Journal of Crohn's and Colitis (2014) 8, 654–661

Available online at www.sciencedirect.com

ScienceDirect

Phenotypic concordance in familial inflammatory bowel disease (IBD). Results of a nationwide IBD Spanish database

Eduard Cabré[a,o,*], Míriam Mañosa[a,o], Valle García-Sánchez[b], Ana Gutiérrez[c], Elena Ricart[d,o], Maria Esteve[e,o], Jordi Guardiola[f], Mariam Aguas[g,o], Olga Merino[h], Angel Ponferrada[i], Javier P. Gisbert[j,o], Esther Garcia-Planella[k], Gloria Ceña[l], José L. Cabriada[m], Miguel Montoro[n], Eugeni Domènech[a,o], on behalf of the ENEIDA Project of the Spanish Working Group in Crohn's Disease and Ulcerative Colitis (GETECCU)

[a] *Hospital Universitari Germans Trias i Pujol, Badalona, Spain*
[b] *Hospital Universitario Reina Sofía, Córdoba, Spain*
[c] *Hospital General Universitario, Alicante, Spain*
[d] *Hospital Clínic, Barcelona, Spain*
[e] *Hospital Universitari Mútua de Terrassa, Terrassa, Spain*
[f] *Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain*
[g] *Hospital Universitari La Fe, Valencia, Spain*
[h] *Hospital de Cruces, Barakaldo, Spain*
[i] *Hospital Universitario Infanta Leonor, Madrid, Spain*
[j] *Hospital Universitario de La Princesa, IP, Madrid, Spain*
[k] *Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[l] *Hospital Royo Villanova, Zaragoza, Spain*
[m] *Hospital Galdakao-Usansolo, Galdakao, Spain*
[n] *Hospital General San Jorge, Huesca, Spain*
[o] *Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain*

Received 8 November 2013; received in revised form 6 December 2013; accepted 10 December 2013

KEYWORDS:
Inflammatory bowel disease;
Crohn's disease;
Ulcerative colitis;
Familial aggregation;

Abstract

Background & aims: Disease outcome has been found to be poorer in familial inflammatory bowel disease (IBD) than in sporadic forms, but assessment of phenotypic concordance in familial IBD provided controversial results. We assessed the concordance for disease type and phenotypic features in IBD families.

* Corresponding author at: G-I & IBD Unit, Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Carretera del Canyet s/n., 08916 Badalona, Catalonia, Spain. Tel.: +34 93 497 8909; fax: +34 93 497 8951.
E-mail address: ecabre.germanstrias@gencat.cat (E. Cabré).

1873-9946/$ - see front matter
http://dx.doi.org/10.1016/j.crohns.2013.12.005

Concordance analysis

Methods: Patients with familial IBD were identified from the IBD Spanish database ENEIDA. Families in whom at least two members were in the database were selected for concordance analysis (κ index). Concordance for type of IBD [Crohn's disease (CD) vs. ulcerative colitis (UC)], as well as for disease extent, localization and behaviour, perianal disease, extraintestinal manifestations, and indicators of severe disease (i.e., need for immunosuppressors, biological agents, and surgery) for those pairs concordant for IBD type, were analyzed.
Results: 798 out of 11,905 IBD patients (7%) in ENEIDA had familial history of IBD. Complete data of 107 families (231 patients and 144 consanguineous pairs) were available for concordance analyses. The youngest members of the pairs were diagnosed with IBD at a significantly younger age ($p < 0.001$) than the oldest ones. Seventy-six percent of pairs matched up for the IBD type ($\kappa = 0.58$; 95%CI: 0.42–0.73, moderate concordance). There was no relevant concordance for any of the phenotypic items assessed in both diseases.
Conclusions: Familial IBD is associated with diagnostic anticipation in younger individuals. Familial history does not allow predicting any phenotypic feature other than IBD type.

1. Introduction

The most widely accepted pathogenic hypothesis for inflammatory bowel diseases (IBD) considers both ulcerative colitis (UC) and Crohn's disease (CD) as conditions characterized by an exaggerated and sustained immune response against intestinal luminal antigens (e.g. the intestinal microbiota),[1,2] which develops in genetically susceptible individuals under the influence of some environmental factors unfortunately not fully understood.[3–5]

Sharing susceptibility genes and/or environmental factors by members of the same family must result in familial aggregation for IBD.[6–9] Indeed, several studies have shown that relatives of IBD patients have a much higher likelihood to develop IBD, as compared to the general population,[10–15] so that familial history is considered to be the strongest risk factor for IBD. Concordance for disease type has been reported by most[16–20] but not all[21] studies of familial aggregation in IBD. However, data on concordance in phenotypic characteristics and severity among disease-concordant family members are more controversial.[13,17–20,22,23] Moreover, data on IBD familial aggregation and concordance in the Mediterranean area are scarce.[16,19,24] Reliable estimates of concordance for phenotypic features and disease severity might be of help in planning therapeutic strategies in the latest affected members of IBD families.

