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Common variants in the obesity-associated genes FTO and MC4R are not associated with risk of colorectal cancer

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Conflict of Interest

None

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Abstract

Background—Obesity is a convincing risk factor for colorectal cancer. Genetic variants in or near *FTO* and *MC4R* are consistently associated with body mass index and other body size measures, but whether they are also associated with colorectal cancer risk is unclear.

Methods—In the discovery stage, we tested associations of 677 *FTO* and 323 *MC4R* single nucleotide polymorphisms (SNPs) 100kb upstream and 300kb downstream from each respective locus with risk of colorectal cancer in data from the Colon Cancer Family Registry (CCFR: 1,960 cases; 1,777 controls). Next, all SNPs that were nominally statistically signif icant ($p<0.05$) in the discovery stage were included in replication analyses in data from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO: 9,716 cases; 9,844 controls).

Results—In the discovery stage, 43 *FTO* variants and 18 *MC4R* variants were associated with colorectal cancer risk ($p<0.05$). No SNPs remained statistically significant in the replication analysis after accounting for multiple comparisons.

Conclusion—We found no evidence that individual variants in or near the obesity-related genes *FTO* and *MC4R* are associated with risk of colorectal cancer.

Keywords

obesity; genetic variants; colorectal cancer; case-control study

Introduction

Obesity is a convincing risk factor for colorectal cancer [1]. Determinants of body mass index (BMI: kg/m^2) are multifactorial, but invariably relate to energy balance; individual differences in the capacity to gain or lose body weight have a strong genetic basis. Genome-wide association studies (GWAS) have identified two loci, for which the genes fat mass and obesity-associated (*FTO*) and melanocortin-4 receptor (*MC4R*) were hypothesized, among other variants, that are consistently associated with body mass index (BMI) and other body size measures [2]. To date, GWAS have not identified any FTO or MC4R variants associated with colorectal cancer risk. Only three case-control studies have assessed the associations of variants in or near *FTO* and *MC4R* with colorectal cancer risk, and all reported null results [3–5]. However, these studies only included a limited number of SNPs in/near these two genes. Also, since the association of a specific SNP with the risk of cancer, if any, is typically relatively weak, insufficient statistical power is a major potential source of false negative findings in studies with smaller sample sizes.

Herein, we aimed to conduct a candidate gene study of *FTO* and *MC4R*, and to be exhaustive in that endeavor for those two genes. Specifically, we evaluated the associations of 1,000 single nucleotide polymorphisms (SNPs) in or near *FTO* and *MC4R* with colorectal cancer risk and whether the associations were mediated by BMI, using a two-stage design in data from the Colon Cancer Family Registry (CCFR) and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO).

Materials and Methods

The initial discovery stage included two case-control series of non-Hispanic white participants from the CCFR. The first case-control series included 1,173 microsatellite-stable/microsatellite instability-low colorectal cancer cases and 984 population-based controls; the second case-control series included 787 cases and 793 of their unaffected siblings as controls. The replication stage comprised an independent series of 9,716 cases and 9,844 controls from GECCO. Details on data collection, selection criteria, and recruitment procedures in the CCFR and GECCO have been described previously [1, 6, 7]. Characteristics of CCFR and studies included in GECCO are demonstrated in Supplementary Table 1. All participants provided written informed consent, and studies were approved by their Institutional Review Boards.

Genotyping, quality control, and imputation procedures for the CCFR and GECCO were previously described [8], and further information can be found in the Supplementary Material. *FTO* and *MC4R* SNPs with >5% missing information or minor allele frequencies (MAF) <5% were excluded from analyses. We examined 677 *FTO* SNPs and 323 *MC4R* SNPs (including SNPs that were 100kb upstream and 300kb downstream from each respective locus) in the discovery stage. The odds ratio (OR) and 95% confidence intervals

