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Differential Effect of Genetic Burden on Disease Phenotypes in Crohn's Disease and Ulcerative Colitis in a Canadian Cohort

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Abstract

Background and Aims: Crohn's disease (CD) and ulcerative colitis (UC) demonstrate considerable phenotypic heterogeneity and course. Accurate predictors of disease behaviour are lacking. The contribution of genetics and specific polymorphisms is widely appreciated; however, their cumulative effect(s) upon disease behaviour remains poorly understood. Here, we investigate the relationship between genetic burden and disease phenotype in a Canadian inflammatory bowel disease (IBD) Cohort.

Methods: We retrospectively examined a cohort of CD and UC patients recruited from a single tertiary referral center genotyped using a Goldengate Illumina platform. A genetic risk score (GRS) incorporating strength of association (log odds ratio) and allele dose for 151 IBD-risk loci was calculated and evaluated for phenotypic associations.

Results: Among CD patients, higher GRS was associated with earlier onset of disease (regression coefficient −2.19, 95% confidence interval [CI] −3.77 to −0.61, $P = 0.007$), ileal disease (odds ratio [OR] 1.45), stricturing/penetrating disease (OR 1.72), perianal disease (OR 1.57) and bowel resection (OR 1.66). Higher GRS was associated with use of anti-tumor necrosis factor (TNF) ($P < 0.05$) but not immunomodulators. Interestingly, we could not demonstrate an association between higher GRS and family history of IBD (OR 1.27, $P = 0.07$). Onset of disease remained statistically significant for never smokers ($P = 0.03$) but not ever smokers ($P = 0.13$). For UC, having a higher GRS did not predict the age of diagnosis nor was it predictive of UC disease extent ($P = 0.18$), the need for surgery ($P = 0.74$), nor medication use (immunomodulators $P = 0.53$, anti-TNF $P = 0.49$). We could not demonstrate an association between increased GRS and having a family history of IBD in the UC group.

Conclusions: Increasing genetic burden is associated with early age of diagnosis in CD and may be useful in predicting disease behaviour in CD but not UC.

Keywords: *Age at diagnosis; Crohn's disease; Genetic burden; Ileal disease; Phenotype*

Introduction

Inflammatory bowel diseases (IBD) encompass a spectrum of intestinal inflammatory disorders ranging from ulcerative colitis (UC), through inflammatory bowel disease type unclassified (IBDU) to Crohn's disease (CD). Indeed, some patients demonstrate clinical overlap between UC and CD and may even

develop one form from another [1,2]. The incidence of IBD are increasing globally with approximately 5 million people around the world affected, including 250,000 in Canada and 3 million in the United States [3]. The costs to the Canadian health system were approximately $2.8 billion in 2012, including direct and indirect medical costs [4,5]. These idiopathic diseases are thought to be caused by a dysregulated immune response to host intestinal microflora, however, their pathogenesis involves distinct genetic, environmental and pathogenic factors [1,2].

One of the most important challenges in the management of autoimmune diseases such as IBD, is the ability to predict the course of disease over time (prognosis) [6–8]. In IBD, it has been demonstrated that early intervention with immunosuppressants and biologic therapy prevents progressive bowel damage and complications such as surgery resulting in better outcomes and lessened complications [9–11]. However, use of these medications as first-line therapy may not be warranted in all patients; patients with mild, indolent disease may be unnecessarily exposed to side effects and incur unnecessary costs if treated with a 'top-down' approach [12].

There have been many attempts at developing predictive models to select patients who would most benefit from early intervention. A comprehensive literature review performed by Torres et al. (2016) looked to identify predictors for IBD prognosis that can help to optimize disease management. They concluded that the most useful prognostic factors in IBD include simple demographics and clinical features which are mostly identified retrospectively. As a result, there is still need for more accurate prognostic factors that can be sensitive and widely available [11].

