Journal of Crohn's and Colitis (2014) 8, 234–239

Available online at www.sciencedirect.com

ScienceDirect

Disease severity in familial cases of IBD☆,☆☆

M. Andreu[a,*], L. Márquez[a], E. Domènech[b,s], J.P. Gisbert[c,s], V. García[d], I. Marín-Jiménez[e], M. Peñalva[f], F. Gomollón[g,s], X. Calvet[h,s], O. Merino[i], E. Garcia-Planella[j,s], N. Vázquez-Romero[k], M. Esteve[l,s], P. Nos[m,s], A. Gutiérrez[n,s], I. Vera[o], J.L. Cabriada[p], M.D. Martín[q], A. Cañas-Ventura[a], J. Panés[r,s],on behalf of Spanish GETECCU group (ENEIDA project)

[a] *Department of Gastroenterology, Hospital del Mar, IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Pompeu Fabra University, Barcelona, Catalonia, Spain*
[b] *Department of Gastroenterology, Hospital Germans Trias, Badalona, Spain*
[c] *Gastroenterology Units of Hospital de La Princesa and Instituto de Investigación Sanitaria Princesa, Madrid, Spain*
[d] *Department of Gastroenterology, Hospital Reina Sofía, Córdoba, Spain*
[e] *Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[f] *Department of Gastroenterology, Bellvitge University Hospital, Hospitalet de Llobregat, Barcelona, Spain*
[g] *Department of Gastroenterology, University Hospital Clínico, Zaragoza, Spain*
[h] *Department of Gastroenterology, University Hospital Parc Tauli, Sabadell, Spain*
[i] *Department of Gastroenterology, Hospital de Cruces, Barakaldo, Spain*
[j] *Department of Gastroenterology, Hospital Sant Pau, Barcelona, Spain*
[k] *Department of Gastroenterology, Hospital General Universitario de Elche, Alicante, Spain*
[l] *Department of Gastroenterology, Hospital Mutua de Terrassa, Barcelona, Catalonia, Spain*
[m] *Department of Gastroenterology, Hospital Universitario La Fe, Valencia, Spain*
[n] *Department of Gastroenterology, Hospital General, Alicante, Spain*
[o] *Department of Gastroenterology, Hospital Universitario Puerta de Hierro, Madrid, Spain*
[p] *Deparment of Gastroenterology, Hospital Galdakao, Viscaya, Spain*
[q] *Department of Gastroenterology, Hospital La Paz, Madrid, Spain*
[r] *Department of Gastroenterology, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Catalonia, Spain*
[s] *Centro de Investigación Biomedica en Red en Enfermedades Hepáticas y Digestivas (Ciberehd), Spain*

Received 18 April 2013; received in revised form 15 August 2013; accepted 16 August 2013

KEYWORDS
Familial aggregation in IBD;
Familial Crohn's disease;

Abstract

Background: Phenotypic traits of familial IBD relative to sporadic cases are controversial, probably related to limited statistical power of published evidence.

☆ All investigators are listed in Appendix 1.
☆☆ Role of the sponsor: The funding sources had no involvement in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

* Corresponding author at: Department of Gastroenterology, Parc de Salut Mar, Passeig Marıtim 25-29, 08003 Barcelona, Catalonia, Spain. Tel.: +34 932 483304; fax: +34 932 218422/279387.
E-mail address: mandreu@parcdeisalutmar.cat (M. Andreu).

1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2013.08.010

Ulcerative colitis phenotypes

Aim: To know if there are phenotype differences between familial and sporadic IBD, evaluating the prospective Spanish registry (ENEIDA) with 11,983 cases.
Methods: 5783 patients (48.3%) had ulcerative colitis (UC) and 6200 (51.7%) Crohn's disease (CD). Cases with one or more 1st, 2nd or 3rd degree relatives affected by UC/CD were defined as familial case.
Results: In UC and CD, familial cases compared with sporadic cases had an earlier disease onset (UC: 33 years [IQR 25–44] vs 37 years [IQR 27–49]; $p < 0.0001$); (CD: 27 years [IQR 21–35] vs 29 years [IQR 22–40]; $p < 0.0001$), higher prevalence of extraintestinal immune-related manifestations (EIMs) (UC: 17.2% vs 14%; $p = 0.04$); (CD: 30.1% vs 23.6%; $p < 0.0001$). Familial CD had higher percentage of ileocolic location (42.7% vs 51.8%; $p = 0.0001$), penetrating behavior (21% vs 17.6%; $p = 0.01$) and perianal disease (32% vs 27.1%; $p = 0.003$). Differences are not influenced by degree of consanguinity.
Conclusion: When a sufficiently powered cohort is evaluated, familial aggregation in IBD is associated to an earlier disease onset, more EIMs and more severe phenotype in CD. This feature should be taken into account at establishing predictors of disease course.

