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Genetic variability in *IL23R* and risk of colorectal adenoma and colorectal cancer

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Abstract

Inflammatory processes, including, specifically, the inflammatory conditions Crohn's disease (CD) and ulcerative colitis (UC) predispose to colorectal cancer. Interleukin-23 is part of pro-inflammatory signaling and genetic variation in the interleukin-23 receptor (*IL23R*) has been consistently associated with CD and UC risk. In three case-control studies of colorectal adenoma (n = 485 cases/578 controls), colon cancer (n = 1424 cases/1780 controls) and rectal cancer (n = 583 cases/775 controls), we investigated associations between 18 candidate and tagSNPs in *IL23R* and risk. The three studies were genotyped using an identical Illumina GoldenGate assay, allowing thorough investigation of genetic variability across stages and locations of colorectal neoplasia. We further investigated associations with molecular subtypes (MSI+, CIMP+, *KRAS2mut*, *TP53mut*) of colon and rectal cancers. In this comprehensive study of genetic variability in *IL23R* across the spectrum of colorectal carcinogenesis, as well as within colon and rectal tumor molecular subtypes, we observed associations between SNPs in *IL23R* and risk of rectal cancer:, the 88413 C > A (rs10889675) and 69450 C > A (rs7542081) polymorphisms were associated with decreased rectal cancer risk overall and specifically with rectal tumors bearing a *TP53* mutation. 88413C > A (rs10889675) was also associated with a statistically non-significant decreased risk of adenomas. After adjustment for multiple comparisons, there were no statistically significant associations in any of the three studies. These data provide some evidence that genetic variability in *IL23R* may contribute to rectal cancer risk and add further support to the role of IL23R in gastrointestinal diseases.

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Keywords

IL23R; colorectal cancer; colorectal polyps; genetics

Introduction

Interleukin-23 (IL-23) is a pro-inflammatory cytokine comprised of two subunits, p40, which is shared with IL-12, and p19, which is unique to IL-23. IL-23 is produced by dendritic cells and macrophages (reviewed in [1]) and has been associated with inducing a chronic inflammatory state.[2] IL-23 p19 mRNA was upregulated in 36 human colorectal cancer tissue samples compared to paired adjacent normal tissue.[3] Mice with a genetic deletion of the p19 subunit of IL-23, and therefore deficient for IL-23, were resistant to the formation of chemically induced tumors.[3, 4] IL-23 is also upregulated in inflammatory bowel-disease (reviewed in [5]) as well as several other auto-immune diseases,[2, 6, 7] reflecting its general role in inflammation and immunity.

IL-23 signals through the IL-23 receptor. This receptor is also comprised of two subunits, the IL12Rβ1 subunit, which is shared with several cytokines, and a subunit that is unique to IL-23 (IL23R). The receptor for IL-23 is expressed on T cells, NK cells, dendritic cells, and macrophages.[1] In mice with *il23r* deleted, lung and skin tumors showed reduced tumor volume compared to wildtype mice.[3] In genome-wide association studies, polymorphisms in *IL23R* have been associated with risk of Crohn's disease and ulcerative colitis,[8–12] two chronic inflammatory conditions associated with markedly increased colorectal cancer risk.[13]

No study has yet assessed the role of genetic variability in *IL23R* in colorectal neoplasia. Using a linkage disequilibrium (LD)-based tagSNP approach, we comprehensively assessed genetic variation in *IL23R* in three independent case-control studies of colorectal adenoma or cancer, using identical genotyping methods. In addition, we explored the associations of *IL23R* polymorphisms with specific molecular subtypes of colon and rectal cancer, including *KRAS2*, CIMP, *TP53* and MSI. Thus, we thoroughly evaluated the roles of genetic variability in *IL23R* throughout the stages of colorectal carcinogenesis, as well as in different tumor locations and molecular subtypes.

Materials and Methods

Study Design and data collection

The analyses are based on three US population-based case-control studies of colorectal adenomas,[14] colon cancer,[15] and rectal cancer[16] using subjects with available DNA from collected blood samples. Methods have been described in detail elsewhere;[14, 15] a brief description is provided here.