Individuals with IBD are believed to harbour a genetic predisposition to these disorders. For example, population-based studies have shown that 5 to 10% of patients with IBD have a first-degree relative with IBD with a calculated relative risk of 30- to 40-fold for CD and 10- to 20-fold for UC. In addition, twin studies have shown that concordance rates are significantly greater in monozygotic than in dizygotic twins for both CD (50 to 58% versus 0 to 12%) and UC (6 to 14% versus 0 to 5%) [13]. This has led to multiple large genome-wide association studies (GWAS) looking to identify genetic variants associated with risk of developing IBD. A meta-analysis of several GWAS identified 163 IBD loci, 60 loci with heterogenous effects while 50 were not distinguishable in CD or UC. The remaining 53 loci were specific only for CD ($n = 30$) or for UC ($n = 23$) [14]. More recently, Immunochip data from European, East Asian, Indian or Iranian cohorts have implicated an additional 38 loci in IBD risk with 27 contributing to both diseases (CD and UC), with 11 specific for CD and 4 for UC [15]. Thus, there are currently over 200 single-nucleotide polymorphism (SNPs) associated with CD and UC. There have been multiple attempts to characterize associations between specific genotypes and disease behaviour (phenotype), and develop these as reliable and stable prognostic markers to guide personalized care [16]. However, there has been relatively little attention placed upon the cumulative effect of multiple genetic variants upon disease behaviour in IBD.

A study conducted by Ananthakrishnan et al. established a framework for the calculation of genetic risk scores (GRS) incorporating strength of association and allele dose of IBD-associated risk loci. Their results suggest that GRS is associated with earlier age of onset of CD and ileal disease with a trend toward more severe disease related to ileal involvement [17]. This is in contrast to an earlier study which suggested that combined information from just five genetic variants was predictive of disease severity [18]. Neither study found an association between genetic burden and age of onset or disease behaviour in UC.

In this present study, we calculated GRS in a Canadian cohort of CD and UC patients ($n = 542$, 400 CD, 142 UC), and examined the relation between increasing genetic risk burden on phenotype and progression of the disease.

Methods

Inclusion/Exclusion Criteria

We selected all adult patients, age >18 years, with CD or UC, with existing genotyping data from the University of Calgary IBD clinic recruited between 2007 and 2014. We have a 99.76% complete genotyping dataset of 151 IBD-associated SNPs for 542 patients included in this study (Supplementary Appendix 1b). The Calgary IBD clinic patient research database stores a wide array of information including patient demographics, diagnoses, disease phenotype (confirmed endoscopically), medications, surgeries and genotyping, which are updated regularly by research coordinators through comprehensive chart reviews. The database was manually curated and updated during the preparation of this manuscript. The Montreal classification was adopted to record CD disease location and behaviour and UC disease extent [19]. Smoking history was categorized as current, former or never smoker. 460 of 542 patients in this study filled questionnaires which include the question 'Which genetic (blood-line or biologic ancestry) population group best describes you?' Patients can choose from, aboriginal (North American Indian/First Nations, Metis, or Inuit/Eskimo, Arab, Black, Chinese, Filipino, Hutterite, Japanese, Jewish-Ashkenazi, Jewish-Sephardic, Korean, Latin American, South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.), Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese, etc.), West Asian (e.g., Afghan, etc.), White (European Ancestry) or other. Of these, 396 (86%) identified as White (European Ancestry), 4% as South Asian and 2.8% as aboriginal. The remaining 7.2% encompasses other ethnic groups or unknown (adopted, 3/460) (Supplementary Appendix 2).

Genotyping and GRS

Genetic information was obtained through a previous initiative. DNA was extracted from venous blood samples using the Qiagen (Germantown, MD) DNAeasy kit, which were then sent to BGI-Shenzhen for processing. Genotype information was obtained using a Goldengate platform (Illumina).

GRS were calculated using the same method as presented by Ananthakrishnan et al. Risk alleles as well as their log odds ratios of association with disease were identified from Jostins et al. Each allele was then assigned a weight, with wild type as 0, heterozygous as 1 and homozygous as 2. The overall GRS was the summation of the weighted contribution of each risk allele calculated as Σ [log(odds ratio) × allele weight (0,1,2)]. Missing data on allele genotype were counted as wild type. Unlike Ananthakrishnan et al., we elected to keep GRS as a continuous variable for our analyses rather than arbitrarily dividing it into quartiles. Our Immunochip covers 151 of the 163 risk alleles described by Jostins et al. (14). The list of genes and their odds ratios is included in Supplementary Appendix 1a.

