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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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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) 100 kb upstream and 300 kb downstream from each respective locus with risk of colorectal cancer in data from the Colon Cancer Family Registry (CCFR: 1960 cases; 1777 controls). Next, all SNPs that were nominally statistically significant ($p < 0.05$) in the discovery stage were included in replication analyses in data from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO: 9716 cases; 9844 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.

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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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.

1. 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 1000 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).

2. 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 1173 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 9716 cases and 9844 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 S1. 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 [6], 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 100 kb upstream and 300 kb 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 [8].

3. 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 S2). 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.

4. 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 [9,10]; some of the associations were independent of obesity, but the mechanisms were unclear [10]. 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 1765 colorectal cancer cases and 2077 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 2033 cases and 9640 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