;7:387–388.
- Molinie F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988-1999). *Gut*. 2004;53:843–848.
- Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut*. 1996;39:690–697.
- Pagenault M, Tron I, Alexandre JL. Incidence of inflammatory bowel diseases in Bretagne (1994-1995). ABERMAD. Association Bertonne d'Etude et de Recherche des Maladies de l'Appareil Digestif. *Gastroenterol Clin Biol*. 1997;21:483–490.
- Flamenbaum M, Zenut M, Aublet-Cuvelier B, et al. Incidence of inflammatory bowel diseases in the department of Puy-de-Dome in 1993 and 1994. *Gastroenterol Clin Biol*. 1997;21:491–496.
- Timmer A, Breuer-Katschinski B, Goebell H. Time trends in the incidence and disease location of Crohn's disease 1980-1995: a prospective analysis in an urban population in Germany. *Inflamm Bowel Dis*. 1999;5:79–84.
- Loffler A, Glados M. Data on the epidemiology of Crohn disease in the city of Cologne. *Med Klin (Munich)*. 1993;88:516–519.
- Economou M, Trikalinos TA, Loizou KT, et al. Differential effects of

- NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a metaanalysis. *Am J Gastroenterol.* 2004;99:2393–2404.
22. Manousos ON, Koutroubakis I, Potamianos S, et al. A prospective epidemiologic study of Crohn's disease in Heraklion, Crete. Incidence over a 5-year period. *Scand J Gastroenterol.* 1996;31:599–603.
 23. Lakatos L, Mester G, Erdelyi Z, et al. Epidemiology of inflammatory bowel diseases in Veszprem county of Western Hungary between 1977 and 2001. *Orv Hetil.* 2003;144:1819–1827.
 24. Bjornsson S, Johannsson JH. Inflammatory bowel disease in Iceland, 1990-1994: a prospective, nationwide, epidemiological study. *Eur J Gastroenterol Hepatol.* 2000;12:31–38.
 25. Fidler HH, Avidan B, Lahav M, et al. Clinical and demographic characterization of Jewish Crohn's disease patients in Israel. *J Clin Gastroenterol.* 2003;36:8–12.
 26. Niv Y, Abuksis G, Fraser GM. Epidemiology of Crohn's disease in Israel: a survey of Israeli kibbutz settlements. *Am J Gastroenterol.* 1999;94:2961–2965.
 27. Tragnone A, Corrao G, Miglio F, et al. Incidence of inflammatory bowel disease in Italy: a nationwide population-based study. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Int J Epidemiol.* 1996;25:1044–1052.
 28. Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis Colon Rectum.* 2000;43:S85–93.
 29. Morita N, Toki S, Hirohashi T, et al. Incidence and prevalence of inflammatory bowel disease in Japan: nationwide epidemiological survey during the year 1991. *J Gastroenterol.* 1995;30(suppl 8):1–4.
 30. Abdul-Baki H, ElHajj I, El-Zahabi LM, et al. Clinical epidemiology of inflammatory bowel disease in Lebanon. *Inflamm Bowel Dis.* 2007;13:475–480.
 31. Russel MG, Dorant E, Volovics A, et al. High incidence of inflammatory bowel disease in the Netherlands: results of a prospective study. The South Limburg IBD Study Group. *Dis Colon Rectum.* 1998;41:33–40.
 32. Geary RB, Richardson A, Frampton CM, et al. High incidence of Crohn's disease in Canterbury, New Zealand: results of an epidemiologic study. *Inflamm Bowel Dis.* 2006;12:936–943.
 33. Moum B, Vatn MH, Ekbohm A, et al. Incidence of Crohn's disease in four counties in southeastern Norway, 1990-93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol.* 1996;31:355–361.
 34. Wiercinska-Drapalo A, Jaroszewicz J, Flisiak R, et al. Epidemiological characteristics of inflammatory bowel disease in North-Eastern Poland. *World J Gastroenterol.* 2005;11:2630–2633.
 35. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. *Inflamm Bowel Dis.* 2004;10:106–111.
 36. Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, et al. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh. *World J Gastroenterol.* 2004;10:1341–1344.