Statistical Analyses

All statistical analyses were performed using Stata v15.0 (StataCorp, College Station, TX). Variables were summarized as median and interquartile range or proportions as appropriate. Linear regression was done with age at diagnosis, while univariate logistic regression was used with other categorical outcomes of disease phenotype, medication use, necessity of surgery and family history of IBD. *P*-values <0.05 were considered statistically significant. Adjustment for ileal disease (Montreal classification L1) was done by including ileal disease as another independent variable in the logistic regression models. This study was approved the Research Ethics Board at the University of Calgary.

Results

Study Cohort

Our study included 542 patients, 402 CD and 140 UC patients. Median age at diagnosis was 26 years in the CD group and 29 years among the UC group. Both patient groups consisted of 42% male patients. Median disease duration was 13 years for the CD group and 10 years for the UC group. Family history of IBD was present in 34% of CD patients and 31% of UC patients. Among the CD patients, 26% suffered penetrating disease and 52% had ileocolonic disease. Fifty-four per cent of UC patients had pancolitis. Immunomodulator (methotrexate, azathioprine, 6-mercaptopurine) use was higher in the CD group with 77% having used at least one immunomodulator while only 46% of UC patients have used immunomodulators. Similarly, anti-TNF (infliximab, adalimumab, golimumab) use was also higher in the CD group than the UC group with 67% and 34%, respectively. Bowel resection was also more commonly needed among

the CD group with 51% having had at least one resection and only 11% of the UC group having gone through surgery. Both groups were predominantly never smokers, consisting of 78% and 83% of the CD and UC groups, respectively (Table 1).

GRS and Phenotype in CD

Tables 2–4 describe the association between GRS and disease phenotype in CD. Among CD patients, higher GRS was associated with an earlier onset of disease (Figure 1a) (regression coefficient −2.19, 95% confidence interval [CI] −3.77 to −0.61, *P* = 0.007). However, upon stratification by smoking history, this relation remained statistically significant only for never smokers (*P* = 0.03) but not ever (former or current) smokers (*P* = 0.13).

Higher GRS was also associated with having ileal disease (odds ratio [OR] 1.45), complicated CD with either stricture or penetrating disease behaviour (OR 1.72), perianal disease (OR 1.57) and bowel resection (OR 1.66).

Having a higher GRS did not predict the use of an immunomodulator but was associated with anti-TNF medication use (OR 1.31) (Table 2). In patients with CD, a higher GRS

Table 1. Patient demographics

	Crohn's disease (n = 402)	Ulcerative colitis (n = 140)
Age at diagnosis (years)	26 (20–36)	29 (23–40)
Male	168 (42)	59 (42)
Disease duration (years)	13 (7–21)	10 (5.5–16)
Family history of IBD	135 (34)	44 (31)
≥2 first-degree relatives	35 (9)	7 (5)
Disease behaviour		
Inflammatory	209 (52)	
Stricturing	88 (22)	
Penetrating	105 (26)	
Disease location		
Ileal	104 (26)	
Colonic	87 (22)	
Ileocolonic	211 (52)	
Perianal disease	104 (26)	
Disease extent		
Proctitis		16 (11)
Limited colitis		49 (35)
Pancolitis		75 (54)
Immunomodulators	311 (77)	65 (46)
Anti-TNFs	270 (67)	47 (34)
Bowel resection	206 (51)	16 (11)
Smoking		
Never	277 (78)	106 (83)
Former	29 (8)	13 (10)
Current	48 (14)	9 (7)

Data presented as Median (IQR) or *N* (%).

