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Association of the *TCF7L2* polymorphism with colorectal cancer and adenoma risk

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Abstract

Interaction of *TCF7l2* with translocated β-catenin in the nucleus transiently converts *TCF7L2* to transcription factor activators, which induce the expression of target genes, including *cyclin D1* and *c-myc*, in colorectal carcinogenesis. We evaluated the association of a polymorphism in *TCF7L2* (RS12255372) which previously has been strongly associated with risk of Type II Diabetes, with colorectal cancer (CRC) and adenoma in the prospective Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts. In the NHS and HPFS control populations, the *TCF7L2 T*-allele frequency ranged from 28 to 30% and the genotype distribution was in agreement with Hardy-Weinberg equilibrium. Overall, there was suggestive evidence for an inverse association associated with homozygosity for the minor allele of RS12255372 (*TCF7L2 TT*) and CRC (conditional and covariate adjusted OR=0.63, 95%CI: 0.37–1.08; P for heterogeneity 0.52 for the association in women and men), which was more evident among women (OR=0.39, 95%CI: 0.16 – 0.91). The polymorphism was not associated with risk of colorectal adenoma. Furthermore, we observed no evidence of effect modification between the *TCF7L2* SNP and covariates such as family history (p-interaction=0.45) or BMI (p-interaction=0.27) or with genetic variants in the *APC Asp1822Val* SNP (NHS cancer p-interaction=0.40, NHS adenoma p-interaction 0.10). In summary, the marginal association of *TCF7L2* SNP with CRC may be due to chance, but warrants further laboratory and epidemiological investigation.

Keywords

TCF7L2; polymorphism; Wnt pathway; colorectal cancer

Introduction

T-cell factor (TCF)/LEF proteins facilitate the formation of multiprotein enhancer complexes to modulate the transcription of target genes. Interaction of *T-cell factor 7 like 2* (*TCF7L2*, previously reported as *TCF-4*) with translocated β-catenin in the nucleus transiently converts *TCF7L2* to a transcription factor activator, which induces the expression of target genes,

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including *cyclin D1* and *c-myc*, in colorectal carcinogenesis [1]. Duval et al. (1999; 2000) characterized the genomic structure of *TCF7L2/TCF-4* in colorectal cancer (CRC) cell lines [2–3]. *TCF7L2* has alternative exons leading to isoforms with short, medium, or long C-terminal ends; the long C-terminal ends may mediate transcriptional repression [3]. *TCF7L2* frameshift mutation in MSI-H CRC leads to selective loss of *TCF7L2* isoforms with CtBP-binding abilities [4]. Recently, a genome-wide analysis of 11 CRC tumor cell lines or xenografts classified TCF7L2 [5] as a cancer candidate gene (with a cancer mutation prevalance, CaMP, score of 2.8; >1 is a cancer candidate gene). Polymorphisms in *TCF7L2* have been associated with disease susceptibility. Specifically, Grant et al. (2006) demonstrated that a polymorphism in *TCF7L2* is associated with increased risk of type II diabetes (T2D) [6–12] by impaired beta-cell function [7,9]. Epidemiologic studies have suggested that hyperinsulinemia may be related to the risk of colon adenoma and cancer [13–16]. Given its relevance to the etiology of colorectal cancer, we evaluated the association of the *TCF7L2* (RS12255372) polymorphism with colorectal cancer and adenoma in the prospective Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) cohorts.

Materials and methods

Study population

The NHS began in 1976 when 121,700 female registered nurses in the United States between the ages of 30 and 55 completed a self-administered questionnaire on their medical history and baseline health-related exposures. Subsequently, these participants have completed a mailed, self-administered questionnaire biennially to update information on their lifestyle, medical history, and diet (every 2 to 4 years).