Adenoma study—Colorectal adenoma cases (n = 485) and polyp-free controls (n = 578) were recruited through a large multiclinic gastroenterological practice in the Twin Cities area of Minnesota from April 1991-April 1994, as previously described.[14] All participants received a colonoscopy. Cases were diagnosed with a first colonoscopy; controls were polyp-free. Eligibility criteria have been described elsewhere,[14] participants were aged 30–74 years, English-speaking residents of the Twin Cities metropolitan area with no known genetic syndrome associated with increased risk of colon neoplasia and no individual history of cancer (except non-melanoma skin cancer), prior colorectal polyps, or inflammatory bowel disease. The participation rate for all colonoscoped patients was 68%.

Colon and rectal cancer studies—Colon and rectal cancer cases and controls were recruited from the northern California Kaiser Permanente Medical Care Program (KPMCP), Utah, and the Twin Cities metropolitan area of Minnesota (colon cancer only), as described previously.[15] Two study populations are included in these analyses. The first study includes cases (n = 1424) and controls (n = 1780) from a population-based case-control study of colon cancer recruited between October 1, 1991 and September 30, 1994.[15] The second study, with identical data collection, includes cases with cancer of the rectosigmoid junction or rectum (n = 583) and controls (n = 775) who were identified between May 1997 and May 2001 in Utah and KPMCP.[17] Eligible cases were between 30 and 79 years old at time of diagnosis, English speaking, mentally competent to complete the interview, had no previous history of colorectal cancer, and no known (as indicated on the pathology report) familial adenomatous polyposis, ulcerative colitis, or Crohn's disease.

Controls were matched to cases by sex and by 5-year age group. 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 controls, younger than 65 years, were randomly selected from driver's license lists. In Minnesota (colon cancer only), controls were selected from driver's license and state-ID lists. For the colon study, 75.6% of contacted cases and 63.7% of contacted controls were interviewed; for the rectal study, 73.2% of contacted cases and 68.8% of contacted controls were interviewed. Response proportions (the number interviewed over all persons identified) were 61.4% for colon cancer cases and 52.5% for controls selected for the colon cancer study and 65.2% of cases and 65.3% of controls for the rectal cancer study.

Tumor markers—Tumor DNA was obtained from paraffin-embedded tissue as described.[18] As described in previous publications,[19–22] tumors were characterized by their genetic profile that included: sequence data for exons 5 through 8, the mutation hotspots of the *TP53* gene; sequence data for *KRAS2* codons 12 and 13; microsatellite instability (MSI) status based on *BAT26*, *TGFBR2*, and a panel of 10 tetranucleotide repeats; methylation specific PCR of sodium-bisulfite-modified DNA for five CpG Island markers, *CDKN2A*, *MLH1* and methylated in tumors (MINT) 1, 2 and 31. Tumors with two or more methylated CpG islands were scored as CIMP+. At the time we undertook the methylation-status analysis, there was no consensus CpG-island panel or method of detection to determine CIMP. However, we have used our panel to demonstrate relationships between CIMP and numerous clinicopathologic variables,[19, 23] indeed, this work has supported the legitimacy of the CIMP concept in colorectal cancer.[24, 25]

Tag and candidate SNP selection

An identical tagSNP selection and genotyping procedure was used in all three studies. *IL23R* and 2 kb beyond the 5′ and 3′ ends of *IL23R* were resequenced in 23 individuals of European descent by the Innate Immunity Program for Genomic Applications[1]. TagSNPs in *IL23R* were selected from these resequenced individuals using the LD Select algorithm developed by Carlson and colleagues,[26] with a cutoff minor allele frequency (MAF) of 4% (i.e., any variant that occurred twice) and an r^2 value of 0.90. This resulted in the selection of 23 tagSNPs, which were estimated by the Genome Variation Server[2] to cover ≥ 85% of the common (≥ 4% MAF) variation at these loci (see Supplemental Table S1 for a list of the polymorphisms selected). A total of 21 SNPs was successfully converted to the Illumina™ GoldenGate genotyping platform as described below. Two of the selected SNPs are non-synonymous polymorphisms (rs1884444 – Gln3His and rs11209026 – Arg381Gln). The

[1]=http://www.pharmgat.org/IIPGA2/index_html
[2]=http://gvs.gs.washington.edu/GVS/index.jsp

latter SNP, as well as rs11465804, an intronic SNP, have been associated with Crohn's disease and ulcerative colitis in recent GWAS,[8–12] therefore, these three SNPs were considered candidate SNPs and were not included in adjustments for multiple comparisons.

