Short Communication

Death Receptor 4 Variants and Colorectal Cancer Risk

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Abstract

The tumor necrosis factor–related apoptosis-inducing ligand receptor modulates apoptotic response by binding to the proapoptotic death receptor 4 (DR4). Perturbed apoptosis due to missense alterations in the candidate tumor suppressor gene *DR4* leads to deregulated cell proliferation and cancer predisposition. Recent studies have discussed the association of DR4 variants with cancer risk. We evaluated, for the first time, the role of the Thr^{209}Arg (626C>G) and Glu^{228}Ala (683A>C) polymorphisms on colorectal cancer risk by genotyping 659 incident cases and 607 healthy controls drawn from the German population-based Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study. Whereas DR4 Glu^{228}Ala was not associated with colorectal cancer, Thr^{209}Arg heterozygotes were at a significantly decreased colorectal cancer risk [odds ratio (OR), 0.73; 95% confidence interval (95% CI), 0.54-0.97]. Stratification according to sex and age exhibited a significant association of Thr^{209}Arg with a decreased risk for male heterozygotes (OR, 0.68; 95% CI, 0.46-0.99) and for Arg^{209} carriers ≥65 years of age (OR, 0.65; 95% CI, 0.46-0.92) as well as an enhanced risk for female Ala^{228} carriers in a allele dose-dependent manner (P_{trend} = 0.01). Subsite analysis revealed a protective effect of Thr^{209}Arg for rectal cancer risk (OR, 0.67; 95% CI, 0.48-0.95) and a significant risk increase for Ala^{228} carriers with advanced colorectal cancer stages (P_{trend} = 0.04). Haplotype analysis revealed a 2.4-fold risk for carriers of the rare 626C-683C haplotype (1% prevalence in the general population; OR, 2.37; 95% CI, 0.98-5.76). The score statistic yielded an empirical *P* of 0.03 of the haplotype-specific test for 626C-683C based on 20,000 simulations, suggesting that *DR4* 626C-683C may affect colorectal cancer predisposition. (Cancer Epidemiol Biomarkers Prev 2006;15(10):2002–5)

Introduction

Apoptosis or programmed cell destruction is a key regulator of tissue homeostasis. An imbalance between cell death and proliferation may result in tumor formation. The tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) activates the extrinsic apoptotic pathway through the engagement of the proapoptotic death receptor 4 (DR4, TNFRSF10A, TRAILR-1), a member of the tumor necrosis factor receptor superfamily. DR4 consists of two extracellular cysteine-rich, ligand-binding pseudorepeats (50s and 90s loops), one single transmembrane helix as well as the apoptosis-triggering cytoplasmic death domain. Suppression of cell death signaling due to detrimental alterations in *DR4* involves a deregulated cell proliferation and predisposes to cancer (1-6).

Immunohistochemical studies have shown extensive expression of *DR4* both in sporadic and hereditary colorectal neoplasms together with a higher degree of apoptosis, suggesting neoplastic colorectal cells to be prone to TRAIL-induced apoptosis (5, 6). Moreover, Drosopoulos et al. (7) have reported the induction of cell death in human colon adenocarcinoma cells in a mitogen-activated protein kinase/extracellular signal-regulated kinase kinase–dependent manner by TRAIL. Mutations in *DR4*, mapping to chromosome 8p21-22, have been described in several human cancers, such as breast, lung, head and neck cancer, and non-Hodgkin's lymphoma (8-10), but have not yet been studied in colorectal cancer. However, frequent loss of heterozygosity on chromosome 8p21-23 has been observed in hepatocellular carcinoma as well as in colorectal cancer, pointing to *DR4* as a candidate tumor suppressor gene for both cancers (11).

Recently, we have investigated the effects of DR4 Thr^{209}Arg (626C>G) and Glu^{228}Ala (683A>C) on familial breast cancer risk (12). Although neither variant showed significance regarding disease risk, the analysis of the rare haplotype 626C-683C resulted in an increased risk of breast cancer (12).

Given these findings, we estimated the colorectal cancer risk associated with the DR4 Thr^{209}Arg and Glu^{228}Ala variants in a German population-based case-control study.

