

Research Paper

Genetic Variation in 8q24 Associated with Risk of Colorectal Cancer

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See page 1145.

ABSTRACT

Chromosome 8q24 harbors oncogenes known to be involved in pathogenesis of colorectal cancer (CRC) as well as uncharacterized genetic variants that have recently been shown to influence inherited risk of prostate cancer. In a population-based case-control study of colorectal cancer in northern Israel, we investigated the association between variation in 8q24 and risk of CRC. Among 1,861 incident cases and 1,937 population-based controls matched on age, gender, ethnicity, and clinic, rs10505477 was associated with risk of CRC in a dominant model, with an odds ratio = 1.23, 95% confidence interval = 1.05–1.43, ($p = 0.008$). This association was independently validated in an analysis of cancer among relatives of carriers of the risk allele, with a hazard ratio of 3.2 (95% bootstrap CI = 1.16–17.8). Genetic variation at rs10505477 on 8q24 potentially accounts for 14% of CRC in this population and should be replicated in other studies.

ABBREVIATIONS

OR, odds ratio; 95% CI, 95% confidence interval; CRC, colorectal cancer

INTRODUCTION

There is substantial evidence that 8q24 is implicated in the pathogenesis of colorectal cancer based on the known oncogenic role of *MYC* amplification¹. Other genes in 8q24 such as *BOP1* are overexpressed in CRC², and both *MYC* and *BOP1* overexpression are observed in approximately 40% of tumors³. Several lines of evidence suggest that common genetic variation in 8q24 also explains a substantial fraction of prostate cancer based on admixture mapping⁴, linkage analysis⁵ and case-control studies^{5–8}. Approximately 21% of incident prostate cancer was attributable to a common allele of rs698327 near the pseudo-gene *POU5F1P1* in one study⁹, while a separate fine-mapping study found that multiple independent SNPs in 8q24 accounted for 32% of prostate cancer in European Americans and 79% of prostate cancer in African Americans, with other ethnic populations between 32% and 79%⁷. To test the hypothesis that genetic variation in 8q24 was associated with risk of CRC we investigated genetic variation in rs10505477 within a population-based case-control study of CRC.

PATIENTS AND METHODS

The Molecular Epidemiology of Colorectal Cancer study is a population-based case-control study of incident colorectal cancer in northern Israel that includes 1,861 cases and 1,937 controls with complete interviews, centralized pathologic review, and DNA for genotyping¹⁰. Patients were eligible for participation if they were newly diagnosed with colorectal cancer between May 31, 1998 and March 31, 2004, and lived in the geographically defined area of northern Israel. Controls were identified from the same source population with stratified random sampling of Clalit Health Services (CHS) insurees. CHS is the largest health care provider in Israel and covers approximately 70% of the population at risk for colorectal cancer. Health care coverage in Israel is mandated and is provided by four not-for-profit providers akin to health maintenance organizations. Thus, all study participants had similar health insurance coverage and similar access to health services. Controls were individually matched to patients according to the year of birth, gender, primary-care clinic location and ethnic group (Jews vs. Arabs).

Table 1 **Characteristics of cases and controls**

Characteristic	Number of Cases	%	Number of Controls	%
All Subjects	1861	49.0	1937	51.0
Age*	69.9		71.0	
Sex				
Female	916	49.2	969	50.0
Male	945	50.8	968	50.0
Ethnicity				
Jewish	1610	86.5	1703	87.9
Ashkenazi	1292	69.4	1239	64.0
Sephardi	318	17.1	464	24.0
Other	251	13.5	234	12.1
Family History[†]				
No	1641	88.7	1794	92.6
Yes	209	11.3	143	7.4
Site[‡]				
Right Colon	670	39.3		
Left Colon	606	35.5		
Rectum	429	25.2		
Stage[§]				
I	285	17.4		
II	739	45.1		
III	537	32.8		
IV	76	4.6		
Microsatellite Instability**				
Stable	1233	87.9		
High	166	12.1		

*Mean age in years; [†]Reported history of CRC in a first degree relative, data missing from 11 (0.6%) cases; [‡]Tumor site data not classified/unavailable for 156 (8.4%) of cases; [§]Tumor stage not classified for 190 cases, missing for 34, and therefore unavailable for 224 (12.3%) of cases; **MSI data missing from 462 (24.8%) of tumors with blocks that could not be retrieved or had insufficient tissue for analysis.