Table 2. GRS and CD

	GRS distribution Median (IQR)	OR (95% CI)	P value
All CD patients	16.23 (15.74–16.75)	−2.19 (−3.77 to −0.61)†	0.007
		−0.14 (−0.23 to −0.04)‡	
Age at diagnosis		−2.24 (−4.27 to −0.20)†	0.03
		−0.13 (−0.24 to −0.01)‡	
Never smoker	16.18 (15.73–16.69)	−2.16 (−4.94 to 0.62)†	0.13
		−0.18 (−0.38 to 0.05)‡	
Ever smoker	16.34 (15.74–17.03)	1.45 (1.09–1.94)	0.011
Ileal disease	16.41 (15.97–16.82)		
Without ileal disease	16.15 (15.68–16.71)	1.57 (1.17–2.10)	0.003
Perianal disease	16.44 (15.94–16.86)		
Without Perianal disease	16.14 (15.65–16.68)	1.72 (1.32–2.23)	<0.001
Complicated CD	16.42 (15.92–16.83)		
No complicated CD	16.06 (15.57–16.59)	1.66 (1.28–2.15)	<0.001
Bowel resection	16.39 (15.92–16.81)		
No bowel resection	16.00 (15.52–16.63)	1.06 (0.79–1.42)	0.68
IMM use	16.25 (15.70–16.79)		
No IMM use	16.22 (15.81–16.64)	1.31 (1.01–1.70)	0.04
Anti-TNF use	16.30 (15.82–16.80)		
No anti-TNF use	16.15 (15.54–16.64)	1.27 (0.98–1.65)	0.07
Family history	16.36 (15.88–16.80)	1.25 (0.81–1.95)	0.31
≥2 first-degree relatives	16.36 (15.97–16.81)		
No family history	16.17 (15.64–16.69)		

CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; IMM, immunomodulator; IQR, interquartile range; OR, odds ratio.

Table shows results for a series of univariate regression analyses assessing the association between GRS and CD.

†Regression coefficient.

‡Correlation coefficient.

Table 3. Adjustment for ileal disease in GRS and CD

	OR (95% CI)	P value
Age at diagnosis	−2.13 (−3.72 to −0.53)†	0.009
Never smoker	−2.17 (−4.21 to −0.12)†	0.04
Ever smoker	−2.07 (−4.90 to 0.76)†	0.15
Ileal disease		
Complicated CD	1.63 (1.24–2.14)	<0.001
Bowel resection	1.60 (1.23–2.08)	<0.001
IMM use	1.08 (0.81–1.45)	0.59
Anti-TNF use	1.30 (1.00–1.70)	0.050
Family history	1.27 (0.98–1.66)	0.07
≥2 first-degree relatives	1.26 (0.81–1.96)	0.31

CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; IQR, interquartile range; OR, odds ratio.

†Regression coefficient.

Table shows results for a series of regression analyses with ileal disease added as an independent variable.

was interestingly not associated with having a first-degree relative with IBD (OR 1.27, P = 0.07; Table 2). Adjusting for ileal disease did not have an effect on these associations (Table 3) nor did

adjustment for colonic only disease (Supplementary Table 1). Several studies have shown an association between ileal disease and carriage of NOD2 variants, however, NOD2 status does not predict perianal disease or associated complications. Likewise, NOD2 variant carriers have been shown more likely to require surgery. We therefore classified this cohort based on the presence or absence of the rs2066847 NOD2 loss-of-function SNP. Only 37 of 400 CD patients harboured this SNP but there was a clear strong association seen with ileal disease among NOD2 carriers with an OR of 2.81 (P = 0.048; Table 4).

GRS and Phenotype in UC

Contrary to CD, having a higher GRS did not predict the age of diagnosis in UC (Figure 1B) nor was it predictive of UC disease extent, the need for surgery, nor medication use although there was a trend toward disease extent (P = 0.18). Similarly, GRS was not associated with having a family history of IBD in the UC group (Table 5).

Discussion

There is substantial heterogeneity in the natural history of inflammatory bowel diseases when it comes to disease onset, course and response to medications. There is therefore a need to