Genotyping and QC

All SNPs were genotyped using the Illumina™ GoldenGate bead-based genotyping technology at the Translational Genomics Institute (TGen, Phoenix, Arizona). Intraplate and interplate replicates (5%) were included on all plates and in all batches. Blinded duplicates were also included on all plates as another QC measure. Genotype data from 30 CEPH trios (Coriell Cell Repository, Camden, NJ) that were genotyped by the HapMap project were used to confirm reliability and reproducibility of the genotyping. Genotypes were excluded from analyses by TGen if any of the following were true: GenTrain Score < 0.4, 10%GC Score < 0.25, AB T Dev > 0.1239, Call Frequency < 0.85, Replicate Errors > 2, P-P-C Errors > 2. Additionally, further exclusions were made for SNPs that had < 85% concordance with blinded or non-blinded duplicates (see Supplemental Table S1) and for Hardy-Weinberg Equilibrium p-values < 0.0001. Two SNPs failed in all three study populations, due to being monomorphic or not in Hardy-Weinberg equilibrium; one additional SNP failed in the colon and rectal cancer studies, leaving 18 SNPs included in the analyses presented here.

Questionnaire data

Adenoma study—Information on lifestyle factors and diet, anthropometry, demographics, and medical information, including family history of cancer and polyps, were obtained by questionnaire as described previously.[14]

Colon and rectal cancer studies—Data collection has been described previously.[15, 17] The referent period was the calendar year 2 years prior to date of diagnosis or interview. Questionnaire data included information on physical activity, diet, medication use, family history of cancer, smoking history, and recalled height and weight 2 years prior to interview.

Statistical Analysis

Single SNP Analyses—Unconditional logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the associations between genotypes in *IL23R* and risk of colorectal adenoma or cancer. Most genotypes were modeled using indicator variables for the heterozygous and the homozygous variant genotypes (unrestricted or co-dominant model). If fewer than five cases or controls had the homozygous variant genotype, we grouped the homozygous variant genotypes with the heterozygous genotypes for analysis (dominant model). All models were adjusted for age, and sex; the analyses of colon and rectal cancers were additionally adjusted for study site. Due to racial differences in genotype frequencies, our analyses are restricted to Caucasian individuals. To obtain tests for trend, the genotypes were treated as continuous variables. As a secondary analysis, p-values were adjusted for multiple testing, taking into account the correlation between all 18 tagSNPs and multiple models (i.e. both an unrestricted and a trend test), using the method by Conneely and Boehnke.[27] All analyses, with the exception of the haplotype analyses, were carried out using SAS v.9.

Haplotype and Principal Components analyses—Haplotype analysis was conducted using a modified version of HaploStats which allows adjustment for potential confounders (Version 1.3.8) in R (Version 2.7.1). All haplotypes predicted to occur with more than 5% frequency among controls were analyzed separately. Haplotypes with lower frequency were grouped together for analyses. The most common haplotype among the controls was used as

the referent group. All haplotype analyses were adjusted as in the single SNP models. We used the score test to evaluate whether a haplotype was associated with disease risk. For PCA,[28] we determined the number of principal components that explained at least 80% of the variance in a gene and performed logistic regression using those components, adjusting for age, sex, and study site (colon and rectal cancers only). Gene-level significance was determined using a likelihood-ratio test, comparing a model that contained the principal components and one that did not.

Tumor marker analyses—Tumors were defined by specific alterations detected; any *TP53* mutation, any *KRAS2* mutation, or CIMP+ defined as at least 2 of 5 markers methylated. As the proportion of MSI+ tumors in the rectal cases was < 3%,[29] there was insufficient power to examine rectal MSI. Population-based controls were used to assess associations for the population overall, while examining multiple outcomes defined by tumor status. To compare specific types of mutations to controls while adjusting for the other tumor mutations simultaneously in cases, a generalized estimating equation (GEE) with a multinomial outcome was used as case subjects could contribute to more than one outcome observation depending upon the number of mutations or alterations (*TP53*, *KRAS2*, CIMP+, and additionally MSI+ for colon cases) detected in an individual's tumor DNA expressed.[30] The GEE accounts for correlation introduced by including subjects multiple times and was implemented in SAS using the GENMOD procedure as described by Kuss and McLerran.[31] All GEE models were adjusted for sex, age at diagnosis or selection, and study center. A co-dominant model with three genotype categories was analyzed with molecular subtypes when minor allele frequencies provided sufficient power to examine the minor-allele homozygous genotype; otherwise, a dominant model was assumed. A recessive model was analyzed in addition to the co-dominant, when indicated by co-dominant ORs. P for linear trend was assessed using three ordered genotype categories and comparing the likelihood ratio of a model with the genotype variable (as continuous) to the likelihood ratio of a model without the variable using a chi-squared test with 1 degree of freedom.