The aim of the present study was to assess the prevalence of familial IBD, as well as the concordance for disease type and phenotypic features in IBD families, using data from a nationwide IBD Spanish hospital database.

2. Methods

The ENEIDA Project is a nationwide, hospital-based, prospectively maintained, Spanish database of incident and prevalent IBD cases followed in Spanish hospitals since January 2006, promoted by the Spanish Working Group in Crohn's Disease and Ulcerative Colitis (GETECCU). Clinical and epidemiological data such as the type of IBD, the extent/localization and behaviour (for CD) of the disease, the use of different therapies, the need for surgical treatment, and risk factors for IBD, including familial history, are recorded in ENEIDA, and prospectively updated since the date of inclusion of the patient in the database. Events occurring before the patient's inclusion in ENEIDA were retrospectively acquired from local databases or case records. The ENEIDA database is kept under continuous external monitoring for completeness and consistency of the data entered, but these can only be modified by each local investigator.

The study was approved by the ENEIDA Steering Committee. The ENEIDA Project was approved by the Ethics Committee of each participant hospital. Informed consent to participate in the ENEIDA Project was obtained from all patients.

Patients with familial history of IBD in the ENEIDA database were identified. Among these, those families with at least two members included in the database – and hence with complete epidemiological and clinical data – were selected for concordance assessments.

2.1. Data collection and definitions

Data collected included gender, age at diagnosis, type of IBD (CD, UC, or unclassified IBD), smoking status (active smoker, never smoker, or former smoker) at diagnosis, extent (for UC), localization (for CD), and behaviour (for CD) of the disease, perianal involvement, ever use of immunosuppressors or biological agents, need for intestinal surgical resection, and extraintestinal manifestations. Familial history of IBD was recorded as the presence or absence of any relative with IBD. In patients with positive familial history, the type of the IBD and the familial relationship of the affected relatives were also recorded. In incident cases, all these data were obtained from the anamnesis of the patient at the time of inclusion in the database. In prevalent cases, they were searched for in the patient's case record. In the case that they were not explicitly recorded in the case record, the patient was asked for that at the first routine follow-up visit. No further confirmation of the IBD diagnosis was required for those affected relatives not included in the ENEIDA database.

Diagnosis of CD and UC was based on standard clinical, endoscopic, radiological, and histological grounds.[25] Disease extent/localization and CD behaviour were defined according to the Montreal classification.[26] The extent of UC was

endoscopically classified as proctitis (E1), left-sided colitis (up to the splenic flexure) (E2), and extensive colitis (proximal to the splenic flexure) (E3).[26] The location of CD was based on identifying macroscopic evidence of CD in any part of the gastrointestinal tract. Possible locations included the ileum (L1), colon (L2), ileum and colon (L3), and the upper gastrointestinal tract (L4), with or without perianal involvement (p).[26] CD behaviour included inflammatory (B1) disease (without fistulizing or stricturing complications), stricturing (B2) disease, defined as the presence of clinical symptoms of partial or complete obstruction with fixed narrowing and/or narrowing with proximal dilatation, and fistulizing (B3) disease, which included the presence of enteric fistulas, intraabdominal abscesses, or bowel perforation.[26] Disease extent/location and disease behaviour were determined according to at least one imaging technique (endoscopy, barium meal and follow through, or a cross sectional imaging technique). The maximal extent of involvement and the most severe form of disease behaviour at any time since diagnosis were recorded.

2.2. Concordance assessments

As mentioned, concordance assessments were done in those families with at least two affected members included in the ENEIDA database. For concordance analyses, the members of each family were grouped in as many consanguineous pairs as possible.

Primary concordance analysis was made for the type of IBD. Separate analyses were performed according to the concordance for smoking habit at diagnosis. Secondary concordance analyses – which were separately done in pairs concordant for UC and CD – included phenotypic features (UC extent, CD location and behaviour, perianal involvement, extraintestinal manifestations) and therapeutic requirements (immunosuppressors, biological agents, resective surgery) as indicators of severity of the disease.