 37. Prikazka M, Letkovicova M, Matejickova V. Crohn's disease in Slovakia: prevalence, socioeconomic and psychological analysis. *Eur J Epidemiol.* 1998;14:49–53.
 38. Lopez Miguel C, Sicilia B, Sierra E, et al. Incidence of inflammatory bowel disease in Aragon: outcome of a prospective population-based study. *Gastroenterol Hepatol.* 1999;22:323–328.
 39. Saro Gismera C, Lacort Fernandez M, Arguelles Fernandez G, et al. Incidence and prevalence of inflammatory bowel disease in Gijon, Asturias, Spain. *Gastroenterol Hepatol.* 2000;23:322–327.
 40. Mate-Jimenez J, Munoz S, Vicent D, et al. Incidence and prevalence of ulcerative colitis and Crohn's disease in urban and rural areas of Spain from 1981 to 1988. *J Clin Gastroenterol.* 1994;18:27–31.
 41. Martinez-Salmeron JF, Rodrigo M, de Teresa J, et al. Epidemiology of inflammatory bowel disease in the Province of Granada, Spain: a retrospective study from 1979 to 1988. *Gut.* 1993;34:1207–1209.
 42. Garrido A, Martinez MJ, Ortega JA, et al. Epidemiology of chronic inflammatory bowel disease in the Northern area of Huelva. *Rev Esp Enferm Dig.* 2004;96:687–694.
 43. Brullet E, Bonfill X, Urrutia G, et al. Epidemiological study on the incidence of inflammatory bowel disease in 4 Spanish areas. Spanish Group on the Epidemiological Study of Inflammatory Bowel Disease. *Med Clin (Barc).* 1998;110:651–656.
 44. Arin Letamendia A, Burusco Paternain MJ, Borda Celaya F, et al. Epidemiological aspects of inflammatory bowel disease in the Pamplona area. *Rev Esp Enferm Dig.* 1999;91:769–776.
 45. Lapidus A. Crohn's disease in Stockholm County during 1990-2001: an epidemiological update. *World J Gastroenterol.* 2006;12:75–81.
 46. Seagroatt V, Goldacre MJ. Crohn's disease, ulcerative colitis, and measles vaccine in an English population, 1979-1998. *J Epidemiol Community Health.* 2003;57:883–887.
 47. Rubin GP, Hungin AP, Kelly PJ, et al. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther.* 2000;14:1553–1559.
 48. Thompson NP, Fleming DM, Charlton J, et al. Patients consulting with Crohn's disease in primary care in England and Wales. *Eur J Gastroenterol Hepatol.* 1998;10:1007–1012.
 49. Kyle J. Crohn's disease in the northeastern and northern Isles of Scotland: an epidemiological review. *Gastroenterology.* 1992;103:392–399.
 50. Bland R, Evans TJ, Raine P, et al. Inflammatory bowel disease in Scottish children. *Health Bull (Edinb).* 1999;57:365–373.
 51. Watson AJ, Johnston AT, Barker PM, et al. The presentation and management of juvenile-onset chronic inflammatory bowel disease in Northeastern Scotland. *J Pediatr Surg.* 2002;37:83–86.
 52. Jess T, Loftus EV Jr, Harmsen WS, et al. Survival and cause specific mortality in patients with inflammatory bowel disease: a long term outcome study in Olmsted County, Minnesota, 1940-2004. *Gut.* 2006;55:1248–1254.
 53. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology.* 2004;126:1504–1517.
 54. Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr.* 2003;143:525–531.
 55. Ogunbi SO, Ransom JA, Sullivan K, et al. Inflammatory bowel disease in African-American children living in Georgia. *J Pediatr.* 1998;133:103–107.
 56. Mendelhoff AI, Calkin BM. The epidemiology of inflammatory bowel disease. In: Kirsner JB, Shorter RG, eds. *Inflammatory Bowel Disease*. 3rd ed. Philadelphia: Lea and Febiger; 1988:3–34.
 57. Depew WT. Clinical presentation and course of Crohn's disease in southeastern Ontario. *Can J Gastroenterol.* 1988;2:107–116.