1. Introduction

Familial aggregation in inflammatory bowel disease (IBD) has been documented in numerous studies.[1–4] A positive family history of IBD increases the risk of developing Crohn's disease (CD) and ulcerative colitis (UC). The greatest risk is in first-degree relatives, especially in siblings and it is higher in patients with CD than in those with UC. The rate of family history in CD ranges from 2% to 14%, and in UC from 7% to 11%.[2,5,6] The role of genetic factors in IBD has been shown by epidemiological, familial and genome-wide association (GWA) studies. Previous analyses on the phenotypic differences between familial and sporadic IBD are controversial. Whereas some studies did not show phenotypic differences,[4,7,8] others found that in familial cases, disease onset occurs at an earlier age and suffers from a higher disease extent than in sporadic cases.[9,10] Provision of robust data on this aspect might prove of value in our goal to offer our patients a personalized health care.

As familial aggregation only occurs in a minority of patients with IBD, the main limitation of the published reports addressing this aspect is the limited power to evidence relevant differences in phenotype between sporadic and familial cases. To overcome these limitations we took advantage of the prospective Spanish registry of IBD cases, ENEIDA (Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales), that included 11,983 patients at the time this study was undertaken. This represents a sample size 10-fold higher than the largest study published so far.

1.1. Patients and methods

The study included 11,983 IBD patients (48.3% UC and 51.7% CD) registered in the ENEIDA database, a Spanish database that collects prospective data of incident and prevalent cases of IBD treated at 35 Spanish hospitals since January 2006. Patients diagnosed with other types of IBD (unclassified or, indeterminate IBD or microscopic colitis) were excluded. Events occurring before inclusion of the patient in the database were acquired retrospectively from local database or case records.

1.2. Description of variables

The variables captured included: demographic data, clinical phenotype including IBD type, age at diagnosis, gender, smoking habits before and after diagnosis, family history of IBD including number of affected relatives and degree of kinship, disease location and extent, disease behavior (for CD) according to the Montreal classification,[11] extraintestinal immune-related manifestations (EIMs) of IBD and surgical requirements during follow-up.

1.3. Definitions established in the database are the following

The database prospectively established the following definitions: Smokers were defined as patients who smoked more than 7 cigarettes per week. Ex-smokers were defined as patients who had given up smoking for at least 1 year. Nonsmokers were defined as patients who had never smoked more than 7 cigarettes per week.[12]

1.3.1. Disease location and disease behavior

Disease location and disease behavior were determined according to at least one imaging technique (endoscopy, small bowel follow through, or a cross-sectional imaging technique). The maximal extent of involvement and the most severe form of disease behavior at any time since diagnosis were recorded. Disease phenotype was categorized according to the Montreal classification.[11]

The EIMs of IBD were defined as reactive manifestations including: arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, iritis/uveitis and autoimmune diseases such as primary sclerosing cholangitis.

1.3.2. Familial IBD

Familial IBD was defined as the existence of one or more first, second and/or third degree relatives affected with

either CD or UC. The number of relatives with any IBD was registered. Patients without any relative affected with IBD were categorized as sporadic IBD. An effort was made to verify reported IBD in relatives by obtaining medical records whenever possible. All these terms were prospectively defined and categorized by the investigators in each center.

The database is kept under continuous external monitoring for completeness and consistency of the data entered, but data can only be modified by each local investigator.

The study was approved by the institutional ethics committee of each participating hospital and written informed consent was obtained from all patients.

2. Statistical analysis

Continuous data were compared using Student's t test and were expressed as median and interquartile range (IQR). Categorical data were analyzed by Chi square test.