(CI) for each SNP (in log-additive models) with colorectal cancer was estimated using unconditional or conditional logistic regression, as appropriate depending upon study design, while adjusting for age, sex, and principal components of genetic ancestry (PCAs) to account for potential population substructure (all analyses were restricted to those of European descent). We analyzed models with and without adjustment for BMI to assess if the risk imposed by a given SNP operates through its effects on body size. Results from both CCFR case-control series were combined using random-effects meta-analysis. SNPs that were nominally associated with colorectal cancer risk ($p < 0.05$) in the combined discovery stage (with or without adjustment for BMI) were assessed in GECCO using unconditional logistic regression and adjusted for age, sex, and the top three PCAs. Bonferroni correction was applied to the replication results (Bonferroni-corrected alpha 0.001 for *FTO* SNPs and 0.003 for *MC4R* SNPs, calculated based on the number of SNPs that entered the replication stage for each gene). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Power was estimated using PS Power and Sample Size software [9].

Results

Meta-analyses of the discovery stage data identified 43 *FTO* and 18 *MC4R* SNPs that were nominally associated with colorectal cancer risk ($p < 0.05$) after adjustment for age, sex, and PCAs, with or without further adjustment for BMI (Table 1). In the replication stage, 29 of the *FTO* SNPs and 1 of the *MC4R* SNPs were statistically significantly associated with BMI (Supplementary Table 2). None of the initially-identified SNPs from the discovery stage were associated with colorectal cancer risk with adjustment for age, sex, and PCAs; after additionally adjusting for BMI, two *FTO* SNPs (rs8046502 and rs4784329) had p-values < 0.05; the ORs were 1.04 (95% CI: 1.00 - 1.09; $p = 0.048$) and 0.96 (95% CI: 0.92 - 1.00; $p = 0.048$) for these two SNPs, respectively (Table 1). Associations of these two SNPs with colorectal cancer risk were not statistically significant after applying a Bonferroni-corrected α of 0.001. The results remained unchanged when we additionally adjusted the models for physical activity level and total energy intake.

Discussion

In this study, we found that individual variants in the obesity-related genes *FTO* and *MC4R* were not associated with colorectal cancer risk. Although obesity is an established risk factor for colorectal cancer, our results do not support the hypothesis that obesity and colorectal carcinogenesis share a common genetic predisposition through individual SNPs in or near *FTO* or *MC4R*.

A number of studies have reported associations between *FTO* or *MC4R* variants and risk of various types of cancer [10, 11]; some of the associations were independent of obesity, but the mechanisms were unclear [11]. Our results are consistent with the few previous studies that reported null associations of *FTO* and *MC4R* with risk of colorectal cancer [3–5]. Tenesa *et al.* conducted a two-phase case-control study among 1,765 colorectal cancer cases and 2,077 controls, and observed no association between four *MC4R* SNPs with the risk of colorectal cancer, although these SNPs were associated with intermediate phenotype such as BMI and waist circumference [4]. Similarly, Tarabra *et al.* reported no association between

one *FTO* SNP and colorectal cancer or adenoma risk among 726 patients and 311 controls [3]. Additionally, among 2,033 cases and 9,640 controls in the Multiethnic Cohort and PAGE studies, Lim *et al.* examined 24 SNPs in 15 obesity-related genes, including eight in *FTO* and one near *MC4R*; although the only *MC4R* SNP examined (rs17782313) was associated with colorectal cancer risk (OR 1.12, 95% CI 1.02–1.22; p = 0.02), it was no longer statistically significant after adjustment for multiple comparisons [5]. However, the Lim *et al.* study, being the largest of the three previous studies, was only powered to detect ORs of 1.5 or higher. Our study is the most comprehensive, large-scale evaluation of *FTO* and *MC4R* SNPs in relation to colorectal cancer risk so far. Our null results suggest that although these two genes are associated with body size, they are indeed unlikely to influence the risk of colorectal cancer substantially.

