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No association between *FTO* or *HHEX* andendometrial cancer risk

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Abstract

Introduction—Obesity and diabetes are known risk factors for endometrial cancer; thus genetic risk factors of these phenotypes may also be associated with endometrial cancer risk. To evaluate this hypothesis, we genotyped tagSNPs and candidate SNPs in *FTO* and *HHEX* in a primary set of 417 endometrial cancer cases and 406 population-based controls, and validated significant findings in a replication set of approximately 2,347 cases and 3,140 controls from three additional studies.

Methods—We genotyped 189 tagSNPs in *FTO* (including rs8050136) and five tagSNPs in *HHEX* (including rs1111875) in the primary set and one SNP in each of *FTO* (rs12927155) and *HHEX* (rs1111875) in the validation set. Per allele odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the association between the genotypes of each SNPs(as an ordinal variable)and endometrial cancer risk using unconditional logistic regression models, controlling for age and site.

Results—In the primary study, the most significant findings in *FTO* was rs12927155 (OR=1.56, 95% CI 1.21–2.01, $p=5.8\times10^{-4}$) and *HHEX* was rs1111875 (OR=0.80, 95% CI 0.66–0.97;

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p=0.026). In the validation studies, the pooled per allele ORs, adjusted for age and study, were for *FTO* rs12927155: OR=0.94, 95% CI 0.83–1.06, p=0.29 and for *HHEX* rs1111875: OR=1.00, 95%CI 0.92–1.10, p=0.96.

Conclusion—Our data indicate that common genetic variants in two genes previously related to obesity (*FTO*) and diabetes (*HHEX*) by genome-wide association scans are not associatedwith endometrial cancer risk.

Impact—Polymorphisms in *FTO* and *HHEX* are unlikely to have large effects on endometrial cancer risk but may have weaker effects.

Keywords

endometrial cancer; obesity; genetics; FTO; HHEX

Introduction

Obesity and type II diabetes are major risk factors for endometrial cancer. Genetic variation that is associated with obesity and diabetes may provide clues to the molecular pathways mediating endometrial carcinogenesis. Agenome-wide association study (GWAS) of body mass index (BMI) identified a 47 kb region on chromosome 16 encompassing *FTO* gene intron1-exon2-intron2 that is marked by tagSNP rs8050136 (and the correlated SNP rs9939609 (r^2=1))to be associated with BMI(1). Another GWASof type II diabetes(2)identified the *HHEX* gene region on chromosome 10 marked by rs1111875also to be associated with BMI. To examine whether genetic variants of *FTO* and *HHEX* are associated with endometrial cancer risk, we genotyped tagSNPs and candidate SNPs in the Polish Endometrial Case-Control Study(PECS)of 417 endometrial cancer cases and 406 population-based controls(3). Significant findings in this set were then selected for validation in a replication set of approximately 2,347cases and 3,140controls from three additional studies.

PECS Methods

Genotyping of 189 tagSNPsin *FTO* (including rs8050136)and five tagSNPs in *HHEX* (including rs1111875)were done as part of an Illumina Infinium custom iSelect chip using aSNP selection strategy described previously(4). For *FTO*, four SNPs were excluded due to violations of quality control measures: concordance of 1% replicates, completion proportions, and departure of Hardy-Weinberg proportions ($p<0.05$), and a further 14 SNPs due to minor allele frequency among controls less than 0.05. For *HHEX*, all five SNPs passed quality control filters. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the association between SNPs and endometrial cancer risk using unconditional logistic regression models, controlling for matching factors, age and study site. We also conducted analyses of haplotypes, including the sequential haplotype scan (5)and the variable-sized sliding-window regularized regression association analysis (6), to localize a set of adjacent markers associated with risk. Due to the size of the FTO gene, the sequential haplotype scan was performed in three overlapping sections (section 1 (SNPs 1–65): rs8055834–rs17820875, section 2 (SNPs 60–115): rs10521303–rs8056199, and section 3 (SNPs 110–171): rs16952730–rs16953089).

PECS Results

Among PECS controls, carrying increasing copies of the minor A allele of rs8050136in FTO was associated with increased mean body mass index (BMI) (Kruskal-Wallisp-value=0.015) but not prevalence of diabetes (chi-square p=0.26). rs1111875 in HHEX was not associated