Probability curves for surgery need in sporadic and familial IBD were calculated according to the Kaplan–Meier method and were compared using the log-rank test.

Linear regression was performed to assess whether familial history of IBD was an independent predictor for younger age at diagnosis in UC and CD (dependent variable). Gender, smoking at diagnosis and family history of IBD were included as independent variables. Results are reported as odds ratios (OR) with 95% confidence intervals (95% CI). All p values were two-sided. A p value of less than 0.05 was considered statistically significant difference. p values of t-tests or X^2 tests have not been corrected for multiple comparisons. Analyses were performed with SPSS V19.0 software package (SPSS Inc., Chicago, IL).

3. Results

3.1. Study population

The study cohort included 11,983 patients with an established diagnosis of UC or CD (48.2% females, and 51.8% males); median age at diagnosis, 32 years (IQR 24–44). There were 5783 (48.3%) patients diagnosed with UC and 6200 (51.7%) patients with CD. According to family history, 10,523 patients (87.8%) had sporadic IBD, and 1460 patients (12.2%) had familial IBD. In Table 1 the demographic characteristics of patients with UC and CD are summarized.

3.2. Familial and sporadic ulcerative colitis

There were 5194 patients with sporadic UC (89.8%), and 589 cases with familial UC (10.2%); among the later group 65% had one or more first degree relatives affected by IBD and 35% had only second or third degree relatives affected. As shown in Table 2 median age at diagnosis was significantly lower in the familial group compared to the sporadic group (33 years (IQR 24–44) vs 37 years (IQR27–49); $p < 0.0001$), but no differences were observed in other demographic or environmental risk factors such as gender, smoking habit or previous appendectomy. Although disease extent was similar in both groups, there was a higher proportion of patients with EIMs in the familial group (17.2%) than in the sporadic group (14%) ($p = 0.04$). The analysis of survival time free of surgery through Kaplan–Meier analysis did not show significant differences between groups ($p = 0.1$).

Table 1 Demographic data in ulcerative colitis (UC) and Crohn's disease (CD).

Total cases	UC patients	CD patients	p value
	5783	6200	
Follow-up (months) Median (IQR) [a]	91 (38–166)	92 (39–164)	0.03
Age at diagnosis (years) Median (IQR) [a]	36 (27–49)	29 (22–39)	0.0001
Female gender (%)	46.8	53.2	0.002
Smoking at diagnosis (%)	16.8	44.8	0.0001
EIMs (%) [b]	14.3	24.5	0.0001
Familial cases (%)	10.2	14	0.0001

[a] Interquartile range.
[b] Extraintestinal manifestations.

Duration of follow-up was similar in sporadic and familial cases. No differences were found between the group of patients with familial UC who had first degree relatives affected and the group of patients with only second or third degree relatives in terms of demographic and clinical characteristics.

3.3. Familial and sporadic Crohn's disease

A total of 6200 patients with CD were included in the study. In the sporadic group there were 5329 cases (86%), and the familial group comprised 871 cases (14%); 60.19% of them had at least one or more first degree relatives affected by IBD and 39.8% had only second and/or third degree relatives affected by IBD as shown in Table 4. No differences were found between the group of patients with familial CD who had first degree relatives affected and the group with only second or third degree relatives in terms of demographic and clinical characteristics. The median age at diagnosis was significantly lower in the familial group compared to the sporadic group (27 years (IQR 21–37) vs 29 years (IQR22–40); $p < 0.0001$) and there was a higher proportion of patients with EIMs among the familial cases (30.1%) than in the sporadic cases (23.6%) ($p < 0.0001$). Disease location was different in the two groups of patients. Compared to the sporadic group, familial cases had a significantly higher proportion of cases with ileocolonic location (42.7% vs 51.7%; $p < 0.0001$). The evaluation of disease behavior at the time of diagnosis demonstrated that the penetrating phenotype was significantly more frequent in the familial group than in the sporadic group (21% vs 17.6%; $p = 0.01$). Perianal disease was also more frequent at disease onset in the familial group (32% vs 27.1%; $p = 0.003$) (Table 4). However, the Kaplan–Meier analysis did not show significant differences in the survival time free of surgical treatment among the two groups ($p = 0.3$). The median duration of follow-up was significantly higher in the familial group compared to the sporadic group (106 months [IQR 45–179] vs 90 months [IQR 38–162]; $p < 0.0001$).