 58. Linares de la Cal JA, Canton C, Pajares JM, et al. Inflammatory bowel disease in Argentina and Panama (1987-1993). *Eur J Gastroenterol Hepatol.* 1997;9:1129.
 59. Lapidus A, Bernell O, Hellers G, et al. Incidence of Crohn's disease in Stockholm County 1955-1989. *Gut.* 1997;41:480–486.
 60. Ekbohm A, Helmick C, Zack M, et al. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology.* 1991;100:350–358.
 61. Sepp E, Julge K, Vasar M, et al. Intestinal microflora of Estonian and Swedish infants. *Acta Paediatr.* 1997;86:956–961.
 62. Fellows IW, Freeman JG, Holmes GK. Crohn's disease in the city of Derby, 1951-85. *Gut.* 1990;31:1262–1265.
 63. Pickup RW, Rhodes G, Arnott S, et al. Mycobacterium avium subsp. paratuberculosis in the catchment area and water of the River Taff in South Wales, United Kingdom, and its potential relationship to clustering of Crohn's disease cases in the city of Cardiff. *Appl Environ Microbiol.* 2005;71:2130–2139.
 64. Pozler O, Maly J, Bonova O, et al. Incidence of Crohn disease in the Czech Republic in the years 1990 to 2001 and assessment of pediatric population with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2006;42:186–189.
 65. Yang SK, Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease in Asia. *Inflamm Bowel Dis.* 2001;7:260–270.
 66. Butt MT, Bener A, Al-Kaabi S, et al. Clinical characteristics of Crohns disease in Qatar. *Saudi Med J.* 2005;26:1796–1799.
 67. Al-Nakib B, Radhakrishnan S, Jacob GS, et al. Inflammatory bowel disease in Kuwait. *Am J Gastroenterol.* 1984;79:191–194.
 68. Aghazadeh R, Zali MR, Bahari A, et al. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol.* 2005;20:1691–1695.

69. Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India: is it related to improved sanitation? *Indian J Gastroenterol.* 2005;24:23–24.
70. Tsironi E, Feakins RM, Probert CS, et al. Incidence of inflammatory bowel disease is rising and abdominal tuberculosis is falling in Bangladesh in East London, United Kingdom. *Am J Gastroenterol.* 2004;99:1749–1755.
71. Rerknimitr R, Chalapiat O, Kongkam P, et al. Clinical characteristics of inflammatory bowel disease in Thailand: a 16 years review. *J Med Assoc Thai.* 2005;88(suppl 4):S129–133.
72. Hilmi I, Tan YM, Goh KL. Crohn's disease in adults: observations in a multiracial Asian population. *World J Gastroenterol.* 2006;12:1435–1438.
73. Lee YM, Fock K, See SJ, et al. Racial differences in the prevalence of ulcerative colitis and Crohn's disease in Singapore. *J Gastroenterol Hepatol.* 2000;15:622–625.
74. Jiang L, Xia B, Li J, et al. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis.* 2006;12:212–217.
75. McDermott FT, Whelan G, St John DJ, et al. Relative incidence of Crohn's disease and ulcerative colitis in six Melbourne hospitals. *Med J Aust.* 1987;146:525–529.
76. Phavichitr N, Cameron DJ, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. *J Gastroenterol Hepatol.* 2003;18:329–332.
77. Wright JP, Froggatt J, O'Keefe EA, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980–1984. *S Afr Med J.* 1986;70:10–15.
78. Khalifa SE, Mudawi HM, Fedail SS. Presentation and management outcome of inflammatory bowel disease in Sudan. *Trop Gastroenterol.* 2005;26:194–196.
79. Mahiou H, Nakmouche M, Kaddache N, et al. Outcome of the first corticosteroid treatment course in uncomplicated Crohn's disease: a multicenter study. Proceedings of the 14th United European Gastroenterology Week, Abstract MON-G-107.
80. Joossens M, Simoens M, Vermeire S, et al. 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.
81. Cuthbert AP, Fisher SA, Mirza MM, et al. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. *Gastroenterology.* 2002;122:867–874.
