Published in final edited form as:

Am J Gastroenterol. 2009 September ; 104(9): 2233–2240. doi:10.1038/ajg.2009.267.

Phenotypic & Genotypic Characteristics of Inflammatory Bowel Disease (IBD) in French-Canadians: comparison with a large North American repository

Mamatha Bhat¹, Geoffrey C. Nguyen², Pierre Pare³, Raymond Lahaie⁴, Colette Deslandres⁵, Edmond-Jean Bernard⁶, Guy Aumais⁷, Gilles Jobin⁷, Gary Wild⁸, Albert Cohen⁹, Diane Langelier¹⁰, Steven Brant¹¹, Themistocles Dassopoulos¹¹, Dermot McGovern¹², Esther Torres¹³, Richard Duerr¹⁴, Miguel Regueiro¹⁴, Mark S Silverberg², Hillary Steinhart², Anne M. Griffiths², Abdul Elkadri², Judy Cho¹⁵, Deborah Proctor¹⁵, Philippe Goyette¹⁶, John Rioux¹⁶, and Alain Bitton¹

¹Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada ²Department of Medicine, Mount Sinai Hospital Inflammatory Bowel Disease Centre, University of Toronto, Toronto, Canada ³Hôpital du Saint-Sacrement, Quebec, Canada ⁴Hôpital St. Luc, Centre Hospitalier, Université de Montréal, Quebec, Canada ⁵Hôpital Sainte-Justine, Montreal, Quebec, Canada ⁶Hôpital Hôtel Dieu, Montreal, Quebec, Canada ⁷Hôpital Maisonneuve Rosemont, Montreal, Quebec, Canada ⁸Montreal General Hospital, McGill University, Quebec, Canada ⁹Jewish General Hospital, Montreal, Quebec, Canada ¹⁰Centre Hospitalier de l'Université de Sherbrooke, Sherbrooke, Quebec, Canada ¹¹Harvey M. and Lyn P. Meyerhoff Inflammatory Bowel Disease Center, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland ¹²Division of Medical Genetics and Inflammatory Bowel Disease Center, Cedar-Sinai Medical Center, Los Angeles, California ¹³Department of Medicine, University of Puerto Rico School of Medicine, Medical Sciences Campus, San Juan, Puerto Rico ¹⁴Inflammatory Bowel Disease Center and Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania ¹⁵Department of Medicine, Section of Digestive Diseases, Yale University, New Haven, Connecticut ¹⁶The Montréal Heart Institute and the Université de Montréal, Quebec, Canada

Abstract

BACKGROUND—Phenotype characteristics of inflammatory bowel disease (IBD) may differ significantly among ethnic subpopulations. The aim of this study was to characterize the IBD phenotype in French-Canadians, the most prominent founder population in North America.

METHODS—Using well-characterized phenotype data in the NIDDK-IBD Genetics Consortium repository on IBD patients, we compared phenotypic characteristics of 202 French-Canadians to

CONFLICT OF INTEREST STATEMENT Guarantor of the article: Alain Bitton, MD FRCPC

Specific author contributions: Mamatha Bhat contributed through data collection, data synthesis, and drafting of the manuscript. Geoffrey Nguyen performed the statistical analysis and reviewed the manuscript. Alain Bitton is the senior author on the paper, having been responsible for the study design, patient recruitment, data collection and reviewing of the manuscript. Pierre Pare, Raymond Lahaie, Colette Deslandres, Edmond-Jean Bernard, Guy Aumais, Gilles Jobin, Gary Wild, Albert Cohen, Diane Langelier are members of the Quebec IBD Genetics Consortium (QIGC), were responsible for the recruitment of patients and data collection, and also reviewed the manuscript. Steven Brant, Themistocles Dassopoulos, Dermot McGovern, Esther Torres, Richard Duerr, Miguel Regueiro, Mark S Silverberg, Hillary Steinhart, Anne M. Griffiths, Abdul Elkadri, Judy Cho, Deborah Proctor are members of the NIDDK-IBD consortium who contributed to the study design and reviewed the manuscript. Philippe Goyette and John Rioux oversaw the genotyping of the French-Canadian patients, and contributed to the section of the manuscript dealing with IBD genotype.

Potential competing interests: None.

those of 1287 other Caucasian patients. These included: diagnosis, anatomical location, disease behaviour, extraintestinal manifestations, surgical history, and family history of IBD.

RESULTS—French-Canadian CD patients were less likely to have stricturing disease (11 vs 21%, $P=0.005$; OR 0.45, 95% CI: 0.24–0.85). Using a stringent definition of ethnicity (3 out of 4 grandparents being French-Canadian, as opposed to self-report, $n=148$), French-Canadians had a tendency towards developing fistulizing CD (37% vs 28%, $p=0.07$), and there was an increased prevalence of sacroiliitis among French-Canadians with IBD (4% vs 2%, $p=0.045$). Among French-Canadians, the numbers of current smokers in CD (40 vs 25%, $p=0.006$) and former smokers in UC (35% vs 20%, $p=0.03$) were significantly higher. The prevalence of one of the three main variant NOD2 SNPs among French-Canadian CD patients was 43.2%. The 3020insC SNP correlated with small bowel disease in French-Canadians (75% versus 0%, $P=0.006$).