Table 2 Characteristics of UC, according to sporadic disease and familial aggregation (statistically significant results are highlighted in bold).

	A Sporadic IBD	B Familial IBD	C 1st degree relatives affected	D 2nd, 3rd degree relatives affected	p value		
Total patient	N = 5194	N = 589	N = 354	N = 182	A vs B	A vs C	A vs D
Follow-up median (IQR) [a]	89 (37–165)	100 (44–178)	107 (48–191)	100 (40–174)	0.09	**0.007**	0.7
Age at diagnosis median (IQR) [a]	37 (27–49)	33 (24–44)	33 (25–44)	30 (23–42)	**0.0001**	**0.0001**	**0.0001**
Gender/female (%)	46.5	47.2	47.2	47.3	0.7	0.8	0.8
Smokers at diagnosis (%)	16.7	17.6	17.3	17.3	0.5	0.7	0.2
Appendectomy (%)	4.1	3.8	3.9	4	0.7	1	1
EIMs (%) [b]	14	17.2	17.1	15.8	**0.04**	**0.04**	0.5
Location (%)							
Montreal E1	17.4	18.1	17	20.3	0.6	0.9	0.3
Montreal E2	43.3	39.5	41.5	35.6	0.09	0.5	0.04
Montreal E3	39.3	42.3	41.5	44.1	0.1	0.4	0.2

[a] Interquartile range.
[b] Extraintestinal manifestations.

The results of regression analysis are shown in Table 3. The familial aggregation independently reduces the age at diagnosis by 4.16 years (95% CI 2.82–5.51) in UC and by 3.46 years (95% CI 2.41–4.51) in CD.

4. Discussion

The current study analyzed a large IBD registry comparing the disease phenotype at diagnosis and during follow-up in patients with CD and UC according to existence of familial aggregation. For both diseases familial cases have an earlier disease onset, and a higher prevalence of EIMs. The analysis showed that at the disease onset familial CD is more severe with a higher percentage of penetrating behavior and perianal disease than sporadic disease, and is associated with a higher prevalence of ileocolic disease location. Despite the higher prevalence of penetrating behavior and perianal disease in familial CD cases at the time of diagnosis, surgery requirements did not differ between the two groups, which may be related to initiation of early medical interventions resulting in decreased surgical needs. Differences between sporadic and familial cases were not influenced by the number of relatives affected or the degree of consanguinity (first vs second or third degree relatives).

Table 3 Independent predictors of age at diagnosis in ulcerative colitis and Crohn's disease.

	Ulcerative colitis	Crohn's disease
	N = 5783	N = 6200
Dependent variables	Coefficient β (95% CI) p value	Coefficient β (95% CI) p value
Female gender	−3.09 (−3.90 to −2.27) <0.0001	1.00 (−2.24–3.75) 0.9
Smoking at diagnosis	−3.55 (4.64 to −2.47) <0.0001	−3.42 (−4.15 to −2.70) <0.0001
Familial aggregation	−4.16 (−5.51 to −2.82) <0.0001	−3.46 (−4.51 to −2.41) <0.0001

The strength of this study relies on several facts. First, the large number of cases included in the study makes the results robust. Second, ENEIDA registry standardized data capture on phenotype characteristics of UC and CD (Montreal definition) as well as definitions of smoking and EIMs. This has the advantage of setting a benchmark for data capture and increasing the accuracy of the information obtained. Third, all data collected since January 2006 were prospective, and the information of the patients enrolled in the registry has been updated after each outpatient visit or hospital events, so the data of the disease follow-up are mostly prospective. Fourth, data are subject to external monitoring for completeness and consistency. Finally, we could directly verify familial IBD in 40% of relatives because they were also included in the ENEIDA registry. The coincidences of demographic data of the population included with that of prospective population base studies,[13,14] also confirm the reliability of data captured in ENEIDA database.