82. Vermeire S, Louis E, Rutgeerts P, et al. NOD2/CARD15 does not influence response to infliximab in Crohn's disease. *Gastroenterology.* 2002;123:106–111.
83. Zhou Z, Lin XY, Akolkar PN, et al. Variation at NOD2/CARD15 in familial and sporadic cases of Crohn's disease in the Ashkenazi Jewish population. *Am J Gastroenterol.* 2002;97:3095–3101.
84. Croucher PJ, Mascheretti S, Hampe J, et al. Haplotype structure and association to Crohn's disease of CARD15 mutations in two ethnically divergent populations. *Eur J Hum Genet.* 2003;11:6–16.
85. Cavanaugh JA, Adams KE, Quak EJ, et al. CARD15/NOD2 risk alleles in the development of Crohn's disease in the Australian population. *Ann Hum Genet.* 2003;67:35–41.
86. Leong RW, Armuzzi A, Ahmad T, et al. NOD2/CARD15 gene polymorphisms and Crohn's disease in the Chinese population. *Aliment Pharmacol Ther.* 2003;17:1465–1470.
87. Newman B, Silverberg MS, Gu X, et al. CARD15 and HLA DRB1 alleles influence susceptibility and disease localization in Crohn's disease. *Am J Gastroenterol.* 2004;99:306–315.
88. Karban A, Waterman M, Panhuysen CI, et al. NOD2/CARD15 genotype and phenotype differences between Ashkenazi and Sephardic Jews with Crohn's disease. *Am J Gastroenterol.* 2004;99:1134–1140.
89. Vavassori P, Borgiani P, Biancone L, et al. CARD15 mutation analysis in an Italian population: Leu1007fsinsC but neither Arg702Trp nor Gly908Arg mutations are associated with Crohn's disease. *Inflamm Bowel Dis.* 2004;10:116–121.
90. Arnott ID, Nimmo ER, Drummond HE, et al. NOD2/CARD15, TLR4 and CD14 mutations in Scottish and Irish Crohn's disease patients: evidence for genetic heterogeneity within Europe? *Genes Immun.* 2004;5:417–425.
91. Lakatos L, Lakatos PL, Willheim-Polli C, et al. NOD2/CARD15 mutations and genotype-phenotype correlations in patients with Crohn's disease. Hungarian multicenter study. *Orv Hetil.* 2004;145:1403–1411.
92. Gazouli M, Zacharatos P, Mantzaris GJ, et al. Association of NOD2/CARD15 variants with Crohn's disease in a Greek population. *Eur J Gastroenterol Hepatol.* 2004;16:1177–1182.
93. Gazouli M, Mantzaris G, Kotsinas A, et al. Association between polymorphisms in the Toll-like receptor 4, CD14, and CARD15/NOD2 and inflammatory bowel disease in the Greek population. *World J Gastroenterol.* 2005;11:681–685.
94. Gao M, Cao Q, Luo LH, et al. NOD2/CARD15 gene polymorphisms and susceptibility to Crohn's disease in Chinese Han population. *Zhonghua Nei Ke Za Zhi.* 2005;44:210–212.
95. Kugathasan S, Loizides A, Babusukumar U, et al. Comparative phenotypic and CARD15 mutational analysis among African American, Hispanic, and White children with Crohn's disease. *Inflamm Bowel Dis.* 2005;11:631–638.
96. Braat H, Stokkers P, Hommes T, et al. Consequence of functional Nod2 and Tlr4 mutations on gene transcription in Crohn's disease patients. *J Mol Med.* 2005;83:601–609.
97. Karban A, Atia O, Leitersdorf E, et al. The relation between NOD2/CARD15 mutations and the prevalence and phenotypic heterogeneity of Crohn's disease: lessons from the Israeli Arab Crohn's disease cohort. *Dig Dis Sci.* 2005;50:1692–1697.
98. Vind I, Vieira A, Hougs L, et al. NOD2/CARD15 gene polymorphisms in Crohn's disease: a genotype-phenotype analysis in Danish and Portuguese patients and controls. *Digestion.* 2005;72:156–163.
