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An analysis of genetic factors related to risk of inflammatory bowel disease and colon cancer☆

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ABSTRACT

Background and aims: Patients with inflammatory bowel disease (IBD) have a higher risk of developing colorectal cancer than the general population. Genome-wide association studies have identified and replicated several loci associated with risk of IBD; however, it is currently unknown whether these loci are also associated with colon cancer risk.
Methods: We selected 15 validated SNPs associated with risk of either Crohn's disease, ulcerative colitis, or both in previous GWAS and tested whether these loci were also associated with colon cancer risk in a two-stage study design.
Results: We found that rs744166 in *STAT3* was associated with colon cancer risk in two studies; however, the direction of the observation was reversed in *TP53* mutant tumors possibly due to a nullification of the effect by mutant p53. The SNP, which lies within intron 1 of the *STAT3* gene, was associated with lower expression of STAT3 mRNA in *TP53* wild-type, but not mutant, tumors.
Conclusions: These data suggest that the *STAT3* locus is associated with both IBD and cancer. Further understanding the function of this variant in relation to *TP53* could possibly explain the role of this gene in autoimmunity and cancer. Furthermore, an analysis of this locus, specifically in a population with IBD, could help to resolve the relationship between this SNP and cancer.

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1. Introduction

Inflammatory bowel disease (IBD), a chronic disorder affecting the intestinal mucosa, presents as one of two main forms: Crohn's disease (CD) or ulcerative colitis (UC). UC affects the inner lining of the large intestine, whereas CD is more widespread and extends deeper in to the intestinal wall. Although the exact etiology of these diseases is unknown, genetics, ethnicity, diet, appendectomy, antibiotic use, socioeconomic factors, and non-steroidal anti-inflammatory drugs are considered as risk factors [1]. Decreases in beneficial bacteria and increases in pathogenic bacteria [2–5] have been linked with IBD. Indeed, a key challenge faced by the immune system is maintenance of a balance between commensal and pathogenic microorganisms. It is thought that IBD develops through the loss of such homeostatic controls and a key population of T cells, called Th17 cells, has recently emerged as a player in the context of IBD. The importance of these cells, which express the IL-23 receptor and regulate autoimmunity, is exemplified by recent genome wide association studies (GWAS) that have shown a connection between genetic variation in *IL-23* and risk of both CD and UC [6–9].

Although there is no unifying risk factor for both CD and UC, genetic susceptibility appears to be common to the etiology of both conditions [6,10–15]. Both diseases display strong relative sibling

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Table 1
Characteristics of the study populations.

Characteristics	NCI-MD study				DALS study	
	Cases	Total controls	Population controls	Hospital controls	Cases	Controls
n	245	446	236	210	1578	1980
Age ± SD	64.7 ± 11.7	65.0 ± 11.0	66.8 ± 9.7	63.1 ± 12.1	64.9 ± 9.8	65.0 ± 10.1
Gender (%)						
Male	185 (75)	212 (48)	115 (48)	97 (46)	884 (56)	1060 (54)
Female	60 (25)	234 (52)	121 (51)	113 (54)	694 (44)	920 (46)
Race (%)						
African American[a] or Hispanic	97 (40)	190 (43)	121 (51)	69 (33)	132 (8)	130 (7)
European American	148 (60)	256 (57)	115 (49)	141 (67)	1446 (92)	1850 (93)
Stage (%)						
Unknown	4 (2)				186 (12)	
I	38 (16)				475 (30)	
II	69 (29)				408 (26)	
III	79 (33)				380 (24)	
IV	51 (21)				129 (8)	
Survival						
Overall (median months, IQR)	56 (19–86)				62 (42, 86)	
Colon cancer deaths	19 (9–40)				25 (16, 41)	
All deaths	19 (9–40)				32 (20, 52)	
Alive (includes lost to follow-up)	74 (52–104)				73 (57, 94)	

[a] NCI-MD study did not include Hispanic participants.