The study has limitations that should not be ignored. First, this is not a true population based study. ENEIDA registry covers IBD hospital population, collecting information of cases that require either outpatient control or hospital admission, this could justify that the distribution of cases with UC and CD around 1:1 in our cohort differs from that observed in population-based studies, where the prevalence of UC cases is higher than CD by a 5:3 ratio.[15] The population of patients included in the current study could also contain an overrepresentation of IBD patients with positive family history or with a more severe disease course compared to true population-based studies. Nevertheless due to the open access of patients to referral centers, and the advocacy of patient groups, care of IBD patients in Spain (severe and non-severe) is highly concentrated in the hospital setting. In our study cases with familial IBD had a higher proportion of EIMs. Previous reports on the prevalence of EIMs in sporadic and familial IBD are

Table 4 Characteristics of Crohn's disease, according to sporadic disease and familial aggregation disease (statistically significant results are highlighted in bold).

	A Sporadic IBD	B Familial IBD	C 1st degree relatives affected	D 2nd, 3rd degree relatives affected	p value		
Total patient	N = 6.200	N = 871	N = 520	N = 261	A vs B	A vs C	A vs D
Follow-up (months) median (IQR) [a]	90 (38–162)	106 (45–179)	115 (47–189)	99 (39–158)	**0.0001**	**0.0001**	0.3
Age at diagnosis median (IQR) [a]	29 (22–40)	27 (21–35)	28 (21–37)	25 (21–31)	**0.0001**	**0.001**	**0.0001**
Gender/female (%)	47.5	52.5	53.5	51.2	0.057	**0.04**	0.4
Smokers at diagnosis (%)	49.8	53.5	53.5	54	0.06	0.1	0.1
EIMs (%) [b]	23.6	30.1	28.8	32.3	**0.0001**	**0.01**	**0.001**
Location (%)							
Montreal L1	38.9	37.4	37.1	38.2	0.4	0.4	0.8
Montreal L2	14.1	11.4	11.5	10	0.03	0.07	0.03
Montreal L3	42.7	51.7	51.3	51.8	**0.0001**	**0.002**	**0.01**
Montreal L4	15.3	15.7	15.7	13.8	0.8	0.8	0.5
Disease behavior [c]							
B1 (%)	65.5	67.4	67.7	67.2	0.2	0.3	0.5
B2 (%)	25	25.6	26.2	23.9	0.7	0.5	0.7
B3 (%)	17.6	21	20.3	22.5	**0.01**	0.1	**0.03**
Perianal (%)	27.1	32	31.3	33.1	**0.003**	**0.04**	**0.02**

[a] Interquartile range.
[b] Extraintestinal manifestations.
[c] Disease behavior categorized according to the Montreal classification.

controversial. Some studies have demonstrated a higher prevalence of EIMs in the familial group,[16,17] whereas no difference was found in another study between familial and sporadic IBD.[18] Sensitivity analyses in subgroups of patients with CD/UC or with 1st/2nd–3rd degree relatives provide confirmatory evidence of this association in the current study. The reason for higher EIMs in familial cases is not apparent. It is known that EIMs have a familial predisposition,[17] suggesting the existence of a strong genetic influence on this phenotypic trait. Some studies suggest that genetic load is higher in familial cases[19–21] and some susceptibility genes for IBD confer also susceptibility to other immune mediated inflammatory disorders. One example of this is the HLA system which is one of the major genetic markers associated with IBD and EIMs. [22–25]

Another notable aspect evaluated in this study was the assessment of familial IBD according to the degrees of consanguinity. Interestingly in both, familial UC and CD, patients had the same differences in disease characteristics when compared to sporadic cases whether they had first degree relatives or more distant relatives. Most familial aggregation studies included only first-degree relatives; there is little information about other degrees of consanguinity and IBD characteristics. This study is the first to report robust information about the effect of IBD aggregation when patients only have distant relatives affected.

Finally we want to emphasize the difference in severe phenotype at disease onset between familial CD and familial UC. There are some family data suggesting a stronger genetic influence in CD than in UC, such as more common family history or a higher proportion of concordance among homozygotic twins.[26–28] But genetic risk factors explain only a fraction of the estimated heritability and there are also strong environmental factors such as smoking that increase the predisposition to CD.