Materials and Methods

Study Population. Colorectal cancer cases and controls were drawn from the German Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study, a large population-based case-control study carried out in the Rhine-Neckar-Odenwald region in the southwest of Germany (13). The cases consisted of 659 unrelated male and female subjects (33-91 years of age; median 68) with incident invasive colorectal cancer diagnosed between January 2003 and March 2005. The median time between diagnosis and ascertainment of the cases was 14 days. Detailed information is given in Table 1. The control group comprised 607 unrelated male and female individuals (34-94 years of age; median 67). None of

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Table 1. Characteristics of the German Darmkrebs: Chancen der Verhütung durch Screening (DACHS) study population

	Cases, n = 659 (%)	Controls, n = 607 (%)
Sex		
Male	385 (58.4)	345 (56.8)
Female	274 (41.6)	262 (43.2)
Age (y)		
33-54	65 (9.9)	68 (11.2)
55-64	167 (25.3)	175 (28.8)
65-74	240 (36.4)	230 (37.9)
75-94	187 (28.4)	134 (22.1)
First-degree family history of colorectal cancer*		
No	522 (79.2)	485 (79.9)
Yes	85 (12.9)	68 (11.2)
Unknown	50 (7.6)	54 (8.9)
Cancer localization*		
Colon	410 (62.2)	—
Rectum	247 (37.5)	—
International Union Against Cancer stage at diagnosis†		
I	143 (21.7)	—
II	214 (32.5)	—
III	185 (28.1)	—
IV	114 (17.3)	—
Time between diagnosis and ascertainment of cases‡		
≤6 mo	541 (83.4)	—
>6 mo to ≤1 y	69 (10.6)	—
>1 y	39 (6.0)	—

NOTE: Percentages may not add up to 100% due to missing data.
*Data missing for two cases.
†Data missing for three cases.
‡Data missing for 10 cases.

the controls had a personal history of colorectal cancer. They were randomly selected from lists of population registries and frequency-matched to cases by 5-year age groups, sex, and county of residence. Cases and controls were eligible if they were aged 30 years and above, German-speaking, and mentally and physically capable of participating in an in-person interview of about 1 hour. A detailed description of the study population is given in Table 1. The study was approved by the Ethics Committees of the University of Heidelberg and the State Medical Boards of Baden-Wuerttemberg and Rhineland-Palatinate (Germany).

Data Collection. Details of the data collection procedures are reported elsewhere (13-15). In brief, study subjects were asked to participate in an in-person interview and to give a blood sample or a mouthwash when blood samples were not available. Information on demographic factors, anthropometric measures, medical history, including medication and screening, family history of colorectal cancer, reproductive history, and lifestyle factors were collected by trained interviewers using a standardized questionnaire.

Single Nucleotide Polymorphism Selection. Based on our previous results for familial breast cancer (12), we selected and analyzed the effects of DR4 $Thr^{209}Arg$ (rs4871857) and $Glu^{228}Ala$ (rs17088993) on colorectal cancer risk. In the single nucleotide polymorphism database, there are five additional coding single nucleotide polymorphisms in DR4: $Thr^{33}Ile$ (rs20577), $Pro^{105}Arg$ (rs11986840), $His^{141}Arg$ (rs6557634), $Asn^{297}His$ (rs17088980), and $Arg^{441}Lys$ (rs2230229). To validate these variants, we sequenced 20 randomly selected breast cancer DNA samples (12). DR4 $His^{141}Arg$ was not analyzed because, according to Fisher et al. (9), it segregated together with $Thr^{209}Arg$ in 96% of their samples (n = 243). None of the investigated variants, except for DR4 $Arg^{441}Lys$, could be confirmed. The rare $Arg^{441}Lys$ was shown not to segregate with the high-risk haplotype 626C-683C and therefore not expected to be disease-causing.

Detection of DR4 $Thr^{209}Arg$ and $Glu^{228}Ala$ Genotypes. Blinded genotyping was done by TaqMan allelic discrimination. TaqMan primers and probes were provided by the Assay-by-Design service (Applied Biosystems, Foster City, CA) and designed based on the Genbank NT_023666 sequence. Sequences of primers and probes were as follows: $Thr^{209}Arg$, GGTGGTGAGGAAAGGTCAAG (forward) and ATGGGGTCAGGGCTGATAG (reverse), VIC-TCTCACCCT-GTGCTGC, and FAM-TCTCACCCTCTGCTGC; $Glu^{228}Ala$, CCCCTGCAGATACGAGGAG (forward) and caggaaaagacag-gagtctcg (reverse), VIC-TGACATCGAGTGTGTCC, and FAM-CATCGCGTGTGTCC. Detailed information about sequencing and TaqMan allelic discrimination methods have been described previously (12, 16). To ensure accuracy and to exclude genotyping error, ≥10% of samples were re-genotyped. The duplicates showed a concordance rate of 100%.