Results

Characteristics of the study populations are shown for the genotyped subset in Table 1. Briefly, the study populations were mostly Caucasian (97.2% for the adenoma study; 92.3% for the colon cancer study; and 83.5% for the rectal cancer study); adenoma cases tended to be older and were more likely to be male than controls; the cancer case-control studies were frequency-matched on age and sex. Below we describe results for statistically significant tagSNPs or SNPs that were associated with inflammatory bowel disease in recent GWAS. Associations with all SNPs are displayed in supplementary tables.

Single SNP associations

A decreased risk of rectal cancer was observed for the variant genotypes of 88413 C > A (rs10889675) and 69450 C > A (rs7542081; Table 2). For 88413 C > A, the heterozygous CA genotype was associated with a 24% reduction in risk (OR: 0.76; 95% CI: 0.58-1.00) and the homozygous variant AA genotype with a statistically non-significant 32% reduction in risk (OR: 0.68; 95% CI: 0.27–1.73; p-trend = 0.04). For 69450 C > A, only the homozygous variant AA genotype was associated with decreased risk of rectal cancer (OR: 0.65; 95% CI: 0.45–0.92). These SNPs are in moderate LD with each other ($r^2 = 0.25$). There were no associations with the SNPs that have been previously associated as hits in genome-wide association studies of UC and CD, nor were there any associations with colorectal adenoma or colon cancer risk. Neither of the associations remained statistically significant after adjustment for multiple comparisons.

Haplotype and principal components analyses

There were no statistically significant associations between *IL23R* and cancer or adenoma risk in haplotype analyses (Supplemental Table S3), although there was a suggestion that genetic variation in *IL23R* was associated with rectal cancer risk in the principal components analysis (p = 0.08; data not shown).

Associations with tumor subtypes

We evaluated whether polymorphisms in *IL23R* were associated with specific colon and rectal cancer subtypes (MSI+, CIMP+, *TP53* mutation, or *KRAS2* mutation). In the colon cancers, we observed several associations with molecular subtypes (Table 3 and Supplemental Table S4). Those with at the AA genotype of 38962 G > A (rs7539625) had decreased risk of MSI+ colon cancer compared to those with the GG or GA genotypes (OR: 0.36; 95% CI: 0.16–0.81). Similar associations were observed for the variant genotypes of 88764 C > A (rs10889676) and 51795 A > C (rs11465802). These SNPs were in pairwise LD (r2 ≥ 0.70) and, thus, these results suggest one association. The variant genotypes of candidate SNP Gln3His were associated with decreased risk of colon cancer with a *TP53* mutation (OR: 0.77; 95% CI: 0.60–0.97) and there was a suggestion of decreased risk with the variant genotypes of 39309 G > A (rs4655691).

In rectal cancer, in which MSI+ tumors are too rare to analyze, associations were more broadly observed between *IL23R* polymorphisms and molecular subtypes defined by *TP53* mutations, *KRAS2* mutations, and CIMP+ tumor alterations (Table 4 and Supplemental Table S5). The statistically significantly decreased risks of rectal cancers that were observed for rectal tumors overall (i.e. with the variants of 88413 C > A and 69450 C > A) were present only among those with mutated *TP53*: For 88413 C > A (rs10889675), the variant CA and AA genotypes were associated with a 34% reduction in risk (OR: 0.66; 95% CI: 0.46–0.94). The association was similar for 69450 C > A (OR: 0.60; 95% CI: 0.37–0.98). Increased risk of rectal tumors bearing a *KRAS2* mutation was observed for the variant genotypes of the non-synonymous polymorphism Gln3His (p-trend = 0.03); in contrast, a decreased risk of *KRAS2*-mutated rectal tumors was observed for 38962 G > A (rs7539625).