5. Conclusion

The study demonstrates that when a sufficiently powered cohort of cases is interrogated, familial aggregation in IBD is associated to an earlier disease onset, more severe phenotype, and more EIMs. This feature should be taken into account in future studies aimed at establishing prognostic factors, and may also have practical implications for patient care when the predictive ability of family aggregation is gauged relative to other predictors particularly at the time of diagnosis, when information on disease characteristics is considerably limited.

Appendix 1. Investigators of ENEIDA project

All participants listed below were given an opportunity to comment on the paper:

Hospital Clínic Barcelona: J Panés; Hospital Universitari GermansTrias i Pujol. Badalona: Eugeni Domènech; Hospital de la Princesa. Madrid: J. Pérez Gisbert; Hospital Reina Sofía. Cordoba: V García. Hospital Gregorio Marañón. Madrid: I. Marín; Hospital Universitari de Bellvitge. Barcelona: M. Peñalva; Hospital Lozano Blesa. Zaragoza: F. Gomollón; Hospital Parc Taulí. Sabadell: X. Calvet; Hospital de Cruces. Bizkaia: O. Merino; Hospital de la Sta Creu i Sant Pau. Barcelona: E. García-Planella; Hospital Parc de Salut Mar. Barcelona: M. Andreu; Hospital General Universitario de Alicante. Alicante: A. Gutiérrez; Hospital Universitario Puerta de Hierro. Madrid: I. Vera; Hospital Mutua de Terrassa. Terrassa: M. Esteve; Hospital de la Fe. Valencia: P. Nos; Hospital General Universitario de Elche. Alicante: N. Vázquez; Hospital "General Yagüe". Burgos: E. Gento; Hospital Clínico Universitario. Valladolid: L. Fernández-Salazar; Hospital Rio Hortega. Valladolid: J. Barrio; Hospital La Paz. Madrid: MD.

Martín; Complejo Hospitalario de León. León: F. Muñoz; Hospital Infanta Leonor. Madrid: A. Ponferrada; Hospital de Sagunto. Sagunto: J. Hinojosa; Consorcio Sanitario de Terrassa. Terrassa: M. Piqueras; Hospital Clínico San Carlos. Madrid: JC. Mendoza; Hospital Galdakao. Bizkaia: JL. Cabriada; Hospital de Basurto. Bilbado: C. Muñoz; Hospital Sant Joan de Dèu. Barcelona: P. Vilar; Hospital San Jorge. Huesca: MA. Montoro; Hospital Universitario de Fuenlabrada. Madrid: A. Algaba; Hospital Infanta Cristina. Madrid: B. Botella; Hospital de Cabueñes. Gijón: C. Saro; Hospital Clínico Universitario de Santiago. Santiago. M. Barreiro; Hospital Universitari Doctor Josep Trueta. Girona: X. Aldeguer.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgment

We thank Ferring Pharmaceuticals for sponsoring the development and maintenance of the ENEIDA data base project.