Subgroup analyses, according to the degree of familial relationship, and generation, were also done.

2.3. Statistical methods

Quantitative and qualitative variables are expressed as median plus interquartile range (IQR) and frequencies, respectively. Comparisons of quantitative variables in pairs were made with the Wilcoxon signed rank test.

Concordance within pairs was assessed by computing the linear Cohen's Kappa (κ) index[27] from contingency tables, given by $\kappa = (p_o - p_e) / (1 - p_e)$, where p_o is the proportion of observed agreement, and p_e is the proportion of agreement expected by chance. As the κ index takes into account the probability of agreement by chance, it is a more conservative estimation of concordance than the concordance index (i.e. the proportion of agreements against the total number of pairs).

For those features with more than two categories, the bi-quadratic weighted κ was obtained by giving weights to the frequencies in each cell of the table according to their distance from the diagonal that indicates agreement.[28] Ninety-five percent confidence interval (CI) for every κ value is provided.[29] If the 95%CI contains the zero value, the concordance is considered not significant. Also, a "strength of concordance" was attributed to the κ value, according to the classification by Landis & Koch[30], who characterized values <0 as indicating no concordance, and 0–0.20 as poor, 0.21–0.40 as mild, 0.41–0.60 as moderate, 0.61–0.80 as good/substantial, and 0.81–1.00 as very good/almost perfect concordance.

3. Results

At the time the present study was undertaken, the ENEIDA database included 11,905 patients (40% incident cases), with a year of diagnosis ranging from 1954 to 2009, and a median follow-up of 125.5 months (IQR: 69.9–208.6) from diagnosis of IBD. Seven hundred ninety-eight of these patients had familial history of IBD (418 CD, 364 UC, 16 unclassified IBD) for a 7% global prevalence of familial IBD (8.8% in prevalent vs. 3.5% in incident cases; $p < 0.0005$). Among these, 107 familial groups had two or more affected members included in the database (95 with 2 members, 8 with 3 members, 3 with 4 members and 1 with 5 members) for a total of 231 patients (135 CD, 92 UC, 4 unclassified IBD), and 144 consanguineous pairs available for concordance analyses. Of these, 49 pairs (34.0%) were parent/child, 57 (39.6%) siblings, 15 (10.4%) uncle–aunt/nephew–niece, 20 (13.9%) first cousins, and 3 (2.1%) grandparent/grandchild. No instance of twins was found among the 108 families studied. One hundred and six pairs (73.6%) were first-degree relatives, and 77 pairs (53,5%) were composed of members of the same generation. By the time of diagnosis, 87 out of 231 patients (38%) were active smokers, 124 (54%) never smokers, and 20 (8%) former smokers. For purposes of concordance analysis, both never smokers and former smokers were considered as non-smokers. Sixty-eight and 30 out of 144 pairs agreed for non-smoking, and active smoking, respectively, for a concordance rate of 68% for smoking status [κ = 0.31 (95%CI: 0.15–0.47); mild concordance].

The youngest members in the pairs were followed up for a significantly shorter time (median: 100.5 months, IQR: 65.4–144.2) than the older ones (median: 151.9 months, IQR: 92.2–221.4; p = 0.0005). The youngest members in the pairs were diagnosed with IBD at a significantly younger age than the oldest ones, both for pairs of the same and different generations (Table 1).

3.1. Primary concordance analysis: type of IBD

One hundred and ten out of the 144 pairs (76%) agreed for the type IBD: 41 with UC and 69 with CD, which means a moderate degree of concordance, with a κ = 0.58 (95%CI: 0.42–0.73) (Table 2). When the analysis was performed in the 137 pairs without members with unclassified IBD, the results were similar with a κ = 0.59 (95%CI: 0.42–0.75). Also, the strength of concordance was similar in different subgroups of pairs, as shown in Table 3.

Fifty (73%) out of 68 pairs with both members non-smoking at diagnosis agreed for disease type (30 for UC, 20 for CD), with a κ = 0.49 (95%CI: 0.29–0.69). Twenty-six (87%) of the 30 pairs in which both members were active smokers at diagnosis were concordant for disease type, most of them for CD (n = 22), with κ = 0.60 (95%CI: 0.23–0.96). Finally, 35 (76%) of the 46 pairs discordant for smoking habit at diagnosis were concordant for disease type (8 for UC, 27 for CD) with a κ = 0.43 (95%CI: 0.15–0.70). In 8 of the 11 pairs discordant for both smoking habit and disease type, the smoker member developed CD and the non-smoker one developed UC.