CONCLUSION—French-Canadians exhibit an IBD phenotype profile distinct from other Caucasian IBD populations, with an accentuated association between smoking status and IBD. This unique profile may have implications regarding the need for a different approach to management of IBD in this population.

INTRODUCTION

The inflammatory bowel diseases, comprising Crohn's disease (CD) and ulcerative colitis (UC), are complex polygenic disorders in which genotypic profiles may influence disease characteristics. Consequently, disease phenotype may vary among racial and ethnic groups secondary to variations in IBD genetic susceptibility loci. The NIDDK-IBD genetic consortium has characterized the IBD phenotype in African Americans and Hispanics (1), the two major minority populations in the United States. Knowledge of ethnic variations in the clinical presentation of IBD may facilitate the approach to diagnosis and management of IBD in these populations (2;3).

One of the earliest immigrant populations to North America was the French, and they played a significant role in its early development through widespread colonization (4). In particular, the current French-Canadian population of 6 million people in Quebec descends from around 8500 French colonists who arrived between 1608 and 1759 (5), coming mainly from Atlantic seaports and Paris (6). Thus, the French-Canadian population evolved from a small sample of the French population, and founder effects and distant consanguinity in subsequent generations have created a unique distribution pattern of several diseases (7).

The NIDDK-IBD repository is a North America-wide effort to clinically characterize IBD. It provides an excellent opportunity to clinically characterize the IBD phenotype in the French-Canadian population, genetically more homogeneous than either the Hispanic or the African-American populations our group has previously studied (1). The manifestations of IBD in this population, having immigrated from France 400 years ago and evolved over generations exposed to the North American environment, may have implications for IBD genotype-phenotype correlations in more recent immigrant populations. Given the founder effects in other genetically transmitted conditions prevalent among French-Canadians, including some with a polygenic basis, we hypothesize the presence of a distinct IBD phenotype in this population.

METHODS

Subjects

IBD patients were recruited from multiple centers across the United States and Canada and registered in the Inflammatory Bowel Disease Genetics Consortium (IBDGC). The IBDGC was commissioned by the NIDDK (National Institute of Diabetes & Digestive & Kidney

Diseases) for pooling of genetic specimens and clinical phenotype data for IBD genetic studies. A retrospective analysis of data was conducted in order to assess for any differences in IBD phenotype between the French Canadian patients and the other Caucasians in the repository. The six genetic research centers involved in our consortium were the Université de Montréal, Cedars-Sinai Hospital in Los Angeles, Johns Hopkins University, the University of Chicago, the University of Pittsburgh, and the University of Toronto. The Broad Institute recruited patients from the Quebec IBD Genetics Consortium (QIGC), which consists of 8 adult hospital centers and one pediatric center spanning the province of Quebec. The patients were recruited at each of these centers between January 27th, 1997 and December 20th, 2005. Recruitment of patients was based solely on diagnosis of IBD. Diagnosis of CD, UC, and indeterminate colitis (IC) was confirmed by gastroenterologists through assessment of clinical, endoscopic, radiological and histopathological records using standardized definitions as specified in the NIDDK IBD Genetics Consortium operating manual. This operating manual has been proven to generate reliable and valid phenotypic assessments(8). We accessed the NIDDK-IBDGC database for demographic data, clinical phenotype data including age at diagnosis, disease location and extent, disease behavior (for CD), tobacco use, family history, extraintestinal manifestations (EIMs), and surgical history. Positive family history of IBD, obtained by patient self-report, was the presence of either CD or UC in first- or second-degree relatives, including grandparents, half-siblings, and avuncular relatives. Patients were designated as smokers if they had smoked at least 1 cigarette a day for at least 3 months prior to diagnosis of IBD, and ex-smokers if they had consumed tobacco prior to that point in time.

Designation of Race and Ethnicity

The NIDDK database contains the following racial designations: Caucasian, African American, American Indian/Alaskan Native, Asian or Other by self-report. Our population of interest was the French-Canadian patients from the Quebec centers. Designation of French-Canadian ethnicity was based on self-report. We were able to contact 168 patients to enquire whether at least 3 out of 4 of their grandparents were of French-Canadian ancestry. Excellent correlation has been found between self-identified race/ethnicity and genetic cluster categories (9). However, we used these more stringent criteria in a sensitivity analysis to validate that there were no significant phenotypic differences as compared to self-reported ethnicity. We felt this would consolidate phenotypic characterization and enable future assessment of genetic variations specific to the French-Canadian population.