Table 4. Adjustment for NOD2 status (rs2066847) and GRS in CD

	Phenotype distribution	GRS distribution Median (IQR)	OR (95% CI)	*P* value
Age at diagnosis	26 (20–36)	16.23 (15.74–16.75)	−2.19 (−3.77 to −0.61)†	0.007
			−0.14 (−0.23 to −0.04)‡	
NOD2 variant	20 (17–27)	16.65 (16.36–17.03)	−2.65 (−6.82 to 1.51)†	0.205*
			−0.21 (−0.5 to 0.12)‡	
NOD2 wild type	26 (20–37)	16.19 (15.68–16.68)	−1.65 (−3.38 to 0.08)†	0.062*
			−0.10 (−0.2 to 0.005)‡	
Ileal disease	104 (26)	16.41 (15.97–16.82)	1.45 (1.09–1.94)	0.011
NOD2 variant	18 (49)	16.88 (16.49–17.55)	2.81 (1.01–7.84)	0.048
NOD2 wild type	84 (23)	16.32 (15.87–16.68)	1.24 (0.90–1.70)	0.189*
Perianal disease	104 (26)	16.44 (15.94–16.86)	1.57 (1.17–2.10)	0.003
NOD2 variant	11 (30)	17.00 (16.45–18.16)	3.91 (1.27–12.0)	0.017
NOD2 wild type	92 (25)	16.39 (15.89–16.79)	1.45 (1.06–1.98)	0.021
Complicated CD	193 (48)	16.42 (15.92–16.83)	1.72 (1.32–2.23)	<0.001
NOD2 variant	30 (81)	16.64 (16.22–17.00)	0.83 (0.29–2.38)	0.73*
NOD2 wild type	161 (44)	16.35 (15.91–16.81)	1.64 (1.24–2.17)	0.001
Bowel resection	206 (51)	16.39 (15.92–16.81)	1.66 (1.28–2.15)	<0.001
NOD2 variant	28 (76)	16.58 (16.18–16.98)	0.71 (0.27–1.85)	0.48*
NOD2 wild type	176 (49)	16.35 (15.91–16.78)	1.65 (1.25–2.18)	<0.001
IMM use	311 (77)	16.25 (15.70–16.79)	1.06 (0.79–1.42)	0.68
NOD2 variant	29 (78)	16.72 (16.36–17.55)	1.79 (0.56–5.71)	0.32
NOD2 wild type	280 (77)	16.17 (15.64–16.73)	1.03 (0.75–1.40)	0.87
Anti-TNF use	270 (67)	16.30 (15.82–16.80)	1.31 (1.01–1.70)	0.04
NOD2 variant	27 (73)	16.72 (16.13–17.55)	1.09 (0.42–2.83)	0.86*
NOD2 wild type	241 (67)	16.24 (15.79–16.75)	1.30 (0.99–1.72)	0.06*
Family history	135 (34)	16.36 (15.88–16.80)	1.27 (0.98–1.65)	0.07
NOD2 variant	17 (46)	16.78 (16.36–16.94)	0.88 (0.38–2.05)	0.76
NOD2 wild type	118 (33)	16.27 (15.86–16.75)	1.26 (0.95–1.68)	0.11

CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; IQR, interquartile range; OR, odds ratio.

37/402 CD patients were NOD2 variants, * indicates change in significance.

Phenotype distribution presented as Median (IQR) or *N* (%).

†Regression coefficient.

‡Correlation coefficient.

Table expands on the series of univariate regression analyses as shown in Table 2 with further stratification by NOD2 status.

identify predictors of disease behaviour, response to medications and susceptibility to disease-related and medication-related complications which can in turn be used to optimize therapy and avoid unnecessary side effects. An individual's genome is a stable representation of his/her predisposition to disease, albeit a modest one in IBD. However, it may potentially be utilized to predict the natural history disease in patients with IBD and allow a personalized approach to treatment. Our understanding of the pathogenesis of inflammatory bowel diseases has been revolutionized by genetics. There are now over 200 genetic polymorphisms associated with UC and CD, of which 27 appear to be 'specific' to UC and 41 to CD. The stage is thus set to test whether genetics can be utilized to identify specific disease subgroups and predict disease course. However, many of the identified polymorphisms only moderately increase the risk for the development of disease with allelic odds ratios below 1.5, and therefore, individually have little value in predicting an individuals' risk of developing disease. In the present study, we tested whether genetic burden, the cumulative effect conferred by multiple loci, has prognostic implications in IBD.

We demonstrate that increasing genetic burden of disease predisposes toward disease location and early diagnosis in CD and is associated with more severe manifestations of disease. This is in contrast to UC where we could not show an association between genetic burden and age of diagnosis nor extent of disease.