Statistics. Genotype-specific odds ratios (OR), 95% asymptotic confidence intervals (95% CI), and Ps were computed by unconditional logistic regression using a tool offered by the Institute of Human Genetics, Technical University Munich (Munich, Germany).[7] Hardy-Weinberg equilibrium test was undertaken using Pearson's goodness-of-fit χ^2 test with 1 degree of freedom.

Adjustment for sex and age and the two-sided Cochran-Armitage test for trend were done using the Statistical Analysis System software (version 9.1; SAS Institute, Inc., Cary, NC). The Cochran-Armitage statistic was used to test for trend in genetic ORs with increasing stage. We used the software package haplo.stats to test for association of indirectly deduced haplotypes (17, 18). It does the joint modeling of observed multipoint single nucleotide polymorphism genotype and phenotype, using a generalized linear model framework to test for haplotype-trait association and to calculate ORs and 95% CIs. The most common haplotype was chosen as the reference group. To account for the uncertainty of the haplotype estimation, each haplotype pair, consistent with the genotype of an individual and weighted by its estimated probability, is used to model the individual's phenotype. To support our findings, we derived empirical Ps for haplotype-trait association under an additive model, using the score statistic implemented in haplo.score, based on 20,000 simulations.

Results and Discussion

Genotype frequencies for both polymorphisms analyzed were in agreement with Hardy-Weinberg expectations in controls (P = 0.48 for $Thr^{209}Arg$ and P = 0.55 for $Glu^{228}Ala$, respectively). Although there were no significant differences in genotype frequencies between colorectal cancer cases and controls for DR4 $Glu^{228}Ala$ (683A>C; OR, 1.19; 95% CI, 0.94-1.50; Table 2), heterozygous carriers of DR4 $Thr^{209}Arg$ (626C>G) showed a significant association with a decreased colorectal cancer risk (OR, 0.73; 95% CI, 0.54-0.97; Table 2). The risk, however, did not decrease with the number of variant alleles, which may point to a finding by chance. Adjustment for sex and age made no relevant difference to the findings. The allele frequencies for both single nucleotide polymorphisms among cases and controls were consistent with the allele frequencies reported in Caucasian populations (9, 12). Stratification by sex and age revealed a significant association of DR4 $Thr^{209}Arg$ with a decreased colorectal cancer risk for male heterozygotes (OR, 0.68; 95% CI, 0.46-0.99; Table 2). Because the association was independent of allele dosis (Table 2), it may be a chance finding. DR4 $Glu^{228}Ala$ showed

[7] http://ihg.gsf.de/cgi-bin/hw/hwa1.pl.

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Table 2. Genotype frequencies of DR4 Thr^{209}Arg (626C>G) and Glu^{228}Ala (683A>C) in colorectal cancer patients and controls (stratified by sex and age), OR with 95% CIs and respective *P*s