with BMI (p=0.16) or diabetes (p=0.56). In the PECS case-control analyses, the minor A allele of rs8050136 was not associated with endometrial cancer risk(per allele OR=1.05, 95% CI 0.86–1.28, p=0.64). However, 20 of the remaining 171 *FTO* tagSNPs were significantly associated with endometrial cancer risk (per allele p-values ranged from 0.00068–0.027) and represented independent SNPs (n=4) or clustered into three linkage disequilibrium blocks. Haplotype analyses identified strong signals (haplotype p-values $<10^{-3}$)in two of these regions (Figures 1–2). The first region resides in intron 4 and is marked by SNP rs8063241 (OR=0.71, 95% CI 0.56–0.88, p-value=1.7×10^{-3}) (Figure 1). The second region in intron 8 is marked by 3 correlated tagSNPs that also had the lowest p-values in the single locus analysis [rs2689264 (MAF=0.17): OR=1.57, 95% CI 1.22–2.02, p=4.5×10^{-4}; rs12927155(MAF=0.17): OR=1.56, 95% CI 1.21–2.01, p=5.8×10^{-4}; and, rs2540776 (MAF=0.17): OR=1.54, 95% CI 1.19–1.99, p=8.7×10^{-4}] (Figure 2). The candidate SNP in HHEX, rs1111875, was associated with a 20% lower risk of endometrial cancer for each minor T allele (per allele OR=0.80, 95% CI 0.66–0.97; p=0.026). No other *HHEX* loci were associated with risk.

Replication Studies

In an attempt to replicate our findings for *FTO* SNP rs12927155 and *HHEX* SNP rs1111875, we approached three independent case-control studies of women of European ancestry (5,522 subjects, Table 1), including the Study of Epidemiology and Risk Factors in Cancer Heredity (SEARCH)with 1,494endometrial cancer cases and 1,600community controls, the Australian National Endometrial Cancer Study (ANECS)with 1,048 endometrial cancer cases and 1,010population-based controls(http://www.anecs.org.au/; (7)), and the Leuven Endometrial Cancer Study (LES)(8)with 206 endometrial cancer cases and 649hospital-based controls. The distribution of age and BMI were similar for the three studies (age range (median): SEARCH, 26–71 (56); ANECS, 26–80 (62); LES, 20–80 (48); and BMI range (median): SEARCH, not reported; ANECS, 15.1–67.3 (28.0); LES, 16.4–89.0 (24.9)) and with the PECS. We excluded controls with a history of hysterectomy (including 249 for SEARCH, 95 for ANECS, and 1 for LES). The SEARCH samples were genotyped using TaqMan assays, ANECS and LES samples were genotyped using the Sequenom iPLEX platform.

Among these three studies, the pooled per allele ORs, adjusted for continuous age and study, were for *FTO* rs12927155: OR=0.94, 95% CI 0.83–1.06, p=0.29andfor *HHEX* rs1111875: OR=1.00, 95%CI 0.92–1.10, p=0.96 (Table 1). Between-study heterogeneity was not evident among these studies(p=0.23 and 0.74, respectively), and the CIs for both SNPs excluded the ORs from the PECS.

Conclusion

Our data indicate that common genetic variants in two genes previously related to obesity (*FTO*) and diabetes (*HHEX*) by genome-wide association scans are not associated with endometrial cancer risk.

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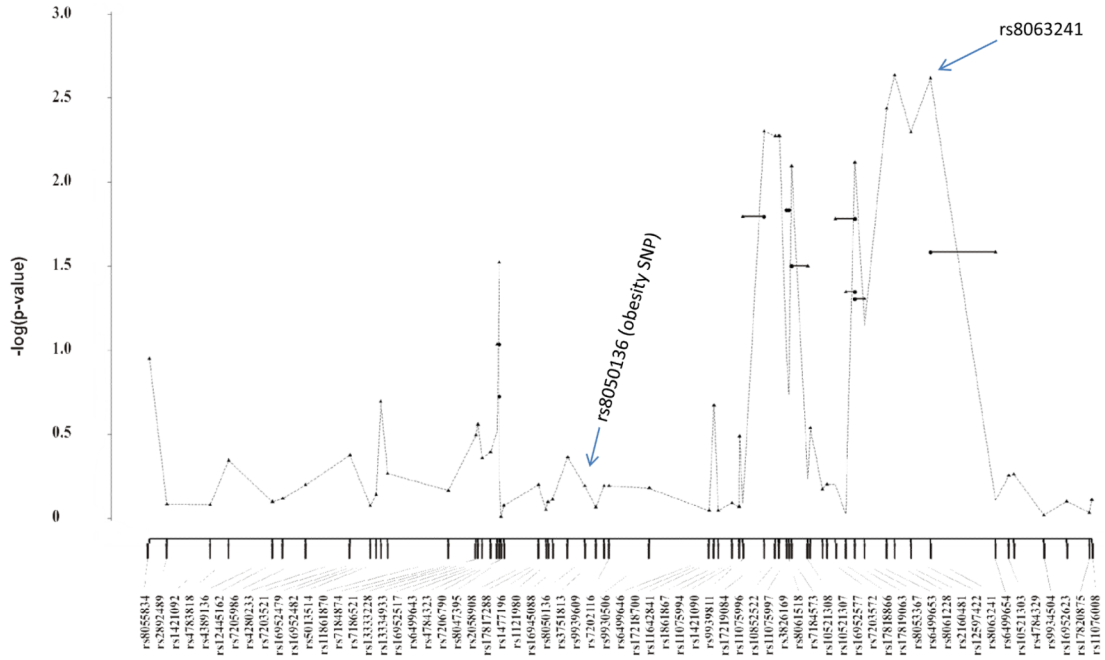

