

# 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.

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**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.<sup>1</sup> 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)<sup>2</sup>; 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.<sup>3</sup> 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

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“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,<sup>53</sup> 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,<sup>52</sup> 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 4.5/10<sup>5</sup> is double that of pediatric ulcerative colitis (UC),<sup>54</sup> while the incidence in children of Afro-American origin in Georgia was much higher (7.1/10<sup>5</sup>/year).<sup>55</sup>

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 0.7/10<sup>5</sup> and prevalence of 33/10<sup>5</sup> (reflecting a low incidence), respectively.<sup>56,57</sup> 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.<sup>58</sup>

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 3.9/10<sup>5</sup>), 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.<sup>59,60</sup>

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 Estonia<sup>61</sup> may offer general etiologic implications for the disease.

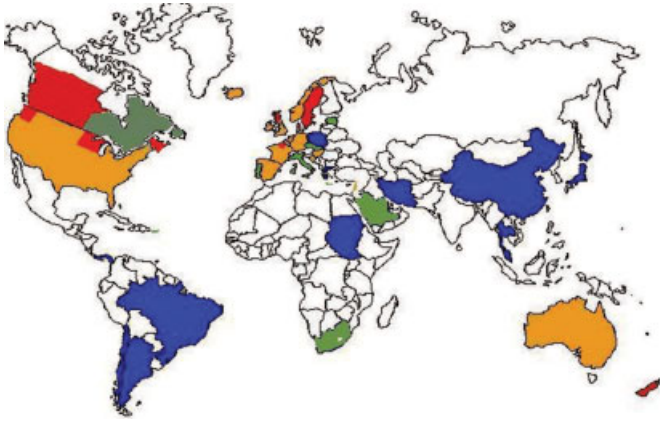
The United Kingdom would theoretically serve as a more localized typical model of the north–south gradient, with a potentially higher incidence in Scotland compared to England and Wales. The older studies from Aberdeen may highlight an increased incidence in the north, but newer data are lacking. The increased incidence of pediatric CD recently reported (doubling in the 1990s, reaching a median annual rate of 4.4/10<sup>5</sup>) 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.<sup>62</sup> 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.<sup>63</sup> 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 <sup>Reference</sup>	Incidence (Cases/ 10 <sup>5</sup> )	Trend	Comments
Belgium <sup>4,5</sup>	4.1-4.5	Minimally rising	Incidence significantly higher in Moroccan Brussels immigrants (6.4/10 <sup>5</sup> )
Brazil (Janeiro) <sup>6</sup>	Low	Rising	Cases of 1995-1999 almost double compared to 1980-1984
Canada <sup>7,8</sup>			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 <sup>9</sup>	Low	Rising	Cases of 1996-2002 more than double compared to 1990-1995
China <sup>10</sup>	0.3		
Croatia (Rijeka) <sup>11</sup>	6.5	Rising	Urban male predominance
Denmark <sup>12</sup>	8.6	Rising	Double incidence compared to 1981-1992 <sup>13</sup> data, but similar to 1977
Estonia <sup>14</sup>	1.4	Rising	
France (N) <sup>15</sup>	6.4	Rising	Amiens (NE) incidence 9/10 <sup>5</sup> ; <sup>16</sup> Bretagne (N) lower; <sup>17</sup> Puy-de-Dome (mid-S) similar to north <sup>18</sup>
Germany <sup>19,20</sup>	5.2	Moderately rising	
Greece			Crete: predominance of young urban males
• Epirus (NW) <sup>21</sup>	0.9	Rising	
• Crete (S) <sup>22</sup>	3		
Hungary (W) <sup>23</sup>	4.68	Rising	Six-fold increase compared to 1977
Iceland <sup>24</sup>	5.5	Rising	
Ireland <sup>16</sup>	6		
Israel <sup>25</sup>	4.2-5		Incidence similar between Ashkenazi and Sephardic Jews, natural history may differ; incidence extremely low in Arab population <sup>26</sup>
Italy <sup>27</sup>	2.3		No N-S gradient
Japan <sup>28,29</sup>	0.5-1.2	Rising	
Lebanon <sup>30</sup>	1.4		
Netherlands <sup>31</sup> (Maastricht)	6.9	Rising	In the original EC-IBD study the incidence reported from Maastricht was 9/10 <sup>5</sup>
New Zealand <sup>32</sup> (Canterbury)	16.5		disease extremely rare in Maoris
Norway (SE) <sup>33</sup>	5.8		
Poland <sup>34</sup>	Low		
Portugal (N) <sup>16</sup>	4.2		
Puerto Rico <sup>35</sup>	1.9	Rising	Young males predominate; females are on average older
Saudi Arabia <sup>36</sup>	1.66	Rising	
Slovakia <sup>37</sup>	Low		
Spain			No N-S gradient
• Aragon (NE) <sup>38</sup>	3.9	Rising	
• Asturias (NW) <sup>39</sup>	6.1	Rising	
• Central <sup>40</sup>	1.6	Rising	
• Granada (S) <sup>41</sup>	0.9		
• Huelva (SW) <sup>42</sup>	6.6	Steady	
• Mallorca (SE) <sup>43</sup>	5.8		
• Motril (S) <sup>43</sup>	6.5		
• Pablona (N) <sup>44</sup>	2.5	Steady	
• Sabadell (NE) <sup>43</sup>	5.2		
• Vigo (NW) <sup>43</sup>	5		
Sweden <sup>45</sup>	8.9	Fluctuating	
United Kingdom			England: varying incidence according to different studies Scotland: young urban female predominance; increasing rates of paediatric disease also <sup>50-51</sup>
• England & Wales <sup>46-48</sup>	5.9-11.1		
• Scotland <sup>49</sup>	11.7 (1985-7)		
US (Minnesota) <sup>52</sup>	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.<sup>64</sup>