In 1989 and 1990, 32,826 women, between the ages of 43 and 69, provided blood samples. Upon receipt, samples were immediately centrifuged and aliquoted into plasma, red blood cells, and buffy coat fractions for storage in liquid nitrogen. After blood collection through June 2000, 197 incident cases of colorectal cancer were confirmed through medical records or death reports, of which 190 cases were successfully genotyped. Controls were randomly selected from women who were alive and free of cancer at the time of case ascertainment. One control was matched to each case on year of birth and month of blood draw. As previously described, [17], cases of colorectal adenoma and controls were chosen from among women who supplied a blood sample, had a sigmoidoscopy or colonoscopy (by 1998) after providing a blood sample, and were free from diagnosed cancer (except nonmelanoma skin cancer), ulcerative colitis, and adenoma before endoscopy. Newly diagnosed polyps (in individuals who never had a polyp diagnosed before the date of blood draw) were reported on the 1990, 1992, 1994, 1996, or 1998 questionnaire. These polyps were confirmed to be adenomatous by review of histopathological reports and were classified by location (proximal or distal colon, or rectum), size (<1 cm, ≥1 cm), and histology (tubular, tubulovillous, villous, carcinoma-in-situ (CIS)) by study investigators blinded to the exposure information. Advanced adenoma was defined as large adenomas ≥1 cm in size and [Aditi – do you mean "or" as well here – typically advanced adenoma also includes polyps < 1cm with any villous component) tubulovillous, villous, or carcinoma in situ histology. Between 1989 and 1998, 557 women with colorectal adenoma were identified, and one control was selected for each case, matched on year of birth, year of blood draw, time period of recent endoscopy, indication for endoscopy, and time period of first or most recent endoscopy. One case was subsequently found to be hyperplastic and was excluded from the analysis. Thus, the total number of cases and controls analyzed in this study were 556 cases and 557 controls. Diet was assessed in 1986, 1990, 1994 and 1996 with a semiquantitative food frequency questionnaire.

The HPFS began in 1986 when 51,529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, ages 40 to 75 years, responded to a mailed questionnaire [18].

These men provided baseline information on age, marital status, height, weight, ancestry, medications, smoking history, medical history, physical activity, and diet. Exposure and medical history information are updated every 2 years. Blood samples were collected from 18,225 of the HPFS participants between 1993 and 1995. Among these men, 168 incident cases of CRC were identified between the date of blood draw and January 2002. Men who were alive and free of diagnosed cancer at the time of case ascertainment were selected as controls and were matched to cases on year of birth and month of blood draw.

Genotyping methods

Genotyping was performed at the Dana-Farber/Harvard Cancer Center High-Throughput Polymorphism Core. DNA was extracted from 50-μL buffy coat fractions diluted with 150 μL of PBS by the Qiagen QIAamp Blood Kit (Qiagen, Chatsworth, CA) spin protocol. The genotype of the*TCF7L2* polymorphism was determined by measuring end-point fluorescence using the 5' nuclease assay (Taqman) on the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) [19]. The primers for RS12255372 (G,T) in Intron 3 TCF7L2 were: Forward: GCTGAGCTGCCCAGGAATAT; Reverse: GCAGAGGCCTGAGTAATTATCAGAA.

Quality control was ensured by including a random 10% of the samples in the 96-well plates as duplicates. The quality control samples served as internal controls to validate the genotyping methods; there was 100% concordance of the quality control samples. Laboratory personnel were blinded to the status (case, control, or quality control) of samples.

Statistical analysis

The study population included 357 incident CRC cases and 814 matched controls and 556 incident adenoma cases and 557 matched controls for the analyses. The number of cases and controls for the polymorphism was slightly lower because of missing genotyping data. Genotype distributions were evaluated for agreement with Hardy-Weinberg equilibrium (HWE) by the chi-square test. We evaluated differences among cases and controls using the chi-square test for categorical variables and the paired t-test for continuous variables.

We used both conditional and unconditional logistic regression for the analyses to compute genotype odds ratios (ORs), 95% confidence intervals (CIs), allelic trend tests, and interactions. In the multivariate models, we adjusted for known risk factors for colorectal neoplasia, including family history of CRC, pack-years of smoking, postmenopausal hormone use, body mass index (BMI), physical activity, aspirin use, total energy intake, and consumption of red meat, alcohol, and folate. Unconditional logistic analyses explicitly adjusted for matching variables, including age, history of previous endoscopy (before blood draw), year of endoscopy, (endoscopy variables I assume are only for the polyps) and blood draw factors.