References

1. Lewkonia RM, McConnell RB. Familial inflammatory bowel disease—heredity or environment? *Gut* Mar 1976;**17**(3):235–43.
2. Yang H, McElree C, Roth MP, Shanahan F, Targan SR, Rotter JI. Familial empirical risks for inflammatory bowel disease: differences between Jews and non-Jews. *Gut* 1993;**34**:517–24.
3. Satsangi J, Rosenberg WMC, Jewell DP. The prevalence of inflammatory bowel disease in relatives of patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 1994;**6**:413–6.
4. Ben-Horin S, Avidan B, Yanai H, Lang A, Chowers Y, Bar-Meir S. Familial clustering of Crohn's disease in Israel: prevalence and association with disease severity. *Inflamm Bowel Dis* Feb 2009;**15**(2):171–5.
5. Probert CS, Jayanthi V, Hughes AO, Thompson JR, Wicks AC, Mayberry JF. Prevalence and family risk of ulcerative colitis and Crohn's disease: an epidemiological study among Europeans and south Asians in Leicestershire. *Gut* 1993;**34**:1547–51.
6. Halme L, Turunen U, Helio T, Paavola P, Walle T, Miettinen A, et al. Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population. *Scand J Gastroenterol* 2002;**37**:692–8.
7. Carbonnel F, d'Almagne H, Lavergne A, Matuchansky C, Brouet JC, Sigaux F, et al. The clinicopathological features of extensive small intestinal CD4 T cell infiltration. *Gut* Nov 1999;**45**(5):662–7.
8. Henriksen M, Jahnsen J, Lygren I, Vatn MH, Moum B, IBSEN Study Group. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. *Am J Gastroenterol* Sep 2007;**102**(9):1955–63.
9. Colombel JF, Grandbastien B, Gower–Rousseau C, Plegat S, Evrard JP, Dupas JL, et al. Clinical characteristics of Crohn's disease in 72 families. *Gastroenterology* 1996;**111**:604–7.
10. Monsén U, Bernell O, Johansson C, Hellers G. Prevalence of inflammatory bowel disease among relatives of patients. *Scand J Gastroenterol* Mar 1991;**26**(3):302–6.
11. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A):5–36.
12. Cottone M, Rosselli M, Orlando A, Oliva L, Puleo A, Cappello M, et al. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* Mar 1994;**106**(3):643–8.
13. Henriksen M, Jahnsen J, Lygren I, Sauar J, Kjellevold Ø, Schulz T, et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm Bowel Dis* Jul 2006;**12**(7):543–50.
14. Henriksen M, Jahnsen J, Lygren I, Sauar J, Schulz T, Stray N, et al. Change of diagnosis during the first five years after onset of inflammatory bowel disease: results of a prospective follow-up study (the IBSEN study). *Scand J Gastroenterol* Sep 2006;**41**(9):1037–43.
15. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. *Clin Epidemiol*. Jul 25 2013;**5**:237–47.
16. Annese V, Andreoli A, Andriulli A, Dinca R, Gionchetti P, Latiano A, et al. Familial expression of anti-*Saccharomyces cerevisiae* Mannan antibodies in Crohn's disease and ulcerative colitis: a GISC study. *Am J Gastroenterol* 2001;**96**:1396–400.
17. Satsangi J, Grootscholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996;**38**:738–41.
18. Ricart E, Panaccione R, Loftus Jr EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, et al. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case–control study. *Inflamm Bowel Dis* 2004;**10**:207–14.
19. Bhat M, Nguyen GC, Pare P, Lahaie R, Deslandres C, Bernard EJ, et al. Phenotypic and genotypic characteristics of inflammatory bowel disease in French Canadians: comparison with a large North American repository. *Am J Gastroenterol* Sep 2009;**104**(9):2233–40.
20. Peeters M, Cortot A, Vermeire S, Colombel JF. Familial and sporadic inflammatory bowel disease: different entities? *Inflamm Bowel Dis* Nov 2000;**6**(4):314–20.
21. Halme L, Turunen U, Heliö T, Paavola P, Walle T, Miettinen A, et al. Familial and sporadic inflammatory bowel disease: comparison of clinical features and serological markers in a genetically homogeneous population. *Scand J Gastroenterol* Jun 2002;**37**(6):692–8.
22. Chapman RW, Varghese Z, Gaul R, Patel G, Kokinon N, Sherlock S. Association of primary sclerosing cholangitis with HLA-B8. *Gut* 1983;**24**:38–41.
23. Roussomoustakaki M, Satsangi J, Welsh K, Louis E, Fanning G, Targan S, et al. Genetic markers may predict disease behavior in patients with ulcerative colitis. *Gastroenterology* 1997;**112**:1845–53.
24. Orchard TR, Chua CN, Ahmad T, Cheng H, Welsh KI, Jewell DP. Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of HLA genes. *Gastroenterology* 2002;**123**:714–8.
25. Peeters H, Vander Cruyssen B, Laukens D, Coucke P, Marichal D, Van Den Berghe M, et al. Radiological sacroiliitis, a hallmark of spondylitis, is linked with CARD15 gene polymorphisms in patients with Crohn's disease. *Ann Rheum Dis* 2004;**63**:1131–4.
26. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* Jun 15 2011;**474**(7351):307–17.
27. Tysk C, Lindberg E, Jarnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* 1988;**29**:990–6.
28. Halfvarson J, Bodin L, Tysk C, Lindberg E, Järnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003;**124**:1767–73.