risk [16,17] and through GWAS, multiple risk loci have been identified and indeed replicated [6,10–14,17,18]. Patients with IBD have a higher risk of developing colorectal cancer than the general population [19–22], an association that was first described by Crohn in 1925 [23]. Risk of colorectal cancer is a direct function of the length of time an individual has had IBD and the extent of intestinal involvement [24]. Colorectal cancer accounts for between 10% and 15% of deaths in patients with IBD [25]. In addition, mortality rates for colorectal cancer patients are higher among IBD-associated colorectal cancer cases, compared with colorectal cancer associated with other risk factors [26,27]. Collectively, this suggests a directional link between IBD and colorectal cancer. Current trends in molecular pathological epidemiology converge on the theme of defining risk in terms of tumor subtype or tumor-specific exposures [28–30] and accumulating evidence suggests that IBD-associated colorectal cancer has a pathobiology that is distinct from non-IBD colorectal cancer. For example, the mean age of developing CRC in the setting of IBD is lower than for non-IBD CRC (40–50 vs. 60 years); dysplasia in ulcerative colitis (UC) is preceded by a long history of chronic inflammation whereas dysplasia in non-IBD colon cancer is usually associated with a discrete polyp without inflammation; *RAS* mutations are frequent in sporadic colon cancers but are not as common in IBD-associated colorectal cancer [31]; and loss of heterozygosity and mutations in *TP53* are more common in IBD-associated colon cancer than non-IBD colorectal cancer [32,33].

There is currently no clear way of identifying which patients with IBD will develop colorectal cancer [34], something which has substantially impacted and overburdened the clinical management of IBD. In this study we reasoned that, if some forms of colorectal cancer shared a common pathobiology with IBD, then loci associated with susceptibility to IBD might also be associated with risk of colorectal cancer. To test this hypothesis, we analyzed SNPs previously identified from GWAS of IBD and asked whether these loci are also associated with risk of colorectal cancer.

2. Materials and methods

2.1. Study populations

2.1.1. The NCI-University of Maryland Colorectal Cancer Case–Control Study

This study population consisted of 691 subjects. Incident colorectal cancer cases ($n = 245$) and controls ($n = 446$) were recruited from 1992 to 2003 and from 1998 to 2003, respectively, from the greater Baltimore, Maryland area. The controls were accrued from both a hospital setting ($n = 236$) and a community setting ($n = 210$). The inclusion and exclusion criteria have been previously described [35]. In brief, subjects were self-reported European American or African American born in the United States. Subjects were excluded if they self-reported a history of cancer other than colon, HIV, HBV, HCV, or IV drug use, were institutionalized, or had a mental impairment. Information to determine disease stage, treatment, and survival was obtained from medical records and pathology reports, Social Security Death Index, and the National Death Index. Disease staging was completed according to the tumor-node-metastasis system of the American Joint Committee on Cancer. The survival period was determined from date of hospital admission for surgery to date of last completed search for death entries in the Social Security Death Index (2010). Informed consent was obtained from all participants, and epidemiological questionnaires including personal history, family medical history, past medical history, tobacco history, dietary information, and information on work environment, were administered to all subjects. The study was approved by the institutional review boards of the participating institutions. The characteristics of this study population are described in Table 1.

2.1.2. Diet activity and lifestyle study

Participants from the Diet, Activity and Lifestyle Study were enrolled in a population-based case–control study of incident colon cancer (cases $n = 1555$) and population-based controls ($n = 1956$) who were identified between October 1, 1991, and September 30, 1994. It included people living in the Twin Cities Metropolitan Area, Kaiser Permanente Medical Care Program of Northern California (KPMCP) and a seven-county area of Utah. Cases were between 30 and 79 years old at time of diagnosis with adenocarcinoma, English speaking, mentally competent to complete the interview, with no previous history of colorectal cancer (CRC), and no known familial adenomatous polyposis, ulcerative colitis, or Crohn's disease. Controls were matched to cases by sex and by 5-year age groups. At KPMCP, controls were randomly selected from membership lists; in Utah, controls 65 years and older were randomly selected from the Health Care Financing Administration lists and younger controls were randomly selected from drivers' license lists. Controls were selected from drivers' license and state-identification lists in Minnesota. Details of the