Disease Site Designation

Medical, radiological, endoscopic, operative and pathological records were reviewed for all areas of the gastrointestinal tract macroscopically involved throughout the disease course. For CD the anatomic location of disease was designated as: esophagogastrroduodenal, jejunal, ileal, colonic, and perianal. If information regarding involvement of a certain portion of the GI tract was missing, disease status was designated as “unknown”. History of perianal abscess and/or fistula, anal canal ulcer or stenosis, and chronic edematous skin tags were designated as perianal disease, whereas hemorrhoids or fissures were not. We employed the Vienna classification system in our protocol as a framework for disease site designation and disease behavior, with adjustments that rendered it consistent with the Montreal classification system. We thus classified patients into three groups based on disease location: (1) ileal: macroscopic disease solely of the ileum; (2) colon-only: involvement limited to colon or rectum; (3) ileocolonic: both ileal and colonic involvement without proximal small bowel inflammation. As per the Montreal classification, we categorized the presence of upper gastrointestinal and perianal involvement as an adjunct or independent designation. Disease location designation was based on maximal extent of involvement at any point during the course of the disease. The Montreal classification system for CD has been found to be accurate and reproducible on testing with clinical databases (10–12).

Patients with UC were classified based on colonoscopy, barium enema, or colectomy pathology reports as follows: (1) proctitis: involvement limited to the rectum without crossing the rectosigmoid junction; (2) left-sided colitis: inflammation distal to the splenic flexure; (3) extensive colitis: inflammation proximal to the splenic flexure.

Extraintestinal manifestations

The extraintestinal manifestations of IBD were defined on the basis of objective diagnostic criteria in the NIDDK IBDGC phenotyping and operating manual (13;14). In a previous validation of this phenotyping manual, we have certified the accuracy of the manual criteria for the following extraintestinal manifestations: sacroiliitis, ankylosing spondylitis, uveitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis, and arthritis (8).

Clinical Disease Behavior

Crohn's disease behavior was reported as one of 3 categories based on the Vienna classification. These included (1) *inflammatory*: inflammation with no stricturing or fistulizing complications during the course of the disease; (2) *stricturing*: constant luminal narrowing demonstrated by radiological, endoscopic or surgical/pathological means, along with prestenotic dilatation or obstructive signs/symptoms without fistulizing disease at any time during the disease course; and (3) *fistulizing*: intra-abdominal fistulas, bowel perforation, inflammatory masses, and/or abscesses at any time during the disease course. Secondary post-operative intra-abdominal complications were excluded, as were perianal and rectovaginal fistulae. The most severe form of disease behaviour at any time point in the disease course was recorded in the database. If both fistulizing and stricturing disease were present, the patient's disease behavior was classified as fistulizing. Because the risk of developing stricturing or fistulizing phenotype increases with disease duration, we carried out a sensitivity analysis of disease behavior for a subgroup of patients diagnosed at least 5 years prior.

Surgical History

Medical records were checked for surgical procedures performed to treat CD and its complications: (1) bowel resection or stricturoplasty; (2) diversions performed prior to definitive bowel resection or to enable healing of perianal disease; (3) surgery for abdominal fistula/abscess; (4) surgery for perianal fistula comprising placement of a Seton, fistulotomy, or intestinal diversion to allow for healing of perianal disease. Data on bowel resection for UC was documented as: (1) dysplasia or malignancy; (2) chronic continuous disease; (3) acute fulminant disease, defined as onset of severe colitis within a period of 2 to 12 wks in a patient with hitherto undiagnosed or indolent colitis. We have verified the accuracy of these criteria for surgery in our study validating the NIDDK-IBDGC operating manual (8).

NOD2 SNP analysis

The genotyping of the 3 key NOD2 variants (R675W, G881R, 3020insC) among the French-Canadian patients was performed on serum samples using primer extension chemistry and mass spectrometric analysis (iPlex assay, Sequenom, San Diego, CA) on the Sequenom MassArray at the Montréal Heart Institute and the Université de Montréal.

Statistical Analysis

The categorical characteristics of French-Canadian patients were compared to those of other Caucasians using χ^2 analysis or Fisher's exact test of proportions. Multiple logistic regression models were developed to isolate the independent effect of French-Canadian ethnicity on the relative odds of colonic, fistulizing, and stricturing disease, adjusting for age at study entry, age at diagnosis, gender, tobacco use, and disease duration. The NOD2 data was analyzed using

χ^2 analysis, in order to determine whether any correlations between NOD2 SNPs with either disease behavior or location existed within the French-Canadian population.

Ethical Considerations

The Institutional Review Boards at all Quebec Inflammatory Bowel Disease Genetic Consortium centers, Université de Montréal, Cedars-Sinai Hospital, Johns Hopkins University, the University of Chicago, the University of Pittsburgh, the University of Toronto and the University of Puerto Rico Medical Sciences Campus approved the data collection protocols for their respective sites.