Discussion

In this comprehensive study of genetic variability in *IL23R* across the spectrum of colorectal carcinogenesis as well as within colon and rectal tumor molecular subtypes, we observed associations between SNPs in *IL23R* and risk of rectal cancer: the 88413 C > A and 69450 C > A polymorphisms were associated with decreased rectal cancer risk overall and, specifically, with rectal tumors bearing a *TP53* mutation. In tumor subtype analyses, we observed a decreased risk of colon tumors with a *TP53* mutation with the nonsynonymous SNP Gln3His, but an increased risk of rectal tumors with a *KRAS2* mutation, perhaps indicating that this SNP may have functional effects that influence etiology of colon and rectal cancer differentially. However, evaluation of this polymorphism using SIFT[32] suggests that this amino acid substitution is likely to be tolerated. Further, although evidence suggests that colon and rectal cancer may arise through different mechanisms,[29, 33] the inconsistency between colon and rectal tumors suggests that these findings may be due to chance. We also observed several other associations between genetic variability in *IL23R* and colon and rectal cancer molecular subtypes. Although tumor heterogeneity is important to study, because varying etiologic risk factors are relevant for subclasses of colorectal cancers,[22, 23, 34–36] these associations should be confirmed in future studies.

The 69450 C > A polymorphism, which was associated with a 35% reduced rectal cancer risk is in minor linkage disequilibrium with Leu310Pro (rs7530511; $r^2 = 0.24$), a non-synonymous SNP in exon 4. We did not genotype this SNP because it interfered with the genotyping assays for other SNPs in the gene. However, we did genotype 71923G > A (rs10886971), which was in high LD with Leu310Pro ($r^2 > 0.90$) and observed no association, indicating that the association observed with 69450C > A was not through its LD with Leu310Pro.

To our knowledge, this is the first investigation of genetic variability in *IL23R* and colorectal neoplasia risk. However, several studies have shown associations between *IL23R* SNPs and risk of Crohn's disease and ulcerative colitis, two inflammatory conditions of the colon that greatly increase colorectal cancer risk.[37, 38] We have genotyped two of these candidate SNPs, rs11209026 and rs11465804 ($r^2 > 0.81$), but neither was associated with risk of colorectal neoplasia in our study. It is worth noting that ulcerative colitis and Crohn's disease patients were excluded from our study populations. However, it has recently been shown that IL-23 suppresses innate immunity in several mouse carcinogenesis models,[4] indicating that IL-23 may play a role in carcinogenesis above and beyond its role in chronic inflammation.

In a recent study of 1043 cases of gastric cancer and 1089 age- and sex-matched controls, the variant genotypes of Gln3His (rs1884444) were associated with decreased risk (OR: 0.74; 95% CI: 0.62–0.89).[39] We observed no overall association with this polymorphism, but saw a decreased risk of *TP53*-mutated colon cancer, similar to the reported results for gastric cancer. However, risk for *KRAS2* mutated rectal cancer was increased, indicating some inconsistency, but probably a need for further study of this non-synonymous polymorphism. A small study of 96 gastro-esophageal reflux patients vs. controls showed an increased risk associated with the Arg/His or His/His genotypes of Arg381His (rs11209026).[40] We observed no association with this polymorphism.

This study was limited to Caucasians, which limits its generalizability to non-Caucasian populations. However, as the majority of our study participants (> 90%) were Caucasian, we had limited power to detect associations with other races. Additionally, due to the number of statistical tests that were performed in this study, the likelihood of false positives is high. However, because we conducted a parallel investigation of identical candidate and tagSNPs in three independent study populations, we decided to present uncorrected p-values and evaluate whether the associations with any of these SNPs were consistent across the three study populations. Further, this is the first study that has specifically targeted and comprehensively examined *IL23R* genetic variability in relation to colorectal adenoma and cancer risk; thus, we report any observed associations to inform future studies.