Figure 1.
FTO Sequential haplotype scan analysis of tagSNPs rs8055834 through rs17820875. Polish Endometrial Cancer Study (417 cases and 406 controls)

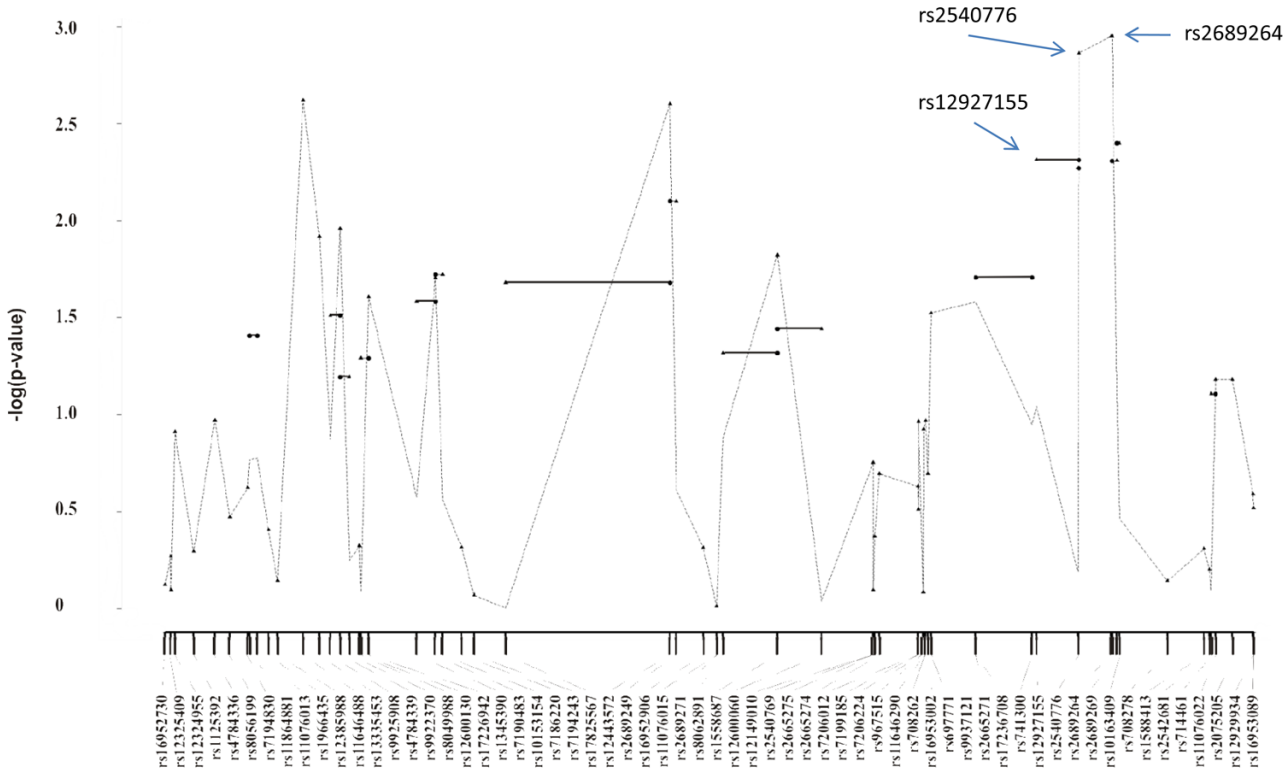

Figure 2.
FTO sequential haplotype scan analysis of tagSNPs rs16952730 through rs16953089, Polish Endometrial Cancer Study (417 cases and 406 controls)

Table 1

Age-adjusted odds ratios (OR) and 95% confidence intervals for the association between candidate polymorphisms and endometrial cancer risk in four independent case-control studies

Study	*FTO* rs12927155						*HHEX* rs1111875					
	Cases	Controls		Per allele			Cases	Controls		Per allele		
	N	N	MAF[1]	OR	(95% CI)	p-value	N	N	MAF[1]	OR	(95% CI)	p-value
PECS	417	406	0.17	1.53	(1.19–1.97)	0.001	417	406	0.42	0.80	(0.66–0.97)	0.026
SEARCH	1121	1596	0.16	1.01	(0.85–1.21)	0.88	1119	1591	0.41	1.01	(0.88–1.14)	0.93
ANECS	1022	896	0.15	0.89	(0.74–1.08)	0.24	992	898	0.40	1.01	(0.88–1.15)	0.91
LES[2]	204	648	0.16	1.08	(0.70–1.68)	0.72	0	0				
Pooled[3]	2347	3140	0.15	0.94	(0.83–1.06)	0.29	2111	2489	0.40	1.00	(0.92–1.10)	0.96

[1] MAF=minor allele frequency among controls

[2] rs1111875 was not genotyped in LES

[3] Pooled estimates were calculated for the three replication studies (SEARCH, ANECS, and LES); therefore, models were also adjusted for study. Numbers do not sum to the total samples available because of missing genotype data.