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.<sup>65</sup> 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 Qatar<sup>66</sup> and Kuwait.<sup>67</sup> A report from Iran shows that UC vastly predominates at a rate of 9:1.<sup>68</sup> In India, CD was considered nonexistent until 1986, and is still frequently misdiagnosed as enteric tuberculosis, or even amebic colitis.<sup>69</sup> 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.<sup>70</sup> Reports on CD in Thailand indicate a random existence.<sup>71</sup> In Malaysia, a 2001–2003 study including only 34 patients showed an increased prevalence in Indians, compared to Chinese and particularly Malay populations.<sup>72</sup> 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.<sup>73</sup>

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).<sup>74</sup> 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.<sup>75</sup> 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.<sup>76</sup>

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  $2.6/10^5$ <sup>77</sup> and a study from Sudan evaluated 12 patients in a period of 12 years<sup>78</sup>; significantly more patients were recently reported from the city of Algiers for the 1993–2003 period.<sup>79</sup> 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.<sup>80</sup>

## 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-analysis<sup>145</sup> 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 <sup>Reference</sup>	Relation to Crohn's	Localization/ age correlations	Comments
Europe 2002 <sup>81</sup>	+	Related to ileal-specific disease	Increased frequency in familial cases
Belgium, France 2002 <sup>82</sup>	+	-	Not related to infliximab response
US 2002 <sup>83</sup>	- (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 <sup>84</sup>	+	(Germany)-(Korea)	Complete absence of variants in Korea
Australia 2003 <sup>85</sup>	+	-	Overall frequency though is low
China 2003 <sup>86</sup>	-	-	Complete absence of variants
Canada 2004 <sup>87</sup>	+	Related to ileal disease when associated with specific HLA DRB1 variants	-
Israel 2004 <sup>88</sup>	+	-	Heterozygosity 47.4% in Ashkenazi versus 27.6% in Sephardic Jewish patients
Italy 2004 <sup>89</sup>	+	(L1007fs)- (G908R, R702W)	Related to distal ileal fibrostenotic disease
UK and Ireland 2004 <sup>90</sup>	+	(G908R, L1007fs)	Related to ileal disease, penetrating disease, early-onset
Hungary 2004 <sup>91</sup>	+	(R702W)	Relation to ileal disease
Greece 2004 <sup>92</sup>	+	Related to early-onset, ileal/ ileocolonic disease	Inverse relation to extra-intestinal manifestations (arthritis, PSC)
Greece 2005 <sup>93</sup>	+	-	Variants in <u>81.7%</u> of CD patients
China 2005 <sup>94</sup>	-	-	Possible synergistic action with TLR4
US (Wisconsin) 2005 <sup>95</sup>	+	(Caucasian)-(African-American and Hispanic)	Complete absence of variants
Netherlands 2005 <sup>96</sup>	+	(R702W, L1007fs)	Paediatric population