3.2. Concordance analyses for phenotypic characteristics

3.2.1. Pairs concordant for UC (Table 4)

Seventeen out of the 41 pairs with both members suffering from UC (41%) were also concordant for extension of the disease, with a κ index of 0.15 (poor concordance). Immunosuppressors were used in 28 of the 82 patients in UC pairs, with a poor degree of concordance (κ = 0.02). Biological agents and colectomy were required in only seven and six of these patients, respectively. There was no concordance at all for any of these two events, with κ indices of −0.07 and −0.04, respectively. Concordance was also absent for extraintestinal manifestations (κ = −0.06), which only occurred in 10 out of the 82 patients in UC pairs. These results were similar in different subgroup analyses (see Supplemental Table 1).

3.2.2. Pairs concordant for CD (Table 5)

Thirty-one out of the 69 pairs with both members suffering from CD (45%) were also concordant for localization of the disease, with a κ index of 0.11 (poor concordance). Stricturing and fistulizing behaviour occurred in 34 and 29 of the 138 members of the CD pairs, respectively, with a mild degree of concordance for both features (κ = 0.26 in both). There was a poor concordance (κ = 0.07) for perianal disease, which occurred in 47 of the 138 patients of the CD pairs. Immunosuppressors and biological agents were used in 105 and 46 patients of the CD pairs, with poor (κ = 0.01) and no concordance at all (κ = −0.04), which was needed in 61 patients, showed a mild degree of concordance in CD pairs (κ = 0.23). Concordance was absent for extraintestinal manifestations (κ = −0.04), which occurred in 25 out of the 138 patients in CD pairs. Similar results were found in subgroup analyses (See Supplemental Table 2).

4. Discussion

In the present study, we assessed the prevalence of familial IBD in a very large cohort of patients, and the phenotypic concordance in 144 family pairs (belonging to 107 families with two or more members with IBD). For this purpose, we used data from the Spanish database ENEIDA. In this database, phenotypic characteristics are recorded in a standardized way according to the Montreal classification,[26] which improves the accuracy of the information obtained. Also, events occurring since January 2006 are prospectively collected, and the information of patients enrolled is updated after each outpatient visit or hospital event, so that follow-up data are mostly prospective. Furthermore, data collection is externally monitored for completeness and consistency. All these facts make our results particularly robust and reliable, with a large number of subjects included, allowing for subgroup analyses as well.

A limitation of the present study is that it is not truly population-based. Being hospital-based, the ENEIDA database might a priori overrepresent IBD patients with positive family history or with a more severe disease course, as compared to population-based cohorts. Nevertheless, due to the open access of patients to referral centres, the growing number of IBD units in hospitals, and the advice of patients associations, care of IBD patients in Spain (both as an in-patient and out-patient basis) is nowadays highly concentrated in the hospital setting, regardless of severity. Indeed, our 7% prevalence of familial IBD fits well within the range of prevalence reported in population-based studies in Western countries, which varies from 4.5% to 11.5%,[11,14,20] and is quite similar to that reported in the Mediterranean area (Italy).[16,24] Anyway, describing the prevalence of familial disease was not the primary aim of this study since, for those relatives with IBD not included in the database, no further confirmation of the diagnosis was looked for beyond the information obtained from the index patient included in ENEIDA.

Diagnostic anticipation in familial IBD – i.e. disease diagnosis at an earlier age in the youngest pair member – has been repeatedly reported both in parent–child pairs,[17,18,31–33] and other second generation relationships.[19,34] The reasons for this phenomenon are intriguing and may include true genetic anticipation, a cohort effect (i.e. a greater impact of an environmental factor in recent years), or several biases inherent to the parent–child study design (e.g., ascertainment bias, selection bias).[33] Our data confirm diagnostic anticipation in affected individuals in the second generation but, in contrast to previous reports,[32,35] also in the youngest subject in sib-sib and other family pairs within the same generation, thus arguing for a role of a higher suspicion rate in the youngest members of IBD families, rather that genetic or cohort effects.

Some studies,[18,23,36] including a recent one from the ENEIDA database,[37] reported an earlier disease onset, increased risk for extraintestinal manifestations, as well as a more severe disease in familial IBD as compared to sporadic cases. However, data on concordance in phenotypic characteristics and severity among disease-concordant family members are more controversial.[13,17–20,22,23]

Table 1 Age (years)[a] at diagnosis in the 144 pairs studied.