The SNP was initially examined with the codominant model, evaluating the TCF7L2 as a three-level categorical variable. We also used the dominant model, comparing variant carriers with the referent homozygous wild type. The risk for advanced and small adenoma was evaluated by polytomous logistic regression with an ordinal outcome variable that was modeled as a three-level categorical variable: advanced adenoma, small adenoma, and controls. Effect modification by covariates, family history, and BMI was tested with p-values obtained from the likelihood ratio test comparing models with and without the interaction term between genotype and covariate. Gene-gene interactions with a non-synonymous *Ademato*us *Polyposis Coli (APC) Asp 1822 Val* were tested by likelihood ratio tests comparing the model with main effects for each polymorphism to the model including indicator variables for the cross-tabulation of the two polymorphisms. All p-values reported are two-sided.

Results

Cancer

Details of this study population have been previously reported [17]. Briefly, there were 367 incident cases of CRC and 852 controls. The mean age of cases and their matched controls was 68 years. As expected, family history was more common in the cases, whereas aspirin use, multivitamin use, and being a never smoker was more common among controls.

Adenoma

Details of this study population have been previously reported [18]. The mean age of cases and their matched controls was 62.3 years. Family history of CRC, smoking >25 pack-years, BMI > 30 kg/m^2, and consumption of >1 serving of red meat/day were associated with an increased risk of colorectal adenoma. In addition, cases were less likely than controls to be current users of postmenopausal hormones or to take multivitamins and aspirin (<7 aspirin tablets/week). A sub-analysis of distal-only adenoma did not reveal a point estimate that varied (point estimate varied less than 10%) from the overall main effect of the SNP.

TCF7L2 polymorphism

The *TCF7L2 T*-allele frequency ranged from 28 to 30% and the genotype distribution was in agreement with Hardy-Weinberg equilibrium. Overall, there was a marginal inverse association with the minor allele of RS12255372 (*TCF7L2 TT*) and CRC (conditional and covariate adjusted OR=0.63, 95%CI: 0.37–1.08; P for heterogeneity 0.52 for the association in women and men). Although limited by sample size and thus perhaps due to chance, this association was more evident among women (OR=0.39, 95%CI: 0.16 – 0.91). The *TCF7L2* polymorphism was not associated with risk of small (multivariate OR=0.95 (95% CI: 0.74 – 1.18)) or advanced (multivariate OR=1.01 (95% CI: 0.78 – 1.32)) colorectal adenomas (p-value=0.82 for 2- degree of freedom likelihood ratio test, data not shown). Furthermore, we observed no evidence of effect modification between the *TCF7L2* SNP and covariates such as family history (p-interaction=0.45) and BMI (p-interaction=0.27) or with genetic variants in the *APC Asp1822Val* SNP (NHS cancer p-interaction=0.40, NHS adenoma p-interaction 0.10).

Discussion

APC is the gatekeeper tumor suppressor gene associated with CRC. High-penetrance mutations in the *APC* pathway are a hallmark of familial CRC (familial adenomatus polyposis or FAP). In this pathway, activated *Wnt* signaling leads to the accumulation of nuclear β-*catenin*. The cytoplasmic level of β-*catenin* is regulated by ubiquitin-mediated proteolysis after it is targeted for phosphorylation by *glycogen synthase kinase 3*β (*GSK-3*β). The phosphorylation of β-*catenin* by *GSK-3*β occurs in the context of a structural complex that includes Axin and APC [20]. *GSK-3*β activity is inhibited in the presence of a *Wnt* signal [21]. Interaction of excess translocated β-*catenin* in the nucleus with *TCF7L2* upregulates expression of specific target genes, including *cyclin D1*, *c-myc* [22–23] and GLP-1 [24].

In this study, we observed a marginal inverse association between the *TCF7L2* polymorphism and risk of CRC, but not adenoma. Evaluating the gene-environment association of the SNP with family history and BMI did not reveal a significant interaction. Furthermore, the *APC Asp1822Val* SNP did not modify the risk of CRC and adenoma among women for any *TCF7L2* genotype.