RESULTS

A total of 1489 eligible subjects with IBD (1287 Caucasians and 202 French-Canadians) were included in this study (Table 1). In our primary analysis, French-Canadian ethnicity was determined by self-report (n=202). In a subsequent sensitivity analysis, French-Canadian ethnicity was defined by stricter criteria requiring at least 3 out of 4 grandparents of French-Canadian ethnicity. This stricter definition made 148 subjects eligible for this analysis. The characteristics of French Canadians and other Caucasians are shown in Table 1. There were no statistically significant differences in age, age of diagnosis, gender, family history, smoking history, or history of appendectomy between French Canadians and other Caucasians for either CD or UC. However, in the sensitivity analysis, there was a significantly higher number of former smokers among the French-Canadian UC patients (35% vs 20%, $p=0.03$) when the stricter criterion for ethnicity was used (Table 2). The percentage of current smokers was also higher among French-Canadians with CD as compared to other Caucasians (40 vs 25%, $p=0.006$).

Family History

A family history of IBD was reported in 21% of all subjects, with no racial or disease subtype differences noted.

CD Phenotype

The breakdown of CD anatomic location and behavioral pattern for all subjects (French-Canadians and other Caucasians) is given in Table 3. There was a greater prevalence of colorectal involvement among French-Canadians when compared to other Caucasians (79% vs 66%, $p=0.006$). However, after adjustment for age, age at diagnosis, gender, and smoking, these ethnic differences were no longer statistically significant (OR, 1.74; 95% CI: 0.80–3.80). There was no difference between the two groups for best-fit disease site. Disease behavior analysis revealed that French-Canadians had a two-fold lower prevalence of stricturing disease (11% vs 21%, $p=0.005$). After adjustment for age, age at diagnosis, gender, smoking, and disease duration, the odds ratio for having stricturing disease was 0.45 (95% CI: 0.24–0.85) for French Canadians compared to other Caucasians. When using the stringent definition of ethnicity, there was a tendency towards fistulizing disease among French-Canadians which did not achieve statistical significance (37% vs 29%, $p=0.07$; OR 1.51, 95% CI: 0.91–2.51). The prevalence of inflammatory disease behavior was similar between groups.

UC phenotype

The anatomic distribution of UC was similar between the French-Canadian and Caucasian subjects (Table 4). The overall prevalence of colonic dysplasia was 3% among all UC patients, with no significant difference between the two groups: French-Canadians (0%), and other Caucasians (3%).

Surgical history

French-Canadians had surgical intervention for Crohn's disease-related complications at a rate not different from other Caucasians (58% vs 55%, $p=0.489$) and remained similar after adjustment for age, age at diagnosis, gender, smoking and family history. In addition, there were no differences between the two groups when looking in particular at the various types of surgery for Crohn's disease, i.e. bowel resection, bowel diversion, surgery for abdominal penetrating disease, and surgery for perianal disease (Table 2). There was no significant difference between French-Canadians and other Caucasians with respect to the rates of colectomy for chronic refractory UC.

Extraintestinal manifestations

Analysis of the data for EIMs revealed no statistically significant differences between French-Canadians and other Caucasians when considering self-report as the determinant of French-Canadian ethnicity (Table 5). However, when the analysis was performed using the strict criteria for French-Canadian ethnicity, sacroiliitis was found to be more prevalent among French-Canadians than in other Caucasians (4% vs 2%, $p=0.045$). There were no statistically significant ethnic differences in the prevalence of PG, EN, uveitis, ankylosing spondylitis and PSC.

NOD2 SNP analysis in French-Canadians

We obtained serum samples on 103 out of 202 French-Canadian subjects. At least one of 3 NOD2 SNPs (R675W, G881R, 3020insC) was present in 43.2% of CD patients and 20.3% of UC patients in the French-Canadian population. Among French-Canadians, the prevalence of the 3020 insC SNP was significantly greater in individuals with small bowel disease compared to those without small bowel involvement (75% versus 0%, $P=0.006$) (Table 6). There was no correlation of the NOD2 variants with either stricturing or fistulizing Crohn's disease behavior.

DISCUSSION

Our results support the concept that phenotypic characteristics of IBD may vary by ethnicity (1;15). The distinct behavior of Crohn's disease in French-Canadians is the most striking finding, with reduced frequency in stricturing disease and a tendency towards fistulizing disease behavior. As well, there seems to be a heightened effect of smoking on IBD onset in this population. The French-Canadian population is a relatively more homogeneous ethnic group when compared to the Hispanics and African Americans of North America. The latter two are a more heterogeneous mixture of subpopulations, whereas the current French-Canadian population has its roots in a cluster of Atlantic seaports in France. This population with founder effects has served as an excellent point of reference for research into genetically-transmitted conditions (5;6), and it has proven to be so in IBD as well.

Defining ethnicity for research remains a challenge, given the growing admixture of cultures. Despite this phenomenon, Tang et al. reported in 2002 that self-identified race/ethnicity was sufficient to categorize individuals into ethnic groups (9). We found that the same held for our study population; when the analysis was performed for the self-identified French-Canadians as whole, similar results were derived as for the French-Canadians defined by strict criteria.