This study has several strengths. By using both tagSNPs and candidate polymorphisms, we achieved comprehensive coverage of genetic variability in *IL23R*. Further, we had access to resequencing data, ensuring that we captured all common variants that are likely to exist among Caucasians. We have comprehensively assessed genetic variation in *IL23R* in three independent case-control studies of colorectal adenoma or cancer, using identical genotyping methods, thus allowing us to replicate any promising findings. We also have access to molecular subtyping in the colon and rectal cancer studies, which permitted the exploration of subtype-specific associations.

In summary, we assessed the role of genetic variability in *IL23R* across the carcinogenic process and among colorectal tumors defined through molecular subtyping. We provide some evidence that *IL23R* may be important in rectal cancer carcinogenesis, specifically for rectal cancer with a *TP53* or *KRAS2* mutation. Given the role of *IL23R* in inflammatory

bowel disease, further study of the impact of genetic variability in *IL23R* should be conducted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the three study populations[a]

	Colorectal adenoma study			Colon cancer study			Rectal cancer study		
	Cases (N = 485)	Controls (N = 578)	p	Cases (N = 1424)	Controls (N = 1780)	p	Cases (N = 583)	Controls (N = 775)	p
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age	58 (9.6)	52.9 (11.0)	< 0.01	65.2 (9.7)	65.1 (10.3)	NA[c]	62.3 (10.8)	62.6 (10.5)	NA[c]
Caloric Intake (kcal)	2101.6 (760.0)	2019.8 (733.1)	0.07	2427.9 (1116.6)	2306.5 (1017.4)	< 0.01	2702.5 (1294.7)	2592.7 (1203.7)	0.11
Dietary Fiber Intake (gm)	21.8 (9.4)	21.8 (9.6)	0.95	24.8 (11.8)	24.9 (11.3)	0.84	26.0 (13.0)	26.7 (13.0)	0.35
Location	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Proximal	104 (21.6)	NA	NA	688 (49.6)	NA	NA	NA	NA	NA
Distal	300 (62.4)	NA		700 (50.4)	NA		NA	NA	
Rectal	77 (16.0)	NA		NA	NA		583	775	
Sex									
Male	304 (62.7)	227 (39.3)	< 0.01	797 (56.0)	946 (53.2)	NA[c]	346 (59.4)	428 (55.2)	NA[c]
Female	181 (37.3)	351 (60.7)		627 (44.0)	834 (46.9)		237 (40.7)	347 (44.8)	
Study Site									
Kaiser Northern California	NA	NA	NA	617 (43.3)	647 (36.4)	< 0.01	349 (59.9)	449 (57.9)	0.48
Minnesota	485 (100)	578 (100)		565 (39.7)	791 (44.4)		NA	NA	
Utah	NA	NA		242 (17.0)	342 (19.2)		234 (40.1)	326 (40.1)	
Regular Use of NSAIDs (Ever vs. Never)									
Yes	180 (37.1)	257 (44.5)	0.02	562 (39.5)	865 (48.6)	< 0.01	263 (45.1)	417 (53.8)	< 0.01
No	305 (62.9)	321 (55.6)		862 (60.5)	915 (51.4)		320 (54.9)	358 (46.2)	
Smoking in pack-years (amt per day)[b]									
0	163 (34.4)	276 (49.0)	< 0.01	840 (47.3)	581 (41.0)	< 0.01	271 (46.5)	401 (51.7)	0.05
1–25 (≤ 20)	152 (32.1)	171 (30.4)		336 (18.9)	250 (17.6)		106 (18.2)	133 (17.2)	
> 25 (21+)	159 (33.5)	116 (20.6)		599 (33.8)	586 (41.4)		206 (35.3)	241 (31.1)	
Post-menopausal Hormone Use (Women only)									
Yes	71 (40.6)	181 (53.2)	0.01	130 (23.9)	221 (31.0)	0.01	110 (56.7)	132 (45.2)	0.01
No	104 (59.4)	159 (46.8)		414 (76.1)	493 (69.1)		84 (43.3)	160 (54.8)	

[a] Numbers may not total to 100% due to rounding and missing values

[b] For adenoma and rectal cancers, pack-years are reported. For colon cancer, number of cigarettes per day is reported.

[c] NA – this was a matching factor.