In the past year several publications have reported an increased risk of T2D (this abbrevation, if you are going to use it, needs to be defined earlier) among *T*-allele carriers. Grant et al. (2006) identified DG10S478 located in intron 3-exon 4 of the *TCF7L2* gene on chromosome 10q25.2

(in a well-defined LD block of 92.1 kb based on CEU HapMap v16; GenBank NM 030756) that had an r^2 of 0.95 with the rs12255372 SNP [6]. The authors suggest that the *TCF7L2* variants increase T2D risk by altering proglucagon gene expression [6] in enteroendrocrine cells [24] via the Wnt signaling pathway [26]. Florez et al. (2006) reported that individuals with the *TT* genotype have decreased insulin secretion [7]. The reduced insulin secretion may be due to decreased expression of proglucagon and glucagons like peptide-1 [24]. Zhang et al. (2006) reported an increased risk for T2D for the *TT* genotype in the NHS (687 T2D, 1051 controls) with an OR of 1.86 (95% CI: 1.30 –2.67) and in the HPFS (886 T2D, 896 controls) with an OR of 2.15 (95% CI: 1.48 – 3.13) [8]. A study of breast cancer risk among 592 German families [25] and 735 controls reported a modest association with increased risk (OR=1.19 (95% CI: 1.01–1.42) for the *T*-allele.

I might include a paragraph here which discussed the assocation between diabetes and CRC and how you would have expected, based on that relationship, to have seen an increased risk with the polymorphism. Hence, this study suggests that there is NO increased risk and possibly an inverse association that warrants more investigation. That might be a better sell overall – as a null study which if anything, shows inverse assocation.

The *TCF7L2* polymorphism is located in interspersed repeat elements, 41 kb upstream and 9 kb downstream of alternatively spliced exon 4 [7]. A limitation of this analysis is that the functional relevance of this SNP is unknown. In summary, the marginal inverse association of *TCF7L2* SNP with CRC may be due to chance, but warrants further laboratory and epidemiological investigation.

Glossary

The commonly used abbreviations are

SNPs
: single nucleotide polymorphisms

TCF7L2
: T-cell factor 7 like 2

CRC
: colorectal cancer

T2D
: Type II Diabetes

NHS
: Nurses' Health Study

HPFS
: Health Professionals Follow-up Study

OR
: Odds Ratio

CI
: confidence interval

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Table 1

Association between the *TCF7L2* (rs12255372) genetic variants with colorectal cancer and adenoma risk in the Nurses' Health Study and Health Professionals Follow-up Study

	Cases N (%)	Controls* N (%)	Conditional OR[1] (95% CI)	Multivariate Conditional OR[2] (95% CI)
	NHS and HPFS CRC[3]			
TCF7 L2	N=357	N=814		
GG	199 (55.7)	413 (50.7)	1.00 (Reference)	1.00 (Reference)
GT	135 (37.8)	328 (40.3)	0.89 (0.68 – 1.16)	0.90 (0.68 – 1.18)
TT	23 (6.4)	73 (9.0)	0.64 (0.38 – 1.07)	0.63 (0.37 – 1.08)
			[4]*P-trend*	*0.10*
GT+TT	158 (44.3)	401 (49.3)	0.84 (0.69 – 1.03)	0.84 (0.68 – 1.04)
	NHS CRC			
TCF7L2				
GG	100 (53.2)	233 (49.7)	1.00 (Reference)	1.00 (Reference)
GT	81 (43.1)	194 (41.4)	0.99 (0.70 – 1.40)	1.00 (0.68 – 1.46)
TT	7 (3.7)	42 (9.0)	0.39 (0.17 – 0.91)	0.39 (0.16 – 0.91)
			P-trend	*0.14*
GT+TT	88 (46.8)	236 (50.4)	0.81 (0.62 – 1.07)	0.81 (0.60 – 1.07)
	HPFS CRC			
TCF L2				
GG	101 (58.7)	186 (52.8)	1.00 (Reference)	1.00 (Reference)
GT	55 (32.0)	135 (38.4)	0.75 (0.50 – 1.13)	0.78 (0.50 – 1.20)
TT	16 (9.3)	31 (8.8)	0.96 (0.48 – 1.91)	0.89 (0.42 – 1.89)
			P-trend	*0.37*
GT+TT	71 (41.3)	166 (47.2)	0.88 (0.66 – 1.17)	0.87 (0.64 – 1.18)
	NHS Adenoma			
TCF7L2				
GG	271 (51.8)	273 (52.4)	1.00 (Reference)	1.00 (Reference)
GT	218 (41.7)	204 (39.2)	1.06 (0.81 – 1.39)	1.12 (0.83 – 1.51)
TT	34 (6.4)	44 (8.4)	0.75 (0.45 – 1.24)	0.74 (0.41 – 1.32)
			P-trend	*0.83*
GT+TT	252 (48.2)	248 (47.6)	0.95 (0.78 – 1.16)	0.98 (0.78 – 1.22)