Table 5. GRS and UC

	GRS distribution Median (IQR)	OR (95% CI)	*P* value
All UC patients	13.34 (12.79–13.92)	−0.52 (−3.32 to 2.29)†	0.72
		−0.03 (−0.2 to 0.14)‡	
Age at diagnosis		−0.15 (−3.44 to 3.14)†	0.93
		0.11 (−0.09 to 0.29)‡	
Never smoker	13.35 (12.79–13.90)	−0.38 (−8.17 to 7.42)†	0.92
		0.05 (−0.39 to 0.47)‡	
Ever smoker	13.32 (12.80–14.32)	0.76 (0.51–1.14)	0.18
Pancolitis	13.32 (12.64–13.83)		
No Pancolitis	13.41 (12.87–14.03)	0.90 (0.49–1.67)	0.74
Colectomy	13.36 (12.56–14.08)		
No colectomy	13.34 (12.81–13.89)	1.13 (0.76–1.68)	0.53
IMM use	13.44 (12.84–13.83)		
No IMM use	13.29 (12.79–13.95)	0.86 (0.57–1.31)	0.49
Anti-TNF use	13.32 (12.61–13.83)		
No anti-TNF use	13.41 (12.84–13.97)	1.05 (0.69–1.60)	0.83
Family history	13.28 (12.79–14.13)	2.19 (0.83–5.76)	0.11
≥2 first-degree relatives	14.07 (12.93–14.32)		
No family history	13.38 (12.85–13.85)		

CD, Crohn's disease; CI, confidence interval; GRS, genetic risk score; IQR, interquartile range; OR, odds ratio.

†Regression coefficient.

‡Correlation coefficient.

Table shows results for a series of univariate regression analyses assessing the association between GRS and ulcerative colitis.

A recent study from Boston prospectively followed 1105 genotyped patients with IBD and demonstrated an association between increasing genetic burden and ileal disease and earlier onset of disease in CD, with a trend toward disease severity and complications driven by disease location (17). However, adjusting for ileal location seemed to neutralize the latter. In the present study, adjustment for disease location did not negate the associations we observed in our study with penetrating, fibrostenotic or surgical CD. Thus, contrary to their study, we suggest there is clinical utility to genotyping, at least in the context of CD. Several studies have shown an association between ileal disease and carriage of NOD2 variants, however, NOD2 status does not predict perianal disease or associated complications (20). Likewise, NOD2 variant carriers have been shown more likely to require surgery (20). We stratified by NOD2 rs2066847 status to assess the effects of genes other than NOD2. For patients who are NOD2 wild type, the contribution of NOD2 rs2066847 to their GRS would be zero. As seen in Table 4, complicated CD and bowel resection remain associated with GRS in the absence of this NOD2 mutation, while ileal disease on the other hand seem to be driven completely by NOD2 status. This suggests that GRS may have utility beyond NOD2 rs2066847 in predicting some CD behaviour.