Table 2

Association between selected candidate and tagSNPs in *IL23R* and risk of colorectal neoplasia[a]

			Adenoma[b]					Colon Cancer[c]					Rectal cancer[c]				
dbSNP ID	**Common Name**	**genotype**	**Cases/Controls**	**OR**	**95%CI**	**p**	**p-trend**	**Cases/Controls**	**OR**	**95%CI**	**p**	**p-trend**	**Cases/Controls**	**OR**	**95%CI**	**p**	**p-trend**
rs10889675	88413 C > A	CC	369/432	**1.00**	ref.			1110/1390	**1.00**	ref.			467/583	**1.00**	ref.		
		CA	108/136	**0.98**	(0.73–1.34)			290/361	**1.01**	(0.85–1.20)			109/179	**0.76**	(0.58–1.00)		
		AA	5/12	**0.46**	(0.15–1.42)	0.38	0.47	19/21	**1.14**	(0.61–2.14)	0.92	0.79	7/13	**0.68**	(0.27–1.73)	0.11	**0.04**
rs10889676	88764 C > A	CC	235/281	**1.00**	ref.			681/885	**1.00**	ref.			280/370	**1.00**	ref.		
		CA	196/268	**0.87**	(0.67–1.14)			614/725	**1.09**	(0.94–1.27)			242/325	**0.99**	(0.79–1.25)		
		AA	50/33	**1.61**	(0.98–2.66)	**0.05**	0.50	127/166	**1.00**	(0.77–1.28)	0.46	0.53	59/76	**1.03**	(0.71–1.50)	0.98	0.94
rs11209026[d]	Arg381Gln	Arg/Arg	418/516	**1.00**	ref.			1231/1544	**1.00**	ref.			506/682	**1.00**	ref.		
		Arg/Gln or Gln/Gln	65/66	**1.07**	(0.73–1.58)	0.72	NA	186/226	**1.03**	(0.84–1.27)	0.76	NA	77/93	**1.12**	(0.81–1.54)	0.50	NA
rs11465804[d]	68723 T > G	TT	426/518	**1.00**	ref.			1248/1554	**1.00**	ref.			507/686	**1.00**	ref.		
		TG or GG	57/64	**1.01**	(0.68–1.51)	0.96	NA	175/218	**1.00**	(0.80–1.23)	0.96	NA	75/87	**1.16**	(0.84–1.62)	0.37	NA
rs1884444[d]	Gln3His	Gln/Gln	140/169	**1.00**	ref.			407/523	**1.00**	ref.			144/229	**1.00**	ref.		
		Gln/His	236/274	**1.05**	(0.78–1.42)			712/829	**1.09**	(0.93–1.29)			307/370	**1.31**	(1.02–1.70)		
		His/His	107/138	**0.97**	(0.68–1.39)	0.88	0.91	302/416	**0.92**	(0.76–1.12)	0.16	0.52	132/176	**1.19**	(0.87–1.61)	0.11	0.23
rs7542081	69450 C > A	CC	198/219	**1.00**	ref.			594/700	**1.00**	ref.			252/314	**1.00**	ref.		
		CA	221/286	**0.86**	(0.65–1.13)			637/834	**0.90**	(0.77–1.04)			271/348	**0.97**	(0.77–1.22)		
		AA	63/76	**0.92**	(0.61–1.38)	0.55	0.44	183/235	**0.92**	(0.74–1.15)	0.35	0.25	58/112	**0.65**	(0.45–0.92)	**0.04**	**0.05**

[a] If a cell had fewer than 5 subjects, dominant models are shown.

[b] Age and sex adjusted

[c] Study site, age, and sex adjusted

[d] Candidate SNP

Table 3

Associations between tagSNPs in IL23R and molecular subtypes of colon cancer[a]