Israel 2005 <sup>97</sup>	-	-	-
Denmark- Portugal 2005 <sup>98</sup>	+	(Denmark)-(Portugal)	Ileal disease
UK (Scotland) 2005 <sup>99</sup>	+	(L1007fs)	Relation to jejunal, jejuno-ileal disease, stricturing disease, need for surgery
Italy 2005 <sup>100</sup>	+	(NOD2-L1007fs)	-
US (Kentucky) 2005 <sup>101</sup>	+	Gastroduodenal disease (homozygosity for L1007fs, or two allelic variants)Ileal (G908R)Early-onset (L1007fs)	Familial cases
Turkey (Istanbul) 2006 <sup>102</sup>	+	(G908R)	Controls exhibited 0% incidence of G908R (OR 36.8)
Sweden 2006 <sup>103</sup>	+	(R702W, G908R)	inverse for colonic
Turkey (Ankara) 2006 <sup>104</sup>	-	-	-
Croatia 2006 <sup>105</sup>	+	(R702W)	Early-onset; surgery
Spain 2006 <sup>106</sup>	+	(R702W)	stricturing; early-onset
Italy (South) 2006 <sup>107</sup>	+	(all)	-
US (Manitoba) 2007 <sup>108</sup>	+	-	OR 3.7 for heterozygotes, 40 for homozygotes/compound heterozygotes
Europe 2007 <sup>109</sup>	+	-	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 <sup>110</sup>	+	(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 <sup>111</sup>	IL4, IL4R	+ (IL4)- (IL4R)	-	Coexistence of IL4 and IL4R also marginally related
China-Netherlands 2002 <sup>112</sup>	CTLA4	+ (Chinese) - (Dutch)	More common in older patients	
Japan 2003 <sup>113</sup>	IL18	+	-	A specific polymorphism related, especially in females
Germany 2004 <sup>114</sup>	DLG5	+	-	Synergy with NOD2
UK and Ireland 2004 <sup>90</sup>	TLR4	-	-	
Greece 2005 <sup>93</sup>	TLR4	+		Possible synergistic action with NOD2
Spain 2006 <sup>115</sup>	OCTN1, OCTN2	+	Relation to fistulizing disease when NOD2-	Homozygous mutants related to lack of response to infliximab
UK 2005 <sup>116</sup>	DLG5	-	-	
Greece 2005 <sup>117</sup>	OCTN1, OCTN2, DLG5	+(OCTN1, OCTN2)-(DLG5)	TC haplotype related to ileitis/ ileocolitis and tendency for fibrostenotic disease	DLG5 polymorphism completely absent
Netherlands 2005 <sup>96</sup>	TLR4	+	-	
Spain 2005 <sup>118</sup>	IL10	+(IL10G microsatellite and -1082G SNP)	-	
India 2005 <sup>119</sup>	IL-1receptor-a	+(allele2)		
Germany 2005 <sup>120</sup>	TLR4	+	Stricture disease Penetrating disease in TLR4-/NOD2+	Relation to stricturing disease particularly in NOD2- patients
Japan 2005 <sup>121</sup>	TNFSF15	+	-	Also included two European cohorts
China 2005 <sup>122</sup>	TNF- $\alpha$ , TNF- $\beta$	-	-	TNF- $\alpha$ related to UC
Italy 2005 <sup>100</sup>	TLR4	-	-	TLR4 mutations statistically significantly increased in relatives but not in patients!
Canada 2005 <sup>123</sup>	DLG5	+	none	Modest relation, clearer for UC; not observed in Ashkenazi Jews; no interaction with NOD2/OCTN
UK 2006 <sup>124</sup>	TNF- $\alpha$ , DLG5	+(TNF- $\alpha$ )-(DLG5)	-	No interaction with NOD2 mutations
Israel 2006 <sup>125</sup>	TNF- $\alpha$	-	-	
Turkey (Ankara) 2006 <sup>104</sup>	ICAM1	-	-	
UK 2006 <sup>126</sup>	NOD1	-	-	
UK 2006 <sup>127</sup>	TUCAN	+	Non-colonic disease	Association more significant in NOD2- negative patients