Potential controls were excluded if they had a history of colorectal cancer. Participants provided written informed consent at the time of enrollment, and all procedures were approved by Institutional Review Boards at each participating center in the United States and Israel. Methodologic details of the epidemiologic and biomarker data collection have been reported elsewhere¹¹. The response rate for cases was 67.5% of all eligible patients in northern Israel, and the overall response rate for controls was 52.1%.

Genotyping was performed by chip hybridization using whole-genome amplified DNA. Snap-frozen tumor samples were also collected at the time of surgical resection. Transcript expression data were determined for known genes within 7.4 mB of rs10505477 using Affymetrix U133A, using methods as previously described^{12,13}.

Analytic methods included unconditional logistic regression to calculate odds ratios as implemented in R (version 2.4.1) and SAS (version 9.1). Results are reported for unmatched analysis for ease of interpretation and completeness, since matched and unmatched analyses did not differ substantively. All analyses were adjusted for age and gender, and analyses were also stratified by

Table 2 **Risk of colorectal cancer associated with variation in SNP rs10505477**

	Number of Cases	Number of Controls	Odds Ratio*	95% C.I.	p
Codominant					0.03
C/C	389	473	1.0		
C/T	936	932	1.23	1.04-1.44	
T/T	535	531	1.23	1.03-1.48	
Dominant					0.008
C/C	389	473	1.0		
C/T- T/T	1471	1463	1.23	1.05-1.43	

*Adjusted for age, gender and ethnicity. Genotype calls were equivocal for 1 case and 1 control, and these individuals were excluded from analyses.

ethnicity (Ashkenazi Jewish, Sephardi Jewish, non-Jewish) and family history, using reported history of colorectal cancer in any first degree relative as a binary variable. Kin-cohort analyses were performed using marginal maximum likelihood methods as implemented in the kin.cohort package in R (cran.r-project.org)¹⁴. Expression analysis assumed a dominant model and compared expression data in a linear model.

RESULTS

The distribution of demographic and clinical characteristics of cases and controls is given in Table 1. As specified by the study design, cases and controls were closely matched for age, gender, and Jewish vs. non-Jewish ethnicity, and the total sample size includes a small number of unmatched cases and unmatched controls to enhance power. A family history of CRC was reported more often among first degree relatives of cases than controls. Tumor location, tumor stage, and the proportion of microsatellite unstable tumors all reflect the population distribution of incident CRC in northern Israel.

We found evidence of an association between the T allele of rs10505477 and the risk of CRC (Table 2). Furthermore, the risk was stronger among those under the age of 50 (OR = 1.96, 95% CI 1.02–3.78) than in those 50 or older (OR = 1.2, 95% CI 1.03–1.4), although the multiplicative interaction did not reach statistical significance, $p = 0.15$. The risk did not vary substantially by strength of the family history, measured as a binary variable of family history of CRC in a first degree relative (p interaction = 0.57).

A second approach to quantify risk of putative susceptibility alleles is to take advantage of family history data and measure the cumulative incidence of cancers reported in relatives of carriers and non-carriers¹⁵. This kin-cohort method provides another indirect validation of the association, although typically this approach has limited power due to smaller number of events in the relatives and is vulnerable to misclassification of reported cancer by family history. Reported family histories of colorectal cancer in first degree relatives were analyzed by tabulating the cumulative age contributed by each relative to estimate the total person-years of risk, and counting the number of first degree relatives reported to have had CRC. Age was censored at time of diagnosis, so that relatives did not contribute additional person-years after diagnosis. Relatives were not interviewed, and cancer diagnoses were not confirmed in relatives. We identified 386 reported cases of colorectal cancer in 1,606,200 person-years of experience among first degree relatives of MECC cases and controls. Using the marginal likelihood method, we found that relatives of carriers were 3.2 times more

Table 3 **Cumulative risk of colorectal cancer in relatives of carriers and non-carriers**

Age	C/C Genotype		C/T + T/T Genotype			
	Cumulative Risk	95% C.I.	Cumulative Risk	95% C.I.	Cumulative Risk Ratio	95% C.I.
<40	0.000	0.000-0.001	0.001	0.000-0.001	-	
<50	0.000	0.000-0.004	0.003	0.002-0.004	13.2	0.59 - inf
<60	0.004	0.001-0.010	0.008	0.006-0.010	1.6	0.67 - 26.3
<70	0.014	0.004-0.024	0.019	0.016-0.023	1.4	0.72 - 5.01
<80	0.019	0.006-0.038	0.045	0.037-0.052	2.5	1.05 - 8.05

*Adjusted for age, gender and ethnicity.

likely to have CRC than non-carriers (95% bootstrap CI 1.16–17.8). Cumulative risks for carriers and non-carriers, as well as the age specific cumulative risk ratios are shown in Table 3.