The tendency toward fistulizing disease among French-Canadians may be due to a genetic predisposition to more severe Crohn's disease. Interestingly enough, the higher prevalence of fistulizing disease did not translate into an increased need for surgical intervention. This may have been partly offset by the lesser degree of stricturing disease among French-Canadians. The tendency towards fistulizing disease among French-Canadians could encourage clinicians to adopt a more anticipatory therapeutic approach upon initial diagnosis, or at the first hint of

a more rapidly progressing clinical course. There are several previous phenotypic studies that have attempted to characterize various ethnic populations based on clinical characteristics of IBD including disease location, behavior, EIMS and disease modifiers (16,17). These studies confirm that IBD phenotype varies among ethnicities.

The genotypic basis of Crohn's disease behavior and location is gradually being unraveled, with the discovery of 11 confirmed disease loci within the last decade (18) and significant evidence for 21 additional loci more recently (19). Single nucleotide polymorphisms (SNPs) of NOD2 such as R675W, G881R, and 3020insC have been associated with CD, with homozygous or compound heterozygous patients having a 10 to 40 times higher relative risk of developing CD than the general population (20). The 43.2% prevalence of NOD2 variants among French-Canadians is congruent with the stated prevalence of 35 to 45% among populations of European ancestry (21). NOD2 prevalence has previously been examined within the Quebec population: Vermeire et al. found that 45% of Quebec IBD patients carried NOD2 variants, and that ileal disease correlated significantly with the presence of NOD2 variants (22). However, only 58% of the studied subjects were French-Canadian. A recent genome-wide association study of the French-Canadian population identified a number of disease loci that increase the risk of CD (23).

Several studies in the literature have reported the association of NOD2 variants with stricturing and fistulizing Crohn's disease behavior, small bowel involvement, and earlier age of onset (24;25). However, such a correlation could not be established in our French-Canadian population, which runs counter to the strong associations found among other Caucasian groups (26;27). This lack of association could be due to Type II error. However, the 3020insC SNP did correlate with small bowel involvement in French-Canadians with CD.

Smoking has been described in the literature as a moderating factor in the etiopathogenesis of Crohn's disease, with current smokers having an increased risk of developing Crohn's disease in a meta-analysis by Calkins (pooled OR of 2.0, with CI 1.65–2.47) (17;28), and more recently in a meta-analysis by Mahid et al. (OR 1.76, with CI of 1.40–2.22) (29). We found this association to be stronger among French-Canadians than in other Caucasians in the strict criteria analysis. French-Canadians also had a greater propensity to develop UC upon cessation of smoking than other Caucasians in the strict ethnicity analysis. This is in accordance with a recent case-control study showing that patients who had never smoked or who were former smokers had an increased risk of UC (30). This indicated that smoking was more protective against UC among French-Canadians, with hitherto quiescent UC flaring upon smoking cessation. Given that smoking has been shown to modulate cellular and humoral immunity, the intestinal microcirculation, and smooth muscle contractility through altered nitric oxide levels (31), the differential effect of smoking on IBD in French-Canadians may potentially reflect unique inflammatory cascade regulation.

Sacroiliitis, an EIM linked to the HLA B27 antigen, was more common among French-Canadians when the stricter ethnic definition was employed.

A major strength of our study was the access to a well-characterized, large population of IBD patients across North America, which facilitated the detection of racial differences in IBD phenotype with adjustment for confounders. The homogeneity in genetic background of the French-Canadian population was another advantage, allowing for a more dependable characterization of this condition.

The main limitation of our study was the potential for inherent referral bias, given that the majority of our patients were recruited at tertiary care centers. This may have affected the phenotypic characterization of IBD to some degree. On the other hand however, the two populations being compared (French-Canadian and Caucasian) were both tertiary care referral

populations, thus being of comparable severity. There was also lack of information on medications used in the treatment of IBD. The point of initiation during the course of disease, and whether these agents were therapeutically effective, would have given us further insight into the severity of IBD in the studied population. Data on level of education and socioeconomic status were not obtained either. These may have repercussions on access to appropriate treatment, and may play a role in severity of disease or its complications.

In conclusion, our description of the IBD phenotype in French-Canadians serves as a launching point for further exploration into the genotypic basis of this condition. The French-Canadian population with its founder effects offered a unique opportunity for genotype-phenotype correlations. The result of particular interest was the significantly decreased prevalence of stricturing disease and a tendency towards fistulizing disease in the French-Canadian Crohn's disease population. The accentuated response to smoking status in IBD among French-Canadians (current smoking in CD, and ex-smoker status in UC) may reflect a genotype sensitive to the inflammatory effects of smoking. Phenotypic characterization among ethnic groups enhances the clinician's diagnostic and therapeutic approach to IBD in these populations, and allows for appreciation of the role of IBD-specific genes in generating disease manifestations.

Genotype-phenotype correlations are also likely to play a pivotal role in clinical practice as we enter the era of pharmacogenomics, enabling more targeted pharmacotherapy. Earlier initiation of biologic agents or even a "top-down" approach may be warranted in the future depending on the presence of mutations associated with aggressive disease. Thus, characterization of IBD in ethnic groups has the potential to greatly benefit patient care through ethnocentric management.