	Oldest member	Youngest member	p-Value[b]
All pairs (n = 144)	34.2 (24.5–46.2)	22.4 (18.8–29.4)	0.0005
Same generation[c] (n = 77)	28.0 (21.7–35.4)	23.5 (18.8–31.4)	0.0005
Different generation[d] (n = 67)	43.5 (32.2–51.6)	21.2 (18.1–26.9)	0.0005

[a] Median (IQR).
[b] Wilcoxon test.
[c] Siblings or first cousins.
[d] Parent/child, uncle–aunt/nephew–niece, or grandparent/grandchild.

Table 2 Concordance for type of inflammatory bowel disease in the 144 pairs studied.

		Youngest member				κ (95%CI)	p-Value	Strength of concordance
		UC	CD	uIBD	Total			
Oldest member	UC	41	18	0	59	0.58 (0.42 to 0.73)	<0.001	Moderate
	CD	9	69	5	83			
	uIBD	0	2	0	2			
	Total	50	89	5	144			

UC = ulcerative colitis; CD = Crohn's disease; uIBD = unclassified inflammatory bowel disease.

The main objective of the present study was to assess the degree of concordance either in the disease type, or in the phenotypic features and indicators of disease severity in pairs of relatives concordant for both EC and UC. Most studies dealing with these issues have assessed concordance using the simple concordance index (i.e. the proportion of agreements against the total number of pairs) with reported rates of concordance for disease type ranging from 67% to 86%,[16–20] which are usually qualified as "high". Instead, we chose to compute the κ index,[27] which provides a more conservative estimate of concordance, as it takes into account the probability of agreement by chance. This is particularly relevant for items (or their absence) that are very frequent in the sample studied since the greater the frequency of an item, the greater the probability to be concordant for that item by chance. Our concordance index of 76% for disease type compares well with those previously described[16–20] but, when interpreted in terms of κ index (0.58) it can just be qualified as "moderate". Concordance for disease type remained unchanged when it was separately assessed in pairs concordant for active smoking or non-smoking at diagnosis, and in those discordant for the smoking habit as well. In agreement with previous reports,[38] in the majority of pairs discordant for both disease type and smoking habit, the smoker developed CD and the non-smoker was diagnosed with UC.

Phenotypic concordance in familial IBD has been reported to be higher in CD than UC families. Several studies have reported a high degree of agreement for both location and clinical disease behaviour in pairs of relatives with CD, with concordance indices ranging from 46% to 83%, and 49% to 73%, respectively[18,19,22,23]. In agreement with other studies,[13,17,20] however, we were unable to find relevant concordance for these phenotypic features as well as for the presence of perianal disease and extraintestinal manifestations in CD pairs. Also, in our series concordance was poor or absent for the extension of the disease and the presence of extraintestinal manifestations in pairs of UC relatives, in accordance with previous reports[17,19,21]. These results are in contrast with the high degree of phenotypic concordance in studies on monozygotic twins,[39,40] even in those assessing concordance by means of the κ index.[41] Of note, no instance of twin pairs was found in our series. As a whole, these findings support the idea that genetic factors predominantly account for concordance in familial IBD. In line with this concept, Bengtson et al.[42] reported the highest disease concordance in monozygotic twins, and the lowest in ordinary siblings, while dizygotic twins showed intermediate values. However, the increased risk for concordant disease among dizygotic twins, as compared to ordinary siblings, might underscore the importance of shared environment already in utero or during childhood in familial IBD[42].

As for disease phenotype, we were unable to demonstrate any relevant concordance for indicators of disease severity – namely, the need for immunosuppressors, biological agents or resective surgery – both in UC and CD pairs of relatives. As far as we know, these aspects had not previously been assessed, except for bowel resection in familial CD, with poor concordance rates reported.[13,19] One can argue that period or cohort

Table 3 Subgroup analyses of concordance for type of inflammatory bowel disease.