DR4 Thr^{209}Arg (626C>G)	All, *n* (%)		Male, *n* (%)		Female, *n* (%)		Age <65 y, *n* (%)		Age ≥65 y, *n* (%)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
CC	156 (24.0)	118 (20.2)	93 (24.4)	65 (19.6)	63 (23.4)	53 (21.1)	43 (18.7)	50 (21.6)	113 (26.9)	68 (19.4)
CG	286 (44.0)	298 (51.1)	166 (43.6)	172 (51.8)	120 (44.6)	126 (50.2)	111 (48.3)	120 (51.7)	175 (41.7)	178 (50.7)
GG	208 (32.0)	167 (28.6)	122 (32.0)	95 (28.6)	86 (32.0)	72 (28.7)	76 (33.0)	62 (26.7)	132 (31.4)	105 (29.9)
OR (95% CI), *P* [CG] vs. [CC]	0.73 (0.54-0.97), 0.03		0.68 (0.46-0.99), 0.04		0.80 (0.52-1.25), 0.33		1.08 (0.66-1.74), 0.77		0.59 (0.41-0.85), 0.005	
OR (95% CI), *P* [GG] vs. [CC]	0.94 (0.69-1.29), 0.71		0.90 (0.59-1.36), 0.61		1.01 (0.62-1.63), 0.98		1.43 (0.84-2.42), 0.19		0.76 (0.51-1.12), 0.17	
OR (95% CI), *P* [GG+CG] vs. [CC]	0.80 (0.61-1.05), 0.11		0.75 (0.53-1.08), 0.12		0.88 (0.58-1.32), 0.53		1.20 (0.76-1.89), 0.44		0.65 (0.46-0.92), 0.01	
DR4 Glu^{228}Ala (683A>C)										
AA	399 (62.0)	384 (65.9)	240 (63.5)	207 (62.7)	159 (59.8)	177 (70.0)	138 (61.1)	158 (67.8)	261 (62.4)	226 (64.6)
AC	216 (33.5)	181 (31.0)	123 (32.5)	113 (34.2)	93 (35.0)	68 (26.9)	82 (36.3)	70 (30.0)	134 (32.1)	111 (31.7)
CC	29 (4.5)	18 (3.1)	15 (4.0)	10 (3.0)	14 (5.3)	8 (3.2)	6 (2.7)	5 (2.1)	23 (5.5)	13 (3.7)
OR (95% CI), *P* [AC] vs. [AA]	1.15 (0.90-1.46), 0.26		0.94 (0.69-1.29), 0.70		1.52 (1.04-2.22), 0.03		1.34 (0.91-1.99), 0.14		1.05 (0.77-1.42), 0.78	
OR (95% CI), *P* [CC] vs. [AA]	1.55 (0.85-2.84), 0.15		1.29 (0.57-2.94), 0.54		1.95 (0.80-4.77), 0.14		1.37 (0.41-4.60), 0.61		1.53 (0.76-3.09), 0.23	
OR (95% CI), *P* [CC+AC] vs. [AA]	1.19 (0.94-1.50), 0.15		0.97 (0.71-1.31), 0.83		1.57 (1.09-2.26), 0.02		1.34 (0.92-1.97), 0.13		1.10 (0.82-1.47), 0.54	

an increased colorectal cancer risk for females in an allele dose-dependent manner (OR, 1.52; 95% CI, 1.04-2.22 and OR, 1.95; 95% CI, 0.80-4.77; $P_{trend} = 0.01$; Table 2) as well as a decreased risk for Arg^{209} carriers ≥65 years (OR, 0.65; 95% CI, 0.46-0.92; Table 2), the equivalent of an increased risk for homozygote carriers of the common C allele (Thr^{209}). Analysis by subsite showed the same effect on rectal cancer risk (OR, 0.67; 95% CI, 0.48-0.95; Table 3). Moreover, the risk associated with the DR4 Glu^{228}Ala variant increased with advanced colorectal cancer stages, revealing a significant risk for Ala^{228} carriers (OR, 1.40; 95% CI, 1.04-1.86; $P_{trend} = 0.04$; Table 3), which may be a sign of a greater tumor aggressiveness in Ala^{228} (683C) carriers.

When analyzing haplotypes, the results from logistic regression pointed to a haplotype effect (global $P = 0.07$). The combination of DR4 Thr^{209}Arg and Glu^{228}Ala led to four distinct haplotypes (Table 4). In the generalized linear model framework, 626C-683A, 626G-683A, and 626G-683C haplotypes showed no association with colorectal cancer. The rare haplotype 626C-683C was found to be more common in cases than in controls, resulting in an increased colorectal cancer risk (OR, 2.37; 95% CI, 0.98-5.76; $P = 0.06$; Table 4). The score statistic yielded a significant empirical P of 0.03, based on 20,000 simulations, for 626C-683C. The identification of the 626C-683C haplotype as risk factor for colorectal cancer is in line with our recently published findings on familial breast cancer risk (626C-683C: OR, 3.52; ref. 12). Because both DR4 Thr^{209}Arg and Glu^{228}Ala reside next to the DR4 TRAIL-binding ectodomain, the observed association may be due either to the joint effects of Thr^{209} and Ala^{228} by altering ligand-binding and thus apoptotic signaling or to an unknown causative variant in strong linkage disequilibrium with the haplotype.