STUDY HIGHLIGHTS

What Is Current Knowledge:

- Phenotype characteristics of inflammatory bowel disease may differ significantly among ethnic subpopulations.
- Certain ethnic populations manifest with particularly aggressive IBD, possibly reflecting an underlying predisposing genotype.

What Is New Here:

- French-Canadians exhibit an IBD phenotype profile distinct from other Caucasian IBD populations.
- The tendency towards fistulizing disease may have implications regarding the need for an anticipatory approach to management of IBD in this founder population.
- There is an accentuated association between smoking status and IBD among French-Canadians (current smokers in CD, ex-smokers in UC) as compared to other Caucasians
- Sacroiliitis is more common among French-Canadians than in their Caucasian counterparts

ACKNOWLEDGMENTS

The authors would like to sincerely acknowledge the IBD patients who agreed to participate in this study. We thank C. Tsagarelis and D. Browning for their data collection and entry as QIGC coordinators. We are grateful to C. Bergeron, S. Paris, C. Lamoureux, L. Henri, N. Godin, S. Rousseau, and J. Cousineau, the coordinators at the QIGC centres, for their assistance in data collection from the French-Canadian patients. Thanks to L. Wu Datta, J. Fultz and J. Stempak

for coordinating study subject recruitment, to A. Andriulli and O. Palmieri for providing clinical data and to J. Lian, A. Liew and H. Khalili for technical support.

Financial support: This publication was made possible by the following grants attributed to the NIDDK IBD Genetics Consortium: DK062431 (S.R.B.), DK062422 and DK062429 (J.H.C.), DK062420 (R.H.D.), DK062432 (J.D.R.), DK062423 (M.S.S.), DK062413 (K.D.T.), DK062432 (J.D.R.). The activities of the QIGC are supported by the Université de Montréal Genetic Research Center (J.D.R.; DK062432). The authors would also like to acknowledge additional support from the Atran Foundation (S.R.B.), National Center for Research Resources (NCRR) grant 5P20RR011126 (E.T.), Bohmfalk Funds for Medical Research (J.H.C.), Burroughs Wellcome Medical Foundation (J.H.C.), Crohn's and Colitis Foundation of America (S.R.B., J.H.C., R.H.D., J.D.R.), Crohn's and Colitis Foundation of Canada (M.S.S.), Gale and Graham Wright Research Chair in Digestive Diseases (M.S.S.), Harvey M. and Lyn P. Meyerhoff Inflammatory Bowel Disease Center (S.R.B.), US National Institutes of Health grants RR00052 (S.R.B.), DK072373 (J.H.C.), RR024139 (J.H.C.), DK076025 (R.H.D.), DK064869 (J.D.R.), MH057881 and the W. Buford Lewis family (S.R.B.).

Reference List

- (1). Nguyen GC, Torres EA, Regueiro M, Bromfield G, Bitton A, Stempak J, Dassopoulos T, Schumm P, Gregory FJ, Griffiths AM. Inflammatory Bowel Disease Characteristics Among African Americans, Hispanics, and Non-Hispanic Whites: Characterization of a Large North American Cohort. *The American Journal of Gastroenterology* 2006;101(5):1012–23. [PubMed: 16696785]
- (2). Gasche C, Grundtner P. Genotypes and phenotypes in Crohn's disease: do they help in clinical management? *British Medical Journal* 2005;54(1):162.
- (3). Straus WL, Eisen GM, Sandler RS, Murray SC, Sessions JT. Crohn's disease: does race matter? *American Journal of Gastroenterology* 2000;95(2):479–83. [PubMed: 10685754]
- (4). Holbrook, S. *The French Founders of North America and Their Heritage*. Atheneum; New York: 1976.
- (5). Laberge AM, Michaud J, Richter A, Lemyre E, Lambert M, Brais B, Mitchell GA. Population history and its impact on medical genetics in Quebec. *Clinical Genetics* 2005;68(4):287–301. [PubMed: 16143014]
- (6). De Braekeleer M, Dao TN. Hereditary disorders in the French Canadian population of Quebec. I. In search of founders. *Hum Biol* 1994;66(2):205–23. [PubMed: 8194844]
- (7). Brunet G, Bouchard G, De Braekeleer M. *Histoire d'un génome*, Laval, Presses de l'Université du Québec, 1991. *Annales Histoire, Sciences Sociales* 1991;46(6):1470–1.
- (8). Dassopoulos T, Nguyen GC, Bitton A, Bromfield GP, Schumm LP, Wu Y, Elkadri A, Regueiro M, Siemanowski B, Torres EA. Assessment of reliability and validity of IBD phenotyping within the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium (IBDGC). *Inflamm Bowel Dis* 2007;13(8):975–83. [PubMed: 17427244]
- (9). Tang H, Quertermous T, Rodriguez B, Kardia SLR, Zhu X, Brown A, Pankow JS, Province MA, Hunt SC, Boerwinkle E. Genetic Structure, Self-Identified Race/Ethnicity, and Confounding in Case-Control Association Studies. *The American Journal of Human Genetics* 2005;76(2):268–75.
- (10). Gasche C, Scholmerich J, Brynskov J, D'Haens G, Hanauer SB, Irvine EJ, Jewell DP, Rachmilewitz D, Sachar DB, Sandborn WJ. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. *Inflamm Bowel Dis* 2000;6(1):8–15. [PubMed: 10701144]
- (11). Freeman HJ. Application of the Vienna Classification for Crohn's disease to a single clinician database of 877 patients. *Can J Gastroenterol* 2001;15(2):89–93. [PubMed: 11240378]
- (12). Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *British Medical Journal* 2006;55(6):749.
- (13). Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterology Clinics of North America* 2002;31(1):307–27. [PubMed: 12122740]
- (14). Mintz R, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2004;10(2):135–9. [PubMed: 15168814]
- (15). Basu D, Lopez I, Kulkarni A, Sellin JH. Impact of Race and Ethnicity on Inflammatory Bowel Disease. *The American Journal of Gastroenterology* 2005;100(10):2254–61. [PubMed: 16181378]