99. Russell RK, Drummond HE, Nimmo EE, et al. Genotype-phenotype analysis in childhood-onset Crohn's disease: NOD2/CARD15 variants consistently predict phenotypic characteristics of severe disease. *Inflamm Bowel Dis.* 2005;11:955–964.
100. Fries W, Renda MC, Lo Presti MA, et al. 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.
101. Mardini HE, Gregory KJ, Nasser M, et al. Gastrointestinal Crohn's disease is associated with NOD2/CARD15 gene polymorphisms, particularly L1007P homozygosity. *Dig Dis Sci.* 2005;50:2316–2322.
102. Uyar FA, Over-Hamzaoglu H, Ture F, et al. Distribution of common CARD15 variants in patients with sporadic Crohn's disease: cases from Turkey. *Dig Dis Sci.* 2006;51:706–710.
103. Torkvist L, Noble CL, Lordal M, et al. Contribution of CARD15 variants in determining susceptibility to Crohn's disease in Sweden. *Scand J Gastroenterol.* 2006;41:700–705.
104. Ozen SC, Dagli U, Kilic MY, et al. NOD2/CARD15, NOD1/CARD4, and ICAM-1 gene polymorphisms in Turkish patients with inflammatory bowel disease. *J Gastroenterol.* 2006;41:304–310.
105. Cukovic-Cavka S, Vermeire S, Hrstic I, et al. NOD2/CARD15 mutations in Croatian patients with Crohn's disease: prevalence and genotype-phenotype relationship. *Eur J Gastroenterol Hepatol.* 2006;18:895–899.
106. De Diego C, Alcantara M, Valle J, et al. Frequency of CARD15 polymorphisms in patients with Crohn's disease from Toledo, Spain: genotype-phenotype correlation. *Genet Test.* 2006;10:178–185.
107. Cottone M, Renda MC, Mattaliano A, et al. Incidence of Crohn's disease and CARD15 mutation in a small township in Sicily. *Eur J Epidemiol.* 2006;21:887–892.
108. Brant SR, Wang MH, Rawsthorne P, et al. A population-based case-control study of CARD15 and other risk factors in Crohn's disease and ulcerative colitis. *Am J Gastroenterol.* 2007;102:313–323.
109. Riis L, Vind I, Vermeire S, et al. The prevalence of genetic and serologic markers in an unselected European population-based cohort of IBD patients. *Inflamm Bowel Dis.* 2007;13:24–32.
110. van der Linde K, Boor PP, Houwing-Duistermaat JJ, et al. CARD15 mutations in Dutch familial and sporadic inflammatory bowel disease and an overview of European studies. *Eur J Gastroenterol Hepatol.* 2007;19:449–459.
111. Aithal GP, Day CP, Leathart J, et al. Association of single nucleotide polymorphisms in the interleukin-4 gene and interleukin-4 receptor gene with Crohn's disease in a British population. *Genes Immun.* 2001;2:44–47.
112. Xia B, Crusius JB, Wu J, et al. CTLA4 gene polymorphisms in Dutch

- and Chinese patients with inflammatory bowel disease. *Scand J Gastroenterol.* 2002;37:1296–1300.
113. Tamura K, Fukuda Y, Sashio H, et al. IL18 polymorphism is associated with an increased risk of Crohn's disease. *J Gastroenterol.* 2002; 37S14:111–116.
 114. Stoll M, Corneliussen B, Costello CM, et al. Genetic variation in DLG5 is associated with inflammatory bowel disease. *Nat Genet.* 2004;36: 476–480.
 115. Urcelay E, Mendoza JL, Martinez A, et al. IBD5 polymorphisms in inflammatory bowel disease: association with response to infliximab. *World J Gastroenterol.* 2005;11:1187–1192.
 116. Noble CL, Nimmo ER, Drummond H, et al. DLG5 variants do not influence susceptibility to inflammatory bowel disease in the Scottish population. *Gut.* 2005;54:1416–1420.