On the other hand, neither Ananthakrishnan's study nor ours suggest utility for genotyping in the context of UC. There was neither an association between genetic burden and age of onset or extent of disease although in our study we did note a trend toward the latter. Kopylov et al. tried to identify genetic predictors for low-risk UC patients, to spare these patients from early intensive medical therapy and its possible risks. They investigated the clinical and genetic predictors of a benign disease behaviour in a large and well-characterized multicenter cohort of UC patients selected from the NIDDK Inflammatory Bowel Disease Genetics Consortium (NIDDK IBDGC). Benign phenotype was defined as no need for immunomodulatory or biologic therapy, hospitalizations or colectomy. Their study did not identify clear genetic associations with disease course in UC as well (21). This might in part be reflective of a smaller relative contribution of genetic predisposition toward UC relative to CD (14). More recently, Moustafa et al. investigated the clinical features, host genome and stool microbial metagenome of 85 IBD patients using whole-genome sequencing and shotgun metagenomics, and compared the results with 146 control individuals. GRS was assigned to 159 single-nucleotide variants and human leukocyte antigen (HLA) types to differentiate IBD patients from healthy individuals. As in the present study, they suggest an association between host genetic risk and need for
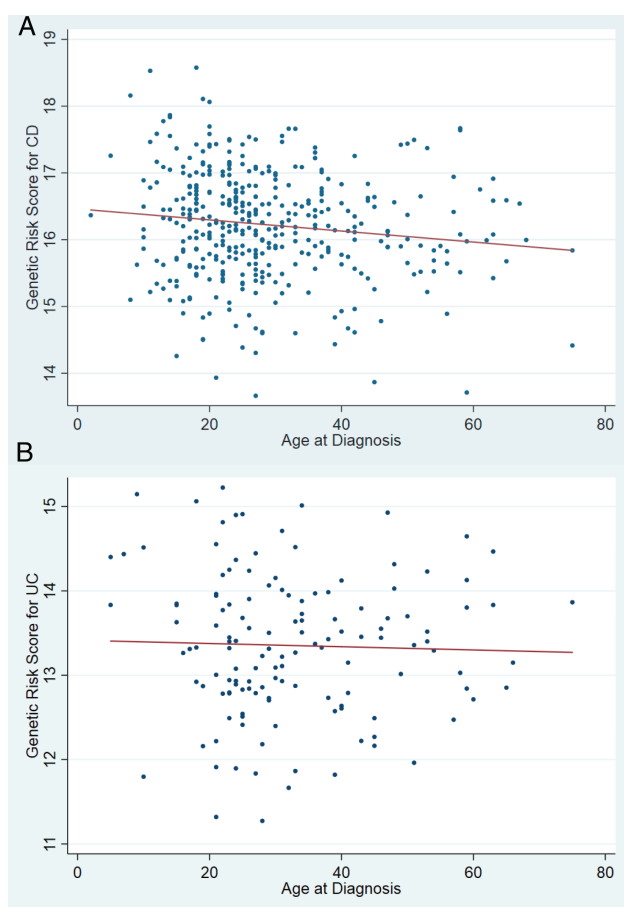
Figure 1. Association between genetic burden and age of diagnosis in Crohn's disease and ulcerative colitis. (a) Crohn's disease. Correlation coefficient −0.135 (95% CI −0.229 to −0.037). (b) Ulcerative colitis. Correlation coefficient −0.031 (95% CI −0.198 to 0.137).

biologics and early escalation of management ([22]). Finally, a multicenter international consortium study involving 29,838 patients (16,902 CD and 12,597 UC) found that GRS were associated with main disease subtypes in particular ileal versus colonic CD, and may be of use in discriminating cases with unclassified colonic inflammatory bowel disease ([23]). However, we were unable to discriminate between CD and UC using GRS (data not shown). Surprisingly, we were unable to find an association between GRS and family history in either UC or CD in contrast to Ananthakrisnan et al. who found such an association with UC. The genetic contribution (variance) in IBD has been estimated at less than 14%; therefore, this study is likely underpowered to demonstrate an association between family history and GRS and underscores the strong role of environment on the development of IBD ([14]).

Strengths and Limitations

Ours is one of a few studies that have addressed the cumulative effect of multiple genetic variants upon disease behaviour in IBD and is the first to do so in a Canadian cohort. However,

it is a single-center study and by current standards for genetic studies, underpowered, particularly when it pertains to subgroup analyses. Because it was conducted within a tertiary care center, it is likely that our cohort manifests more severe disease than might be seen in general community practice, as reflected by the high percentage of patients with stricturing (22%), penetrating (26%) and pan colitis (51%). However, this would not be expected to impact the relationship between genetic burden as defined and disease severity. We have only included 151 SNPs associated with IBD derived from the study by Jostins et al. ([14]). A more accurate genetic burden calculation would include all IBD-associated SNPs (over 200). This may have relevance with regards to generalizability to specific ethnic populations where SNPs not included in our study could have greater impact on disease behaviour. Furthermore, our population was predominantly of white European ancestry therefore perhaps not generalizable to other ethnic populations.

Conclusions

We show that GRS may have a role in an early stratification strategy in the care of IBD patients. As genomic analysis becomes more widely available, it may be possible to use this information to appropriately triage patients into either a 'top-down' versus a 'bottom-up' therapeutic approach, particularly when faced with the escalating costs of biologic therapy for IBD.

Supplementary Data

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

Funding

Conflict of Interest

The authors have no conflicts to declare.

Author Contributions

P.L.B. and H.B.J. conceived the study. J.X.Q.P., H.K. and G.B. collected and analyzed data. R.P., B.E., G.K. and Y.N. provided critical revision of the manuscript for important intellectual content. P.L.B., H.B.J., J.X.Q.P. and H.K. wrote the manuscript.

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