The strengths of our study include its large sample size, centralized data harmonization, and comprehensive evaluation of *FTO* and *MC4R* SNPs. Our study was sufficiently powered to detect a modest association of these SNPs with colorectal cancer risk: for SNPs with a MAF of 0.3, we had >80% power to detect an OR as low as 1.22 in the discovery stage and 1.09 in the replication stage. Limitations of this study include the derivation of BMI from self-reported height and weight, and use of Bonferroni correction for multiple comparisons which may be overly conservative, but these results would still be null even with less conservative multiple testing adjustment. Finally, compared to the more conventional candidate gene approach, Mendelian randomization studies, which use information from multiple genetic variants associated with body size to create a weighted genetic risk score for obesity, may be superior to examine genetically influenced BMI and colorectal cancer risk [12], as we have shown in GECCO and the CCFR more recently.

In summary, we did not observe associations between individual variants in the obesity-related genes *FTO* and *MC4R* with colorectal cancer risk. This study does not support the hypothesis that obesity and colorectal carcinogenesis share a common genetic predisposition through individual SNPs in or near *FTO* or *MC4R*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

BMI	body mass index
CCFR	Colon Cancer Family Registry
CI	confidence interval
FTO	fat-mass and obesity-associated
GECCO	Genetics and Epidemiology of Colorectal Cancer Consortium
GWAS	genome-wide association study
MAF	minor allele frequency

MC4R	melanocortin-4 receptor
OR	odds ratio
PCA	principal component of genetic ancestry
SNP	single nucleotide polymorphism

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Highlights

- We found no evidence that individual variants in or near the obesity-related genes *FTO* and *MC4R* are associated with risk of colorectal cancer.
- This paper is the largest and most comprehensive evaluation of obesity-related genes *FTO* and *MC4R* in relation to colorectal cancer risk.

Table 1

Associations between *FTO* and *MC4R* SNPs and colorectal cancer risk in CCFR and GECCO

SNP	Discovery phase		Replication phase			
			Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
FTO						
rs12149832	1.18 (1.06, 1.32)	0.004	0.99 (0.95, 1.03)	0.543	1.00 (0.95, 1.04)	0.810
rs4784336*	1.30 (1.08, 1.57)	0.005	0.99 (0.92, 1.06)	0.801	1.00 (0.93, 1.07)	0.916
rs11075990	1.17 (1.05, 1.30)	0.006	0.99 (0.95, 1.03)	0.640	1.00 (0.96, 1.04)	0.958
rs9922619	1.17 (1.05, 1.30)	0.006	0.99 (0.95, 1.03)	0.519	0.99 (0.95, 1.04)	0.749
rs11075989	1.17 (1.04, 1.31)	0.006	0.99 (0.95, 1.03)	0.639	1.00 (0.96, 1.04)	0.958
rs9930506	1.16 (1.04, 1.30)	0.007	0.99 (0.95, 1.03)	0.552	0.99 (0.95, 1.04)	0.790
rs9936385	1.16 (1.04, 1.30)	0.007	0.99 (0.95, 1.03)	0.661	1.00 (0.96, 1.04)	0.981
rs9939609	1.16 (1.04, 1.30)	0.007	0.99 (0.95, 1.03)	0.639	1.00 (0.96, 1.04)	0.957
rs9922708	1.16 (1.04, 1.29)	0.007	0.99 (0.95, 1.03)	0.542	0.99 (0.95, 1.04)	0.767
rs9930501	1.16 (1.04, 1.29)	0.007	0.99 (0.95, 1.03)	0.553	0.99 (0.95, 1.04)	0.791
rs8050136	1.16 (1.04, 1.30)	0.007	0.99 (0.95, 1.03)	0.735	1.00 (0.96, 1.04)	0.958
rs8043757	1.16 (1.04, 1.29)	0.008	0.99 (0.95, 1.03)	0.731	1.00 (0.96, 1.04)	0.956
rs17817449	1.16 (1.04, 1.29)	0.008	0.99 (0.95, 1.03)	0.708	1.00 (0.96, 1.04)	0.981
rs9932754	1.16 (1.04, 1.29)	0.008	0.99 (0.95, 1.03)	0.552	0.99 (0.95, 1.04)	0.789
rs7193144	1.16 (1.04, 1.30)	0.008	0.99 (0.95, 1.03)	0.701	1.00 (0.96, 1.04)	0.991
rs8051591	1.16 (1.04, 1.29)	0.008	0.99 (0.95, 1.03)	0.723	1.00 (0.96, 1.04)	0.970
rs9935401	1.16 (1.04, 1.29)	0.008	0.99 (0.95, 1.03)	0.725	1.00 (0.96, 1.04)	0.969
rs1420571*	1.26 (1.06, 1.51)	0.009	0.99 (0.92, 1.06)	0.747	0.99 (0.93, 1.06)	0.827
rs7202116	1.16 (1.04, 1.29)	0.009	0.99 (0.95, 1.03)	0.637	1.00 (0.96, 1.04)	0.955
rs3751812	1.16 (1.04, 1.29)	0.009	0.99 (0.95, 1.03)	0.733	1.00 (0.96, 1.04)	0.964
rs9923233	1.16 (1.04, 1.29)	0.010	0.99 (0.95, 1.03)	0.661	1.00 (0.96, 1.04)	0.981
rs7185735	1.15 (1.03, 1.29)	0.011	0.99 (0.95, 1.03)	0.627	1.00 (0.96, 1.04)	0.940
rs17817964	1.15 (1.03, 1.29)	0.011	0.99 (0.95, 1.03)	0.680	1.00 (0.96, 1.04)	0.977
rs4784337*	1.26 (1.05, 1.51)	0.013	0.99 (0.93, 1.06)	0.790	1.00 (0.93, 1.07)	0.889
rs7201850	1.14 (1.03, 1.28)	0.015	0.99 (0.95, 1.03)	0.579	1.00 (0.96, 1.04)	0.833