The population of Israel is comprised of multiple ethnic groups, and to test the hypothesis that the relative risk and population attributable fraction were similar among Ashkenazi Jews, Sephardi Jews, and Arab/non-Jewish individuals we estimated stratum-specific odds ratios after adjustment for age and gender and looked for evidence of heterogeneity. The risk allele frequency was nearly identical in these three groups (0.51, 0.50 and 0.52, respectively). However, the relative risk was slightly lower among Ashkenazi Jews (OR = 1.13, 0.94–1.36), than among either Sephardi Jews (OR = 1.49, 1.04–2.14) or Arab/non-Jews (OR = 1.45, 95% CI 0.94–2.23). This translates into a higher population attributable fraction for Sephardi Jews (27.2%) or Arab/non-Jews (25.2%) than Ashkenazi Jews (8.9%), although these estimates are imprecise based on small numbers.

We then compared the clinical characteristics of the cancers arising in carriers of the risk allele to non-carriers, and the cancers were similar with respect to stage ($p = 0.88$), tumor location ($p = 0.64$), and survival ($p = 0.38$). After adjustment for age, stage, grade, gender, ethnicity, and microsatellite instability, the hazard ratio for survival of carriers of the risk allele was similar to non-carriers (hazard ratio = 1.09, 95% CI 0.89–1.32). The risk of cancer of the right colon, left colon, and rectum is given in Table 4.

Finally, we evaluated whether there were any detectable expression differences in the tumor expression of known genes within this region. *MYC* is located on 8q24, approximately 400 kb from rs10505477, and other genes in this region might also be reasonable candidate susceptibility genes, especially if a gene is differentially expressed in tumors corresponding with variation in a risk genotype. Using RNA derived from 133 snap-frozen tumors from cases, we tested probe-sets from the Affymetrix U133A chip corresponding to 15 genes within the chromosome 8 region between nucleotides 124,762,215–132,123,854. We found no significant differences in *MYC* expression within the tumor by genotype, with no significant

differences in any of the other genic probe-sets within this 8 Mb region (Table 5).

DISCUSSION

Genetic variation at rs10505477 is associated with risk of colorectal cancer, and this risk appears to be stronger among younger cases and controls. This is consistent with the younger age distinguishing many forms of familial predisposition to cancer^{16,17}. The present study is quite large and the 95% CI are narrow, offering some reassurance that these results did not arise by chance. However, validation of

association studies is critically important to reduce the possibilities of false positive findings and publication bias. We used a second, independent strategy to confirm our findings by taking advantage of the reported family histories of cancer in relatives of carriers and non-carriers. Our observation that relatives of carriers were 3.2 times more likely to have CRC than non-carriers (95% bootstrap CI 1.16–17.8) provides independent confirmation of the association within the same study.

The functional variant responsible for susceptibility to CRC within this region of 8q24 remains elusive. It seems likely that rs10505477 is in linkage disequilibrium with a regulatory element that modifies the expression or functional capacity of a nearby gene, although it is possible that the variation could have a regulatory influence anywhere in the genome via non-coding RNA. Our results also highlight the value of measuring risk in different well-characterized ethnic populations, similar to the recent recognition that the risk of prostate cancer associated with variation in 8q24 differs among ethnic groups⁷. Finally, these data support the hypothesis that common genetic variation accounts for a large fraction of common diseases like CRC, and that even small relative risks are important to understanding the distribution of disease in the population.

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Table 4 **Risk of colorectal cancer associated with variation in SNP rs10505477 by tumor location**

	Controls	Cases (Right)	Odds Ratio*	95% C.I.	Cases (Left)	Odds Ratio*	95% C.I.	Cases (Rectum)	Odds Ratio*	95% C.I.
Codominant										
C/C	473	133	1.0		131	1.0		90	1.0	
C/T	932	339	1.31	1.04-1.65	304	1.18	0.93-1.49	219	1.23	0.94-1.61
T/T	531	197	1.33	1.03-1.71	171	1.17	0.90-1.51	120	1.19	0.88-1.61

*Adjusted for age, gender and ethnicity.