Kind of pair (n)	κ (95%CI)	p-Value	Strength of concordance
Parent/child (n = 49)	0.58 (0.10 to 1.00)	<0.001	Moderate
Siblings (n = 57)	0.52 (0.09 to 0.96)	<0.001	Moderate
Uncle-aunt/nephew-niece (n = 15)	0.54 (0.13 to 0.95)	<0.001	Moderate
First cousins (n = 20)	0.72 (0.37 to 1.00)	<0.001	Good
Grandparent/grandchild (n = 3)	Not calculated	–	–
1st degree relatives[a] (n = 106)	0.56 (0.24 to 0.88)	<0.001	Moderate
2nd degree relatives[b] (n = 38)	0.63 (0.38 to 0.89)	<0.001	Good
Same generation[c] (n = 77)	0.56 (0.16 to 0.95)	<0.001	Moderate
Different generation[d] (n = 67)	0.55 (0.15 to 1.00)	<0.001	Moderate

[a] Parent/child, or siblings.
[b] Uncle–aunt/nephew–niece, grandparent/grandchild, or first cousins.
[c] Siblings or first cousins.
[d] Parent/child, uncle–aunt/nephew–niece, or grandparent/grandchild.

Table 4 Phenotypic concordance in the 41 pairs concordant for ulcerative colitis.

		Youngest member				κ (95%CI)	p-Value	Strength of concordance
1) Extension (E) of the disease		E1	E2	E3	Total			
Oldest member	E1	2	2	2	6	0.15 (0.00 to 0.42)	0.623	Poor
	E2	2	11	8	21			
	E3	3	7	4	14			
	Total	7	20	14	41			
2) Extra-intestinal manifestations		No	Yes	Total				
Oldest member	No	31	2	33		−0.06 (−0.41 to 0.18)	0.571	Absent
	Yes	8	0	8				
	Total	39	2	41				
3) Use of immuno-suppressors		No	Yes	Total				
Oldest member	No	18	9	27		0.02 (0.00 to 0.33)	0.571	Poor
	Yes	9	5	14				
	Total	27	14	41				
4) Use of biological agents		No	Yes	Total				
Oldest member	No	34	5	39		−0.07 (−0.35 to 0.20)	0.589	Absent
	Yes	2	0	2				
	Total	36	5	41				
5) Need for colectomy		No	Yes	Total				
Oldest member	No	35	1	36		−0.04 (−0.26 to 0.18)	0.706	Absent
	Yes	5	0	5				
	Total	40	1	41				

E1 = proctitis, E2 = left-sided colitis (up to the splenic flexure), and E3 = extensive colitis (proximal to the splenic flexure).

effects (availability of new drugs in recent years, different time of follow-up, changes in recommended therapeutic strategies, etc.) may account, at least in part, for the lack of concordance of these evolutive issues. However, this appears not to be the case in our patients, since the frequency of the different items was quite similar in the senior and the junior members of the pairs (see Tables 4 and 5).

Conceivably, the multicentric character of the study (14 hospitals) with a very long follow-up period could account in part for the lack of phenotypic concordance. However, data on extent/localization and clinical behaviour of the disease are based in quite objective data which make interobserver variability scarcely relevant. In is also not probable that different criteria between centres in the management of these patients could contribute to the lack of concordance in need for therapies since, in 143/144 pairs included in the study both members were diagnosed and treated at the same centre.

On the other hand, differences in quitting tobacco during follow-up in pair members could also contribute to the lack of concordance in the outcome of the disease. Unfortunately, data on smoking status during follow-up are not available in ENEIDA database.

In summary, a) the prevalence of familial IBD in Spain compares well with that reported in other Western countries, b) familial IBD is associated with diagnostic anticipation in younger individuals, both in the same and the second generation, and c) familial history of IBD does not allow predicting any phenotypic feature of the disease other that the IBD type, and this only with moderate precision. Having a relative with a severe disease course does not appear to be per se reason enough to adopt more aggressive therapeutic measures in IBD patients.

Potential conflict of interests

None of the authors have conflict of interest to declare.

Author contributions

Eduard Cabré conceived the study, performed data analyses, and drafted the manuscript. Míriam Mañosa, Valle García-Sánchez, Ana Gutiérrez, Elena Ricart, Maria Esteve, Jordi Guardiola, Mariam Aguas, Olga Merino, Angel Ponferrada, Javier P. Gisbert, Esther Garcia-Planella, Gloria Ceña, José L. Cabriada, and Miguel Montoro participated in the acquisition of data and revised the draft of manuscript. Eugeni Domènech conceived the study, performed data analyses, and revised the draft of manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors are grateful with Ferring Pharmaceuticals for kindly sponsoring the development and maintenance of the ENEIDA project. The funding sources had no involvement in

Table 5 Phenotypic concordance in the 69 pairs concordant for Crohn's disease.