- (16). Fidder HH, Avidan B, Lahav M, Bar-Meir S, Chowers Y. Clinical and Demographic Characterization of Jewish Crohn's Disease Patients in Israel. *Journal of Clinical Gastroenterology* 2003;36(1):8. [PubMed: 12488699]
- (17). Triantafyllidis JK, Emmanouilidis A, Manousos O, Nicolakis D, Kogevas M, MD JKT. Clinical Patterns of Crohn's Disease in Greece: A Follow-Up Study of 155 Cases. *Logo* 2000;61(2)
- (18). Economou M, Trikalinos TA, Loizou KT, Tsianos EV, Ioannidis JPA. Differential Effects of NOD2 Variants on Crohn's Disease Risk and Phenotype in Diverse Populations: A Metaanalysis. *The American Journal of Gastroenterology* 2004;99(12):2393–404. [PubMed: 15571588]
- (19). Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nature Genetics*. 2008;(current)
- (20). Hugot JP, Zaccaria I, Cavanaugh J, Yang H, Vermeire S, Lappalainen M, Schreiber S, Annese V, Jewell DP, Fowler EV. Prevalence of CARD15/NOD2 Mutations in Caucasian Healthy People. *The American Journal of Gastroenterology*. 2007;(0)
- (21). Vermeire S, Rutgeerts P. Current status of genetics research in inflammatory bowel disease. *Genes and Immunity* 2005;6:637–45. [PubMed: 16107869]
- (22). Vermeire S, Wild G, Kocher K, Cousineau J, Dufresne L, Bitton A, Langelier D, Pare P, Lapointe G, Cohen A. CARD15 Genetic Variation in a Quebec Population: Prevalence, Genotype-Phenotype Relationship, and Haplotype Structure. *The American Journal of Human Genetics* 2002;71(1):74–83.
- (23). Raelson JV, Little RD, Ruether A, Fournier H, Paquin B, Van Eerdeghe P, Bradley WEC, Croteau P, Nguyen-Huu Q, Segal J. From the Cover: Genome-wide association study for Crohn's disease in the Quebec Founder Population identifies multiple validated disease loci. *Proceedings of the National Academy of Sciences* 2007;104(37):14747.
- (24). Abreu MT, Taylor KD, Lin YC, Hang T, Gaiennie J, Landers CJ, Vasiliauskas EA, Kam LY, Rojany M, Papadakis KA. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology* 2002;123(3):679–88. [PubMed: 12198692]
- (25). Annese V, Lombardi G, Perri F, D'Inca R, Ardizzone S, Riegler G, Giaccari S, Vecchi M, Castiglione F, Gionchetti P. Variants of CARD15 are Associated with an Aggressive Clinical Course of Crohn's Disease-An IG-IBD Study. *The American Journal of Gastroenterology* 2005;100(1):84–92. [PubMed: 15654786]
- (26). Lesage S, Zouali H, Cqzard JP, Colombel JF, Belaiche J, Almer S, Tysk C, O'Morain C, Gassull M, Binder V. CARD15/NOD2 Mutational Analysis and Genotype-Phenotype Correlation in 612 Patients with Inflammatory Bowel Disease. *The American Journal of Human Genetics* 2002;70(4): 845–57.
- (27). Ahmad T, Armuzzi A, Bunce M, Mulcahy-Hawes K, Marshall SE, Orchard TR, Crawshaw J, Large O, De Silva A, Cook JT. The molecular classification of the clinical manifestations of Crohn's disease. *Gastroenterology* 2002;122(4):854–66. [PubMed: 11910336]
- (28). Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Digestive Diseases and Sciences* 1989;34(12):1841–54. [PubMed: 2598752]
- (29). Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and Inflammatory Bowel Disease: A Meta-analysis. *May Foundation* 2006:1462.
- (30). Tuvlin JA, Raza SS, Bracamonte S, Julian C, Hanauer SB, Nicolae DL, King AC, Cho JH. Smoking and inflammatory bowel disease: trends in familial and sporadic cohorts. *Inflamm Bowel Dis* 2007;13(5):573–9. [PubMed: 17345609]
- (31). Lakatos PL, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: Good, bad or ugly? *Gastroenterology* 2007;13(46):6134–9.