Table 5 **Expression analysis of probe sets in 8q24 near rs10505477 (aligns at 128476625) by genotype, comparing carriers of T-allele to C/C homozygotes.**

Gene	Probe*	rs10505477		Mean difference	Std.Error	P value	Alignment	Gene Title
		C/C Mean	C/T-T/T mean					
ANXA13	208323_s_at	1446.2	1314.5	-131.8	85.3	0.125	chr8:124762215-124818823	annexin A13
TRMT12	219299_at	5542.3	4941.2	-601.1	523.0	0.252	chr8:125532242-125534271	tRNA methyltransferase 12 homolog (S. cerevisiae)
RNF139	209510_at	8322.8	8904.4	581.6	1063.0	0.585	chr8:125556294-125569320	ring finger protein 139
MTSS1	203036_s_at	96.3	116.9	20.6	28.2	0.467	chr8:125632211-125641508	metastasis suppressor 1
MTSS1	203037_s_at	1760.6	1407.5	-353.1	211.0	0.097	chr8:125632211-125641508	
MTSS1	210359_at	79.8	83.1	3.2	11.0	0.769	chr8:125637710-125649927	
MTSS1	210360_s_at	634.7	734.7	100.0	218.5	0.648	chr8:125637710-125649927	
SQLE	213562_s_at	4218.3	3935.2	-283.1	399.7	0.480	chr8:126079935-126090658	squalene epoxidase
SQLE	213577_at	1812.4	1603.2	-209.2	100.1	0.039	chr8:126079935-126090658	
SQLE	209218_at	246.1	256.2	10.2	17.7	0.567	chr8:126080671-126103688	
KIAA0196	201985_at	138.5	153.4	14.9	11.8	0.208	chr8:126105690-126173187	KIAA0196
C8orf36	215475_at	364.2	355.3	-8.9	47.4	0.851	chr8:126335690-126337337	Chromosome 8 open reading frame 36
C8orf36	215474_at	2567.3	2536	-31.3	272.6	0.909	chr8:126335690-126337337	
TRIB1	202241_at	173	181.6	8.6	28.0	0.760	chr8:126512053-126519825	tribbles homolog 1 (Drosophila)
MYC	202431_s_at	19.9	29.9	10.0	13.3	0.451	chr8:128817511-128822629	v-myc myelocytomatosis viral oncogene homolog (avian)
PVT1	216249_at	65.8	64.6	-1.2	9.4	0.895	chr8:128875985-129021884	Pvt1 oncogene homolog, MYC activator (mouse)
PVT1	216240_at	86.5	98	11.5	13.2	0.386	chr8:128875985-129021884	
PVT1	222087_at	132.2	152.8	20.6	14.0	0.145	chr8:129077464-129078081	
FAM49B	217916_s_at	115.1	120.2	5.1	13.7	0.711	chr8:130922899-131098100	family with sequence similarity 49, member B
FAM49B	217535_at	27.2	23	-4.1	8.2	0.618	chr8:131051861-131052461	
FAM49B	217534_at	148.8	196.9	48.2	41.6	0.249	chr8:131051865-131052461	
DDEF1	221039_s_at	26	34.3	8.3	7.9	0.294	chr8:131134853-131135282	development and differentiation enhancing factor 1
SCC-112	215435_at	2228.3	2154.3	-74.0	209.4	0.724	chr8:131224839-131226981	SCC-112 protein
DDEF1IT1	220694_at	850.8	897.2	46.5	79.4	0.560	chr8:131376782-131377961	DDEF1 intronic transcript 1
DDEF1	216805_at	302.4	321	18.6	44.5	0.676	chr8:131485151-131486958	Development and differentiation enhancing factor 1
DDEF1	216416_at	317.4	319	1.6	40.1	0.967	chr8:131485151-131486958	
ADCY8	206811_at	320.1	319.9	-0.2	52.3	0.997	chr8:131595775-132123854	adenylate cyclase 8 (brain)