 117. Gazouli M, Mantzaris G, Archimandritis AJ, et al. Single nucleotide polymorphisms of OCTN1, OCTN2, and DLG5 genes in Greek patients with Crohn's disease. *World J Gastroenterol.* 2005;11:7525–7530.
 118. Fernandez L, Martinez A, Mendoza JL, et al. Interleukin-10 polymorphisms in Spanish patients with IBD. *Inflamm Bowel Dis.* 2005;11: 739–743.
 119. Mittal RD, Bid HK, Ghoshal UC. IL-1 receptor antagonist (IL-1Ra) gene polymorphism in patients with inflammatory bowel disease in India. *Scand J Gastroenterol.* 2005;40:827–831.
 120. Brand S, Staudinger T, Schnitzler F, et al. The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease. *Inflamm Bowel Dis.* 2005;11:645–652.
 121. Yamazaki K, McGovern D, Ragoussis J, et al. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Hum Mol Genet.* 2005;14:3499–3506.
 122. Song Y, Wu KC, Zhang L, et al. Correlation between a gene polymorphism of tumor necrosis factor and inflammatory bowel disease. *Chin J Dig Dis.* 2005;6:170–174.
 123. Newman WG, Gu X, Wintle RF, et al. DLG5 variants contribute to Crohn disease risk in a Canadian population. *Hum Mutat.* 2006;27: 353–358.
 124. Tremelling M, Waller S, Bredin F, et al. Genetic variants in TNF-alpha but not DLG5 are associated with inflammatory bowel disease in a large United Kingdom cohort. *Inflamm Bowel Dis.* 2006;12:178–184.
 125. Fidler HH, Heijmans R, Chowers Y, et al. TNF-857 polymorphism in Israeli Jewish patients with inflammatory bowel disease. *Int J Immunogenet.* 2006;33:81–85.
 126. Tremelling M, Hancock L, Bredin F, et al. Complex insertion/deletion polymorphism in NOD1 (CARD4) is not associated with inflammatory bowel disease susceptibility in East Anglia panel. *Inflamm Bowel Dis.* 2006;12:967–971.
 127. McGovern DP, Butler H, Ahmad T, et al. TUCAN (CARD8) genetic variants and inflammatory bowel disease. *Gastroenterology.* 2006;131: 1190–1196.
 128. Hume GE, Fowler EV, Lincoln D, et al. Angiotensinogen and transforming growth factor beta1: novel genes in the pathogenesis of Crohn's disease. *J Med Genet.* 2006;43:e51.
 129. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science.* 2006;314:1461–1463.
 130. Biank V, Friedrichs F, Babusukumar U, et al. DLG5 R30Q variant is a female-specific protective factor in pediatric onset Crohn's disease. *Am J Gastroenterol.* 2007;102:391–398.
 131. Silverberg MS, Duerr RH, Brant SR, et al. Refined genomic localization and ethnic differences observed for the IBD5 association with Crohn's disease. *Eur J Hum Genet.* 2007;15:328–335.
 132. Glas J, Torok HP, Tonenchi L, et al. The 14-bp deletion polymorphism in the HLA-G gene displays significant differences between ulcerative colitis and Crohn's disease and is associated with ileocecal resection in Crohn's disease. *Int Immunol.* 2007;19:621–626.
 133. Magyar L, Farago B, Bene J, et al. No association of the cytotoxic T-lymphocyte associated gene CTLA4 +49A/G polymorphisms with Crohn's disease and ulcerative colitis in Hungarian population samples. *World J Gastroenterol.* 2007;13:2205–2208.
 134. Torkvist L, Noble CL, Lordal M, et al. Contribution of the IBD5 locus to Crohn's disease in the Swedish population. *Scand J Gastroenterol.* 2007;42:200–206.
 135. Glas J, Seiderer J, Wetzke M, et al. rs1004819 is the main disease-associated IL23R variant in German Crohn's disease patients: combined analysis of IL23R, CARD15, and OCTN1/2 variants. *PLoS ONE.* 2007;2:e819.
 136. Tremelling M, Cummings F, Fisher SA, et al. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. *Gastroenterology.* 2007;132:1657–1664.