*HWE p-value for total NHS and HPFS controls is 0.50 (NHS cancer: HWE p=0.86 controls, p=0.05 cases; HPFS cancer: HWE p=0.36 controls, p=0.04 cases; NHS adenoma: HWE p=0.50 controls, HWE p=0.26)

[1]Conditional logistic regression conditioned on the strata defined by the matching variables

[2]Conditional logistic regression conditioned on the strata defined by the matching variables, and adjusted for family history of colon cancer, pack years smoked, body mass index, PMH use, BMI, aspirin intake, physical activity, alcohol intake, total folate consumption, and red meat consumption.

[3]P for heterogeneity 0.52 for the association in women and men

[4]Armitage test for trend

Table 2

Association of *TCF7L2* variants with covariates

		Cases N (%)	Controls N (%)	Multivariate OR[1] (95% CI)	P-int[2]
TCF7L2	***Family History***				
GG	*No*	152 (42.9)	335 (41.9)	1.00 (Ref)	
GT+TT	*No*	120 (33.9)	334 (41.8)	0.78 (0.58 – 1.06)	
GG	*Yes*	45 (12.7)	70 (8.8)	1.35 (0.85 – 2.13)	
GT+TT	*Yes*	37 (10.4)	61 (7.6)	1.39 (0.85 – 2.27)	
					0.45
TCF7L2	BMI				
GG	<25	85 (24.0)	185 (23.3)	1.00 (Ref)	
GT+TT	<25	69 (19.5)	190 (23.8)	0.83 (0.55 – 1.24)	
GG	≥25	112 (31.6)	220 (27.5)	1.02 (0.70 – 1.50)	
GT+TT	≥25	88 (24.9)	205 (25.6)	0.84 (0.55 – 1.24)	0.27

[1]Logistic regression adjusted for family history of colon cancer, pack years smoked, body mass index (BMI), post-menopausal hormone (PMH) use, aspirin intake, physical activity, alcohol intake, total folate consumption, and red meat consumption.

[2]P-int: p-values obtained from the likelihood ratio test (LRT) comparing models with and without the interaction term between genotype and covariate

Table 3

Interaction of *TCF7L2* and *APC 1822* variants and CRC and CRA risk in the NHS

		Cancer Cases	Controls	Multivariate OR[1] (95% CI)	P-int[2]
TCF7L2	***APC 1822***				
GG	*Asp*	50 (28.3)	129 (29.3)	1.00 (Ref)	
GT+TT	*Asp*	55 (31.1)	128 (29.1)	1.13 (0.69 – 1.86)	
GG	*Asp+Val*	42 (23.7)	88 (20.0)	1.23 (0.68 – 2.22)	
GT+TT	*Asp+Val*	30 (17.0)	95 (21.6)	0.76 (0.42 – 1.37)	
					0.40
		Adenoma Cases	**Controls**	**Multivariate OR[2] (95% CI)**	**P-int**
TCF7L2	***APC 1822***				
GG	*Asp*	154 (30.5)	147 (29.3)	1.00 (Ref)	
GT+TT	*Asp*	129 (25.5)	139 (27.7)	0.91 (0.63 - 1.33)	
GG	*Asp+Val*	109 (21.6)	117 (23.4)	0.94 (0.64 – 1.37)	
GT+TT	*Asp+Va1*	113 (22.4)	98 (19.6)	1.21 (0.80 – 1.84)	
					0.10

[1]Logistic regression adjusted for family history of colon cancer, pack years smoked, body mass index (BMI), post-menopausal hormone (PMH) use, aspirin intake, physical activity, alcohol intake, total folate consumption, and red meat consumption.

[2]P-int: P-value from LRT comparing the model with main effects for each polymorphism to the model including crosstabulated indicator variables.