Australia 2006 <sup>128</sup>	Angiotensinogen-6, TGF $\beta$	+	stricturing disease (TGF $\beta$ )	
US <sup>129</sup>	IL23 receptor	+		Different variants predispose to or strongly protect against Crohn; possibly the most interest candidate for further therapeutic targeting
US (Wisconsin)2007 <sup>130</sup>	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 <sup>131</sup>	OCTN1, OCTN2	+	-	Not observed in Ashkenazi Jews; IRF1, PDLIM, and P4HA2 are the potential causal variants
Europe 2007 <sup>109</sup>	TLR4	-	-	
Germany 2007 <sup>132</sup>	HLA-G gene (IBD3)	+	ileocecal disease	14-bp deletion
Hungary 2007 <sup>133</sup>	CTLA4	-	-	+49G polymorphism
Sweden 2007 <sup>134</sup>	OCTN1, OCTN2	+	-	Variant allelic frequency for 1, homozygosity for both
Germany 2007 <sup>135</sup>	IL23 receptor	+	Ileal (rs1004819 variant)	Variants strongly predisposing to or protective for Crohn
UK 2007 <sup>136</sup>	IL23 receptor	+	None	No phenotype associations presented here; variants predisposing to or protective for Crohn
UK 2007 <sup>137</sup>	IL23 receptor	+		variants predisposing to or protective for Crohn; potential epistatic interaction with OCTN
Germany 2007 <sup>138</sup>	ATG16L1	+	-	Confirmed in a UK case-control sample; interaction with NOD2
Canada 2007 <sup>139</sup>	ATG16L1	+	-	
UK 2007 <sup>140</sup>	ATG16L1	+	Ileal	OR 1.65 for Crohn in general, but 2.2 for ileal disease; no interaction with NOD2
UK 2007 <sup>141</sup>	ATG16L1	+	None	No interaction with NOD2
Japan 2007 <sup>142</sup>	ATG16L1/IL23 receptor	-	-	-
US 2007 <sup>143</sup>	ATG16L1	+		Paediatric population
New Zealand 2007 <sup>144</sup>	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.<sup>146</sup> On the other hand, a recent 3-continent study showed that disease incidence was not related to *NOD2* incidence in a healthy population.<sup>147</sup> Another recent European study showed that the frequency of *NOD2* variants exhibits an inverse gradient (south to north).<sup>109</sup> 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,<sup>148</sup> among other areas, while isolated clusters of cases may imply a similar infectious origin.<sup>149</sup> A recent meta-analysis also supported a relationship, despite avoiding characterizing it as etiologic.<sup>150</sup> The epidemiology of MAP, however, cannot be adequately evaluated and compared to that of CD. One indirect attempt failed to elicit any correlation.<sup>151</sup> 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,<sup>152</sup> 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).<sup>153</sup> Sweden has a high CD incidence but low MAP seroprevalence; a recent Korean study<sup>154</sup> 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.<sup>155</sup>

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's<sup>156</sup> 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.

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