SNP	Discovery phase		Replication phase				
			Model 1		Model 2		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	
rs4784346*	1.16 (1.03, 1.31)	0.017	1.00 (0.95, 1.04)	0.891	1.00 (0.95, 1.04)	0.870	
rs8044769	0.88 (0.79, 0.98)	0.018	1.01 (0.97, 1.05)	0.582	1.01 (0.97, 1.05)	0.782	
rs7186220*	1.19 (1.03, 1.37)	0.018	1.00 (0.94, 1.05)	0.844	0.99 (0.94, 1.05)	0.772	
rs9941349	1.14 (1.02, 1.27)	0.019	0.99 (0.95, 1.03)	0.620	1.00 (0.96, 1.04)	0.856	
rs9931494	1.14 (1.02, 1.27)	0.019	0.99 (0.95, 1.03)	0.635	1.00 (0.96, 1.04)	0.866	
rs1107355*	1.16 (1.02, 1.31)	0.020	1.00 (0.95, 1.05)	0.914	1.00 (0.95, 1.05)	0.900	
rs7194243*	1.15 (1.02, 1.30)	0.022	1.00 (0.95, 1.04)	0.859	1.00 (0.95, 1.04)	0.850	
rs9933805*	0.88 (0.79, 0.98)	0.024	0.99 (0.95, 1.03)	0.531	0.99 (0.95, 1.03)	0.570	
rs1421085	1.13 (1.01, 1.26)	0.026	1.00 (0.96, 1.04)	0.928	1.01 (0.96, 1.05)	0.805	
rs1558902	1.13 (1.01, 1.26)	0.032	1.00 (0.96, 1.04)	0.937	1.01 (0.97, 1.05)	0.795	
rs2024471*	1.12 (1.01, 1.25)	0.036	1.04 (1.00, 1.08)	0.069	1.04 (1.00, 1.09)	0.052	
rs12596210*	1.20 (1.01, 1.43)	0.038	0.99 (0.93, 1.06)	0.761	0.99 (0.93, 1.06)	0.824	
rs12918363	1.12 (1.00, 1.24)	0.041	0.97 (0.93, 1.01)	0.182	0.97 (0.93, 1.01)	0.127	
rs1121980	1.12 (1.00, 1.25)	0.041	1.00 (0.96, 1.04)	0.840	1.00 (0.96, 1.04)	0.947	
rs11075987	1.12 (1.00, 1.24)	0.044	1.01 (0.97, 1.05)	0.787	1.00 (0.96, 1.04)	0.968	
rs8046502*	1.12 (1.00, 1.24)	0.045	1.04 (1.00, 1.08)	0.066	1.04 (1.00, 1.09)	0.048	
rs16952770*	1.20 (1.00, 1.42)	0.047	0.99 (0.93, 1.06)	0.791	0.99 (0.93, 1.06)	0.811	
rs4784329*	1.12 (1.00, 1.24)	0.049	0.96 (0.92, 1.00)	0.057	0.96 (0.92, 1.00)	0.048	
MC4R							
rs689353	1.18 (1.06, 1.32)	0.003	1.01 (0.97, 1.05)	0.803	1.01 (0.97, 1.05)	0.798	
rs598214	1.18 (1.05, 1.31)	0.004	1.01 (0.97, 1.05)	0.792	1.01 (0.97, 1.05)	0.789	
rs596340	1.18 (1.05, 1.31)	0.004	1.01 (0.97, 1.05)	0.817	1.01 (0.96, 1.05)	0.811	
rs545195	1.17 (1.05, 1.31)	0.005	1.01 (0.97, 1.05)	0.802	1.01 (0.97, 1.05)	0.797	
rs596365	1.17 (1.05, 1.30)	0.006	1.01 (0.97, 1.05)	0.806	1.01 (0.97, 1.05)	0.801	
rs1943235	0.86 (0.77, 0.96)	0.009	1.03 (0.99, 1.07)	0.228	1.02 (0.98, 1.06)	0.307	
rs579054	1.16 (1.04, 1.30)	0.010	1.01 (0.96, 1.05)	0.824	1.01 (0.96, 1.05)	0.805	
rs1943227*	0.81 (0.69, 0.96)	0.012	0.94 (0.87, 1.02)	0.148	0.95 (0.87, 1.03)	0.218	