		Youngest member				κ (95%CI)	p-Value	Strength of concordance
1) Localization (L) of the disease		L1	L2	L3	Total			
Oldest member	L1	17	9	11	37	0.11 (0.00 to 0.38)	0.980	Poor
	L2	2	2	3	7			
	L3	8	5	12	25			
	Total	27	16	26	69			
2) Stricturing behaviour (B2)		No	Yes	Total				
Oldest member	No	42	3	45		0.26 (0.06 to 0.46)	0.011	Mild
	Yes	17	7	24				
	Total	59	10	69				
3) Fistulizing behaviour (B3)		No	Yes	Total				
Oldest member	No	46	10	56		0.26 (0.03 to 0.49)	0.029	Mild
	Yes	7	6	13				
	Total	53	16	69				
4) Perianal disease		No	Yes	Total				
Oldest member	No	31	12	43		0.07 (0.13 to 0.33)	0.588	Poor
	Yes	17	9	26				
	Total	48	21	69				
5) Extra-intestinal manifestations		No	Yes	Total				
Oldest member	No	46	11	57		−0.04 (−0.30 to 0.21)	0.776	Absent
	Yes	10	2	12				
	Total	56	13	69				
6) Use of immuno-suppressors		No	Yes	Total				
Oldest member	No	4	15	19		0.01 (0.00 to 0.24)	0.676	Poor
	Yes	10	40	50				
	Total	14	55	69				
7) Use of biological agents		No	Yes	Total				
Oldest member	No	30	17	47		−0.04 (−0.28 to 0.19)	0.724	Absent
	Yes	15	7	22				
	Total	45	24	69				
8) Need for bowel resection		No	Yes	Total				
Oldest member	No	25	8	33		0.23 (0.00 to 0.45)	0.029	Mild
	Yes	19	17	36				
	Total	44	25	69				

L1 = Ileal, L2 = colic, and L3 = Ileo-colic.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.12.005.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**:1590–605.
2. Ordas I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012;**380**:1606–19.
3. Abraham C, Cho JH. Mechanisms of disease: inflammatory bowel disease. *N Engl J Med* 2009;**361**:2066–78.
4. Cortot A, Pineton de Chambrun G, Vernier-Massouille G, Vigneron B, Gower RC. Inflammatory bowel disease: genetic or environmental diseases? *Gastroenterol Clin Biol* 2009;**33**:681–91.
5. Fiocchi C. Susceptibility genes and overall pathogenesis of inflammatory bowel disease: where do we stand? *Dig Dis* 2009;**27**:226–35.
6. Sachar DB. Crohn's disease: a family affair. *Gastroenterology* 1996;**111**:813–5.
7. Russell RK, Satsangi J. IBD: a family affair. *Best Pract Res Clin Gastroenterol* 2004;**18**:525–39.
8. Halme L, Paavola-Sakki P, Turunen U, Lappalainen M, Farkkila M, Kontula K. Family and twin studies in inflammatory bowel disease. *World J Gastroenterol* 2006;**12**:3668–72.
9. Nunes T, Fiorino G, Danese S, Sans M. Familial aggregation in inflammatory bowel disease: is it genes or environment? *World J Gastroenterol* 2011;**17**:2715–22.
10. Roth MP, Petersen GM, McElree C, Vadheim CM, Panish JF, Rotter JI. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. *Gastroenterology* 1989;**96**:1016–20.