Table 1
Patient Demographics of IBD Patients by Ethnicity

Characteristics	Crohn's Disease		Ulcerative Colitis	
	Caucasian no. (%)	French Canadian no. (%)	Caucasian no. (%)	French Canadian no. (%)
Ethnic Distribution (no.)	670	136	617	66
Age at study entry, mean (SD) y	34.1 (14.2)	33.1 (13.4)	40.0 (16.6)	38.2 (14.1)
Age at diagnosis, mean (SD) y	24.2 (11.2)	24.0 (12.4)	30.9 (15.2)	29.1 (11.9)
Female, no. (%)	358 (53)	83 (61)	273 (44)	35 (53)
Family history of IBD	139 (21)	18 (16)	124 (20)	13 (20)
Packs/day at diagnosis	0.17	0.22	0.60	0.72
Smoking at diagnosis, no. (%)				
Current	164 (25)	44 (33)	62 (10)	7 (11)
Former	57 (9)	8 (6)	123 (20)	19 (29)
Never	442 (67)	80 (61)	425 (70)	40 (61)
Appendectomy (2y prior to IBD)	38 (14)	5 (10)	14 (15)	3 (38)

Table 2

Patient Demographics of IBD Patients by Ethnicity – strict criteria

Characteristics	Crohn's Disease		Ulcerative Colitis	
	Caucasian no. (%)	French Canadian no. (%)	Caucasian no. (%)	French Canadian no. (%)
Smoking at diagnosis, no. (%)				
Current	164 (25)	37 (40)**	62 (10)	6 (11)
Former	57 (9)	8 (9)	123 (20)	19 (35)*
Never	442 (67)	47 (51)	425 (70)	29 (54)

* P<0.05

** P<0.01

Table 3
CD Phenotype by Ethnicity of the NIDDK-IBDGC Repository

Characteristics	Caucasian no. (%)	French-Canadian Self-identified no. (%)	French-Canadian Strict criteria no. (%)
Disease Involvement			
Upper Gastrointestinal (N=666)	99 (17)	14 (15)	12 (18)
Ileal (N=775)	523 (80)	95 (76)	68 (79)
Colo-rectal (N=780)	436 (66)	98 (79) **	69 (81) **
Perianal disease (N=794)	195 (29)	39 (30)	26 (29)
Best-fit Disease Site (N=746)			
Terminal Ileum	214 (34)	26 (22)	16 (20)
Ileo-colon	295 (47)	60 (52)	45 (55)
Colon	121 (19)	30 (26)	18 (23)
Disease Pattern (N=794)			
Inflammatory	337 (51)	73 (55)	48 (52)
Strictureing	140 (21)	14 (11) **	10 (11) *
Fistulizing	185 (28)	45 (34)	34 (37)
Crohn's Related Surgery	366 (55)	77 (58)	55 (60)
Bowel resection	326 (49)	66 (50)	47 (51)
Bowel diversion	30 (5)	6 (5)	2 (2)
For abdominal fistulizing disease	98 (15)	13 (10)	9 (10)
For perianal disease	97 (15)	19 (14)	14 (15)

P values were calculated based on comparisons between the French-Canadian patients (self-identified or strictly defined) with the Caucasian control population

* P<0.05

** P<0.01.

Table 4

Ulcerative Colitis Phenotype by Ethnicity of the NIDDK-IBDGC Repository

Characteristics	Caucasian no. (%)	French Canadian no. (%)
Disease Extent		
Proctitis	27 (5)	5 (10)
Left-sided	179 (30)	21 (40)
Extensive	390 (65)	26 (50)
Colonic dysplasia/cancer	20 (3)	0 (0)
Colectomy	100 (16)	5 (8)

Table 5
Extraintestinal Manifestations of IBD by Ethnicity- strict criteria

Characteristics	Caucasian no. (%)	French Canadian no. (%)
Arthritis		
Small joint	42 (3)	9 (6)
Large joint	91 (7)	10 (7)
Sacroiliitis	22 (2)	6 (4) *
Ankylosing spondylitis	15 (1)	3 (2)
Erythema nodosum	41 (3)	5 (3)
Pyoderma gangrenosum	22 (2)	2 (1)
Uveitis	20 (2)	2 (1)
Episcleritis	21 (2)	1 (1)
Primary Sclerosing Cholangitis	25 (2)	2 (1)

*
P<0.05

Table 6
Correlation of NOD2 SNPs with Small Bowel Crohn's disease in French-Canadians

Small bowel disease	3020insC		R675W		G881R		Total
	Absent	Present	Absent	Present	Absent	Present	
Absent	22	0	14	8	21	1	22
Present	61	20*	66	15	76	5	81
Total	83	20	80	23	97	6	103

* p<0.01