SNP	Discovery phase		Replication phase			
			Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
rs12962636	0.75 (0.60, 0.96)	0.020	0.98 (0.88, 1.08)	0.638	0.98 (0.88, 1.09)	0.756
rs499219*	1.22 (1.02, 1.47)	0.026	1.02 (0.96, 1.09)	0.549	1.02 (0.96, 1.09)	0.523
rs560248*	1.14 (1.01, 1.28)	0.032	1.02 (0.98, 1.07)	0.359	1.02 (0.98, 1.07)	0.323
rs12966035	0.89 (0.80, 0.99)	0.035	1.01 (0.97, 1.05)	0.692	1.01 (0.97, 1.05)	0.791
rs12953429	1.12 (1.01, 1.25)	0.037	0.99 (0.95, 1.03)	0.683	0.99 (0.95, 1.03)	0.523
rs489310*	1.20 (1.01, 1.43)	0.038	1.02 (0.96, 1.09)	0.511	1.02 (0.96, 1.09)	0.499
rs547363	0.89 (0.80, 0.99)	0.040	1.00 (0.96, 1.04)	0.905	1.00 (0.96, 1.04)	0.983
rs2156335*	0.89 (0.80, 1.00)	0.041	1.02 (0.98, 1.06)	0.412	1.01 (0.97, 1.06)	0.496
rs4378703*	1.15 (1.00, 1.32)	0.047	1.01 (0.96, 1.07)	0.612	1.01 (0.96, 1.07)	0.729
rs612238*	1.20 (1.00, 1.43)	0.048	1.03 (0.96, 1.09)	0.457	1.03 (0.96, 1.10)	0.440

Abbreviations:
CCFR, Colon Cancer Family Registry; CI, confidence interval; FTO, fat-mass and obesity-associated; GECCO, Genetics and Epidemiology of Colorectal Cancer Consortium; MC4R, melanocortin-4 receptor; OR, odds ratio; SNP, single nucleotide polymorphism.

Note:

Model 1: adjusted for age, sex, and the top three principal components of ancestry

Model 2: adjusted for age, sex, body mass index, and the top three principal components of ancestry Odd ratio, 95% CI and P values in the discovery phase obtained from model 1 (SNPs with no *) or model 2 (SNPs with *), whichever generates the smaller p value, from the meta-analyses.