11. Orholm M, Munkholm P, Langholz E, Nielsen OH, Sorensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;**324**:84–8.
12. 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.
13. Peeters M, Nevens H, Baert F, Hiele M, De Meyer AM, Vlietinck R, et al. Familial aggregation in Crohn's disease: increased age-adjusted risk and concordance in clinical characteristics. *Gastroenterology* 1996;**111**:597–603.
14. Russel MG, Pastoor CJ, Janssen KM, van Deursen CT, Muris JW, van Wijlick EH, et al. Familial aggregation of inflammatory bowel disease: a population-based study in South Limburg. The Netherlands. The South Limburg IBD Study Group. *Scand J Gastroenterol Suppl* 1997;**223**:88–91.
15. Freeman HJ. Familial Crohn's disease in single or multiple first-degree relatives. *J Clin Gastroenterol* 2002;**35**:9–13.
16. Meucci G, Vecchi M, Torgano G, Arrigoni M, Prada A, Rocca F, et al. Familial aggregation of inflammatory bowel disease in northern Italy: a multicenter study. *Gastroenterology* 1992;**103**:514–9.
17. Lee JCW, Lennard-Jones JE. Inflammatory bowel disease in 67 families each with three or more affected first-degree relatives. *Gastroenterology* 1996;**111**:587–96.
18. Satsangi J, Grootscholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996;**38**:738–41.
19. Annese V, Andreoli A, Astegiano M, Campieri M, Caprilli R, Cucchiara S, et al. Clinical features in familial cases of Crohn's disease and ulcerative colitis in Italy: a GISC study. Italian Study Group for the Disease of Colon and Rectum. *Am J Gastroenterol* 2001;**96**:2939–45.
20. Henriksen M, Jahnsen J, Lygren I, Vatn MH, Moum B. Are there any differences in phenotype or disease course between familial and sporadic cases of inflammatory bowel disease? Results of a population-based follow-up study. *Am J Gastroenterol* 2007;**102**:1955–63.
21. Reed III JF, Calkins BM, Rosen L. Concordance of familial characteristics in Crohn's disease and ulcerative colitis. *Dis Colon Rectum* 1992;**35**:405–10.
22. Bayless TM, Tokayer AZ, Polito II JM, Quaskey SA, Mellits ED, Harris ML. Crohn's disease: concordance for site and clinical type in affected family members — potential hereditary influences. *Gastroenterology* 1996;**111**:573–9.
23. 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.
24. Cipolla C, Magliocco A, Oliva L, Cottone M. Familial aggregation of inflammatory bowel disease in a Mediterranean area. *Eur J Epidemiol* 1996;**12**:205–10.
25. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol* 1989;**170**(Suppl):2–6.
26. 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.
27. Cohen JA. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;**20**:37–46.
28. Cohen JA. Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychol Bull* 1968;**70**:213–20.
29. Roberts C. Modelling patterns of agreement for nominal scales. *Stat Med* 2008;**27**:810–30.
30. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
31. Grandbastien B, Peeters M, Franchimont D, Gower-Rousseau C, Speckel D, Rutgeerts P, et al. Anticipation in familial Crohn's disease. *Gut* 1998;**42**:170–4.
32. Bengtson MB, Solberg C, Aamodt G, Jahnsen J, Moum B, Sauar J, et al. Clustering in time of familial IBD separates ulcerative colitis from Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:1867–74.
33. Lee JC, Bridger S, McGregor C, MacPherson AJ, Lennard-Jones JE. Why children with inflammatory bowel disease are diagnosed at a younger age than their affected parent. *Gut* 1999;**44**:808–11.
34. Faybush EM, Blanchard JF, Rawsthorne P, Bernstein CN. Generational differences in the age at diagnosis with IBD: genetic anticipation, bias, or temporal effects. *Am J Gastroenterol* 2002;**97**:636–40.
35. 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* 2009;**15**:171–5.
36. Monsen U, Bernell O, Johansson C, Hellers G. Prevalence of inflammatory bowel disease among relatives of patients with Crohn's disease. *Scand J Gastroenterol* 1991;**26**:302–6.
37. Andreu M, Márquez L, Domènech E, Gisbert JP, García-Sánchez MV, Marin I, et al. Disease severity in familial cases of inflammatory bowel diseases. *J Crohn's Colitis* 2013, http://dx.doi.org/10.1016/j.crohns.2013.08.010.
38. Bridger S, Lee JCW, Bjarnason I, Lennard-Jones JE, MacPherson AJ. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis. *Gut* 2002;**51**:21–5.
39. Halfvarson J, Bodin L, Tysk C, Lindberg E, Jarnerot G. Inflammatory bowel disease in a Swedish twin cohort: a long-term follow-up of concordance and clinical characteristics. *Gastroenterology* 2003;**124**:1767–73.
40. Halfvarson J, Jess T, Bodin L, Jarnerot G, Munkholm P, Binder V, et al. Longitudinal concordance for clinical characteristics in a Swedish–Danish twin population with inflammatory bowel disease. *Inflamm Bowel Dis* 2007;**13**:1536–44.
41. Ng SC, Woodrow S, Patel N, Subhani J, Harbord M. Role of genetic and environmental factors in British twins with inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:725–36.
42. Bengtson MB, Aamodt G, Vatn MH, Harris JR. Concordance for IBD among twins compared to ordinary siblings—a Norwegian population-based study. *J Crohn's Colitis* 2010;**4**:312–8.