			Controls	TP53 mutation				KRAS2 mutation				CIMP+				MSI+			
dbSNP ID	**Common Name**	**genotype**	**N**	**N**	**OR**	**95% CI**	**P*b***	**N**	**OR**	**95% CI**	**P*b***	**N**	**OR**	**95% CI**	**P*b***	**N**	**OR**	**95% CI**	**P*b***
rs10889675	88413 C > A	CC	1387	357	**1.00**	ref.		247	**1.00**	ref.		182	**1.00**	ref.		128	**1.00**	ref.	
		CA	360	98	**1.04**	(0.83–1.30)		58	**0.87**	(0.66–1.15)		57	**1.19**	(0.90–1.58)		39	**1.15**	(0.81–1.63)	
		AA	21	7	**1.17**	(0.50–2.75)	0.50	3	**0.68**	(0.22–2.06)	0.51	7	**2.33**	(1.15–4.74)	**0.05**	2	**0.87**	(0.23–3.32)	0.48
rs10889676	88764 C > A	CC or CA	1606	416	**1.00**	ref.		279	**1.00**	ref.		228	**1.00**	ref.		162	**1.00**	ref.	
		AA	166	46	**1.14**	(0.84–1.55)	0.69	29	**1.04**	(0.72–1.52)	0.99	19	**0.79**	(0.51–1.23)	0.29	8	**0.48**	(0.24–0.97)	**0.03**
rs1884444	Gln3His	Gln/Gln	1350	377	**1.00**	ref.		249	**1.00**	ref.		189	**1.00**	ref.		136	**1.00**	ref.	
		Gln/His or His/His	414	85	**0.77**	(0.60–0.97)	**0.02**	59	**0.82**	(0.62–1.09)	0.08	58	**1.08**	(0.81–1.44)	0.99	33	**0.85**	(0.58–1.23)	0.23
rs4655691	39309 G > A	GG	925	270	**1.00**	ref.		172	**1.00**	ref.		132	**1.00**	ref.		87	**1.00**	ref.	
		GA	705	157	**0.78**	(0.64–0.95)		111	**0.88**	(0.69–1.11)		98	**1.02**	(0.80–1.31)		64	**1.03**	(0.75–1.41)	
		AA	140	35	**0.85**	(0.60–1.22)	**0.05**	25	**0.98**	(0.65–1.50)	0.32	17	**0.87**	(0.53–1.41)	0.62	19	**1.50**	(0.92–2.46)	0.39
rs7539625	38962 G > A	GG or GA	1619	413	**1.00**	ref.		277	**1.00**	ref.		229	**1.00**	ref.		164	**1.00**	ref.	
		AA	153	49	**1.32**	(0.98–1.77)	0.17	31	**1.22**	(0.85–1.75)	0.39	18	**0.79**	(0.50–1.25)	0.40	6	**0.36**	(0.16–0.82)	**0.01**

[a]Adjusted for age, sex, and study site

[b]P-value for trend; if dominant or recessive model, p-value for association is shown.

Table 4

Associations between tagSNPs in IL23R and molecular subtypes of rectal cancer[a]

			Controls	TP53 mutation				KRAS2 mutation				CIMP+			
dbSNP ID	**Common Name**	**genotype**	**N**	**N**	**OR**	**95% CI**	**p[b]**	**N**	**OR**	**95% CI**	**p[b]**	**N**	**OR**	**95% CI**	**p[b]**
rs10889675	88413 C > A	CC	583	172	**1.00**	ref.		103	**1.00**	ref.		34	**1.00**	ref.	
		CA or AA	192	37	**0.66**	(0.46–0.94)	**0.03**	31	**0.98**	(0.66–1.46)	0.66	13	**1.27**	(0.68–2.39)	0.63
rs1884444	Gln3His	Gln/Gln	229	48	**1.00**	ref.		29	**1.00**	ref.		9	**1.00**	ref.	
		Gln/His	370	125	**1.51**	(1.07–2.13)		65	**1.24**	(0.80–1.93)		24	**1.46**	(0.68–3.12)	
		His/His	176	36	**0.86**	(0.55–1.34)	0.89	40	**1.75**	(1.08–2.83)	**0.03**	14	**1.92**	(0.83–4.42)	0.10
rs7539625	38962 G > A	GG	383	98	**1.00**	ref.		81	**1.00**	ref.		29	**1.00**	ref.	
		GA or AA	390	111	**1.22**	(0.92–1.61)	0.47	53	**0.65**	(0.46–0.92)	**0.02**	18	**0.63**	(0.35–1.12)	0.10
rs7542081	69450 C > A	CC or CA	662	189	**1.00**	ref.		115	**1.00**			42	**1.00**	ref.	
		AA	112	19	**0.60**	(0.37–0.98)	**0.04**	19	**1.08**	(0.67–1.75)	0.92	5	**0.78**	(0.32–1.92)	0.47

[a]Adjusted for age, sex, center, race

[b]P-value for trend; if dominant or recessive model, p-value for association is shown.