 137. Cummings JR, Ahmad T, Geremia A, et al. Contribution of the novel inflammatory bowel disease gene IL23R to disease susceptibility and phenotype. *Inflamm Bowel Dis.* 2007;13:1063–1068.
 138. Hampe J, Franke A, Rosenstiel P, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet.* 2007;39:207–211.
 139. Rioux JD, Xavier RJ, Taylor KD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet.* 2007;39:596–604.
 140. Prescott NJ, Fisher SA, Franke A, et al. A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5. *Gastroenterology.* 2007;132:1665–1671.
 141. Cummings JR, Cooney R, Pathan S, et al. Confirmation of the role of ATG16L1 as a Crohn's disease susceptibility gene. *Inflamm Bowel Dis.* 2007;13:941–946.
 142. Yamazaki K, Onouchi Y, Takazoe M, et al. Association analysis of genetic variants in IL23R, ATG16L1 and 5p13.1 loci with Crohn's disease in Japanese patients. *J Hum Genet.* 2007;52:575–583.
 143. Baldassano RN, Bradfield JP, Monos DS, et al. Association of the T300A non-synonymous variant of the ATG16L1 gene with susceptibility to paediatric Crohn's disease. *Gut.* 2007;56:1171–1173.
 144. Roberts RL, Geary RB, Hollis-Moffatt JE, et al. IL23R R381Q and ATG16L1 T300A are strongly associated with Crohn's disease in a study of New Zealand Caucasians with inflammatory bowel disease. *Am J Gastroenterol.* 2007 (in press).
 145. Economou M, Trikalinos TA, Loizou KT, et al. Differential effects of NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a meta-analysis. *Am J Gastroenterol.* 2004;99:2393–2404.
 146. Geary RB, Lea RA, Roberts RL, et al. CARD15 allele frequency differences in New Zealand Maori: ancestry specific susceptibility to Crohn's disease in New Zealand? *Gut.* 2006;55:580.
 147. Hugot JP, Zaccaria I, Cavanaugh J, et al. Prevalence of CARD15/NOD2 mutations in Caucasian healthy people. *Am J Gastroenterol.* 2007;102:1259–1267.
 148. Sechi LA, Gazouli M, Sieswerda LE, et al. Relationship between Crohn's disease, infection with *Mycobacterium avium* subspecies paratuberculosis and SLC11A1 gene polymorphisms in Sardinian patients. *World J Gastroenterol.* 2006;12:7161–7164.
 149. Van Kruiningen HJ, Freda BJ. A clustering of Crohn's disease in Mankato, Minnesota. *Inflamm Bowel Dis.* 2001;7:27–33.
 150. Feller M, Huwiler K, Stephan R, et al. *Mycobacterium avium* subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007;7:607–613.
 151. Jones PH, Farver TB, Beaman B, et al. Crohn's disease in people exposed to clinical cases of bovine paratuberculosis. *Epidemiol Infect.* 2006;134:49–56.
 152. Tiwari A, VanLeeuwen JA, McKenna SL, et al. Johne's disease in Canada Part I: clinical symptoms, pathophysiology, diagnosis, and prevalence in dairy herds. *Can Vet J.* 2006;47:874–882.
 153. World Organization for Animal Health. Handistatus II: zoonoses: global cases of paratuberculosis 2004 (http://www.oie.int/hs2/sit_mald_cont.asp?amp;c_mald=27&c_cont=6&annee=2004#). Accessed October 15, 2007.
 154. Park KT, Ahn J, Davis WC, et al. Analysis of the seroprevalence of bovine paratuberculosis and the application of modified absorbed ELISA to field sample testing in Korea. *J Vet Sci.* 2006;7:349–354.
 155. de Lisle GW, Cannon MC, Yates GF, et al. Use of a polymerase chain reaction to subtype *Mycobacterium avium* subspecies paratuberculosis, an increasingly important pathogen from farmed deer in New Zealand. *N Z Vet J.* 2006;54:195–197.
 156. Hugot JP, Alberti C, Berrebi D, et al. Crohn's disease: the cold chain hypothesis. *Lancet.* 2003;362:2012–2015.