In summary, we detected a significant association of the DR4 Thr^{209}Arg variant with a decreased colorectal cancer risk

Table 3. Genotype frequencies of DR4 Thr^{209}Arg (626C>G) and Glu^{228}Ala (683A>C) in colorectal cancer cases and controls, ORs with 95% CIs and respective *P*s

DR4 Thr^{209}Arg (626C>G)	Cases, *n* (%)						Controls, *n* (%)
	FDFH	Colon	Rectum	Stage I	Stage II	Stages III + IV	
CC	21 (25.3)	88 (21.6)	66 (27.4)	31 (22.1)	46 (21.8)	77 (26.0)	118 (20.2)
CG	33 (39.8)	186 (45.7)	100 (41.5)	61 (43.6)	97 (46.0)	127 (42.9)	298 (51.1)
GG	29 (34.9)	133 (32.7)	75 (31.1)	48 (34.3)	68 (32.2)	92 (31.1)	167 (28.6)
OR (95% CI), *P* [GG+CG] vs. [CC]	0.75 (0.44-1.28), 0.29	0.92 (0.67-1.26), 0.60	0.67 (0.48-0.95), 0.03	0.89 (0.57-1.40), 0.62	0.91 (0.62-1.34), 0.63	0.72 (0.52-1.00), 0.05 $P_{trend,\ stages} = 0.30$	
DR4 Glu^{228}Ala (683A>C)							
AA	53 (63.1)	244 (61.0)	154 (63.6)	97 (68.3)	131 (63.0)	169 (58.1)	384 (65.9)
AC	26 (31.0)	137 (34.3)	78 (32.2)	42 (29.6)	66 (31.7)	107 (36.8)	181 (31.0)
CC	5 (6.0)	19 (4.8)	10 (4.1)	3 (2.1)	11 (5.3)	15 (5.2)	18 (3.1)
OR (95% CI), *P* [CC+AC] vs. [AA]	1.13 (0.70-1.82), 0.62	1.23 (0.95-1.61), 0.12	1.10 (0.81-1.51), 0.54	0.90 (0.60-1.33), 0.58	1.13 (0.82-1.58), 0.45	1.40 (1.04-1.86), 0.02 $P_{trend,\ stages} = 0.04$	

NOTE: Patients were subdivided into cases with a first-degree family history of colorectal cancer, into cases with colon or rectum cancer and according to International Union Against Cancer stage at diagnosis (I-IV). Stages III and IV were combined because they represent an advanced disease.
Abbreviation: FDFH, first-degree family history.

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Table 4. Haplotype distributions and frequencies of DR4 Thr^{209}Arg (626C>G) and Glu^{228}Ala (683A>C) in patients with colorectal cancer and control individuals

Haplotype 62 6C/G-683A/C	Pooled N (%)	Cases N (%)	Controls N (%)	OR (95% CI)	*P*
626C-683A	1069 (44.1)	557 (43.7)	513 (44.6)	1 (–)	–
626C-683C	41 (1.7)	28 (2.2)	12 (1.0)	2.37 (0.98 – 5.76)	0.06
626G-683A	870 (35.9)	445 (34.9)	426 (37.0)	0.97 (0.80 – 1.16)	0.70
626G-683C	444 (18.3)	245 (19.2)	200 (17.4)	1.13 (0.91 – 1.41)	0.27

NOTE: Population haplotype frequencies were estimated using the expectation-maximization algorithm implemented in haplo.stats. The counts (*n*) were based on the haplotype frequencies. ORs, 95% CIs, and *P*s were estimated using an additive model for the haplotype effects by the algorithm haplo.glm implemented in the software package haplo.stats. The most common haplotype 626C-683A was used as reference group. Twenty-two cases and 32 controls were removed from haplotype analysis due to missing genotypes.

for heterozygotes and Arg^{209} carriers ≥65 years of age. Female Ala^{228} variant carriers exhibited a significantly enhanced risk dependent on allele dose. Subsite analysis revealed a protective effect of Arg^{209} on rectal cancer risk as well as an increased risk for advanced colorectal cancer stages. In addition, the DR4 626C-683C haplotype conferred a 2.4-fold colorectal cancer risk, suggesting its relevance in human cancer.

Our results on DR4 variants and colorectal cancer risk are explorative. Given the modest stratum-specific *P*s for association, they may be artifacts due to multiple testing and need confirmation in larger studies.

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