*Probes from Affymetrix U133A chip

References

- Alitalo K, Schwab M, Lin CC, Varmus HE, Bishop JM. Homogeneously staining chromosomal regions contain amplified copies of an abundantly expressed cellular oncogene (c-myc) in malignant neuroendocrine cells from a human colon carcinoma. *Proc Natl Acad Sci USA* 1983; 80:1707-11.
- Killian A, Sarafan-Vasseur N, Sesboue R, Le Pessot F, Blanchard F, Lamy A, Laurent M, Flaman JM, Frebourg T. Contribution of the BOP1 gene, located on 8q24, to colorectal tumorigenesis. *Genes Chromosomes Cancer* 2006; 45:874-81.
- Killian A, Di Fiore F, Le Pessot F, Blanchard F, Lamy A, Raux G, Flaman JM, Paillor B, Michel P, Sabourin JC, Tuech JJ, Michot F, Kerckaert JP, Sesboue R, Frebourg T. A simple method for the routine detection of somatic quantitative genetic alterations in colorectal cancer. *Gastroenterology* 2007; 132:645-53.
- Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, Penney K, Steen RG, Ardlie K, John EM, Oakley-Girvan I, Whittemore AS, Cooney KA, Ingles SA, Altschuler D, Henderson BE, Reich D. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. *Proc Natl Acad Sci USA* 2006; 103:14068-73.
- Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsson KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Balter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. A common variant associated with prostate cancer in European and African populations. *Nat Genet* 2006; 38:652-8.

6. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Xu J, Blondal T, Kostic J, Sun J, Ghosh S, Stacey SN, Mouy M, Saemundsdottir J, Backman VM, Kristjansson K, Tres A, Partin AW, Albers-Akkers MT, Godino-Ivan Marcos J, Walsh PC, Swinkels DW, Navarrete S, Isaacs SD, Aben KK, Graif T, Cashy J, Ruiz-Echarri M, Wiley KE, Suarez BK, Witjes JA, Frigge M, Ober C, Jonsson E, Einarsson GV, Mayordomo JI, Kiemeny LA, Isaacs WB, Catalona WJ, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet* 2007; 39:631-7.
7. Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, Greenway SC, Stram DO, Le Marchand L, Kolonel LN, Frasco M, Wong D, Pooler LC, Ardlie K, Oakley-Girvan I, Whittemore AS, Cooney KA, John EM, Ingles SA, Altshuler D, Henderson BE, Reich D. Multiple regions within 8q24 independently affect risk for prostate cancer. *Nat Genet* 2007; 39:638-44.
8. Schumacher FR, Feigelson HS, Cox DG, Haiman CA, Albanes D, Buring J, Calle EE, Chanock SJ, Colditz GA, Diver WR, Dunning AM, Freedman ML, Gaziano JM, Giovannucci E, Hankinson SE, Hayes RB, Henderson BE, Hoover RN, Kaaks R, Key T, Kolonel LN, Kraft P, Le Marchand L, Ma J, Pike MC, Riboli E, Stampfer MJ, Stram DO, Thomas G, Thun MJ, Travis R, Virtamo J, Andriole G, Gelmann E, Willett WC, Hunter DJ. A common 8q24 variant in prostate and breast cancer from a large nested case-control study. *Cancer Res* 2007; 67:2951-6.
9. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF, Jr., Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet* 2007; 39:645-9.
10. Niell BL, Long JC, Rennert G, Gruber SB. Genetic anthropology of the colorectal cancer-susceptibility allele APC I1307K: evidence of genetic drift within the Ashkenazim. *Am J Hum Genet* 2003; 73:1250-60.
11. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, Low M, Greenson JK, Rennert G. Statins and the risk of colorectal cancer. *N Engl J Med* 2005; 352:2184-92.
12. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JM, Lee N, Misek DE, Greenson JK, Kardia SL, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon, and ovarian adenocarcinomas using gene expression profiles. *AmJPathol* 2001; 159:1231-8.
13. Rozek LS, Lipkin SM, Fearon ER, Hanash S, Giordano TJ, Greenson JK, Kuick R, Misek DE, Taylor JM, Douglas JA, Rennert G, Gruber SB. CDX2 polymorphisms, RNA expression, and risk of colorectal cancer. *Cancer Res* 2005; 65:5488-92.
14. Chatterjee N, Wacholder S. A marginal likelihood approach for estimating penetrance from kin-cohort designs. *Biometrics* 2001; 57:245-52.
15. Poynter JN, Cooney KA, Bonner JD, White KA, Tomsho LP, Rennert G, Gruber SB. APC I1307K and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15:468-73.
16. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences of the United States of America* 1971; 68:820-3.
17. Claus EB, Risch NJ, Thompson WD. Using age of onset to distinguish between subforms of breast cancer. *Ann Hum Genet* 1990; 54:169-77.