RESEARCH COMMUNICATION

Relation of the CD36 Gene A52C Polymorphism to the Risk of Colorectal Cancer Among Japanese, with Reference to with the Aldehyde Dehydrogenase 2 Gene Glu487Lys Polymorphism and Drinking Habit

Kiyonori Kuriki[1*], Nobuyuki Hamajima[2], Hitoshi Chiba[3], Yukihide Kanemitsu[4], Takashi Hirai[4], Tomoyuki Kato[4], Toshiko Saito[1], Keitaro Matsuo[1], Koichi Koike[5], Shinkan Tokudome[6], Kazuo Tajima[1]

Abstract

High consumption of white meat (or saturated fatty acids) and alcohol has been demonstrated to have a tendency to increase the risk of colorectal cancer, according to the level of malondialdehyde-deoxyguanosine adducts derived from lipid per-oxidation in the colorectal mucosa. CD36 plays important roles as a long-chain fatty acid translocase and oxidized low-density lipoprotein (LDL) scavenger, while alcohol is metabolized by aldehyde dehydrogenase 2 (ALDH2) and decreases transiently metabolism of dietary fat and serum lipids. To examine associations between the risk of colorectal cancer and the CD36 gene A52C polymorphism according to the ALDH2 gene Glu487Lys polymorphism and drinking habit, a hospital-based case-control study was conducted with 128 colorectal cancer cases and 238 cancer-free controls. Odds ratios (ORs) for the C/C genotype relative to the A/A genotype were 1.70 [95% confidence interval (CI), 0.76-4.11] and 4.24 (95% CI, 1.42-22.66) for men and women, respectively, with the low-activity (Glu/Lys + Lys/Lys) ALDH2 genotype. The high-activity (Glu/Glu) genotype for men and women had no associations. On the other hand, the OR for the C/C genotype with high frequency of drinking habit relative to the A/A genotype with low frequency of drinking habit among men was 3.63 (95% CI, 1.29-13.15). The number of women with a high frequency drinking habit was too small for any corresponding analyses. Our findings suggest a significant interaction between alcohol consumption and the CD36 gene A52C polymorphism related to the metabolism of long-chain fatty acids and oxidized LDL in the etiology of colorectal cancer.

Key Words: Colorectal cancer - CD36 - Oxidized low-density lipoprotein - Aldehyde dehydrogenase 2 - Drinking habit

Asian Pacific J Cancer Prev, **6**, 62-68

Introduction

The incidence and mortality rates of colorectal cancer among Japanese in Japan (J-Japanese) have been rapidly increasing with increment in fat and alcohol consumption, like those among Japanese immigrants to the United States (US-Japanese) (Tominaga, 1985; Tominaga and Kato, 1992; Ogimoto et al., 2000). Today, the incidence rate of colorectal cancer is the same or rather higher among US-Japanese than among US-Whites (Flood et al., 2000; Parkin et al., 2002). Ecological studies have exhibited a positive association between dietary fat intake and the incidence rate of colorectal cancer, and dietary fat intake was estimated as follows; 40-50g (20-25% for energy) for J-Japanese, 70-80g (30-35%) for US-Japanese and 80-90g (35-40%) for US-Whites, respectively (Tokudome, 1996; 2000; Le Marchand, 1999;). On the other hand, many case-control and cohort studies have frequently, but inconsistently, demonstrated positive

[1]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Japan. [2]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Japan [3]Department of Laboratory Medicine, Hokkaido University School of Medicine, Japan [4]Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Japan. [5]Division of Clinical Laboratories, Aichi Cancer Center Hospital, Japan ; [6]Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Japan

**Correspondence to: Kiyonori Kuriki, PhD. Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681 Japan. Phone: +81-52-762-6111; Fax: +81-52-763-5233; E-mail: kkuriki@aichi-cc.jp.*

associations between dietary fat intake and the risk of colorectal cancer (WCRF/AICR, 1997). However, the associations often disappeared when attempts were made to disentangle the effects of fat from those of calories (Potter, 1996).

CD36 plays important roles as a long-chain fatty acid translocase and oxidized low-density lipoprotein (LDL) scavenger, and gene polymorphisms have been predicted to be linked to modulation of CD36 expression and an abundance of transcription-binding sites (Greenwalt et al., 1992; Abumrad et al., 1993; Endmann et al., 1993; Fernandez-Ruiz et al., 1993). The frequency of CD36 deficiency appears to be much higher among J-Japanese (3-11%) than among US-Whites (0.3%) (Yamamoto et al, 1991; Greenwalt et al., 1992). The present authors have demonstrated that moderate-high consumption of meat as one of foods rich in animal fat/saturated fatty acids (SFAs) has a significant positive interaction with the C/C genotype of the CD36 gene A52C polymorphism for the risk of colorectal cancer (Kuriki et al, in press).

Metabolism of dietary fat and serum lipids is transiently decreased while alcohol is metabolized (Lieber, 1988). Recently, high levels of malondialdehyde-deoxyguanosine in colorectal mucosa have demonstrated a positive link with lipid peroxidation through metabolism for high consumption of white meat/SFA and alcohol, and had a trend to increase the risk of colorectal adenoma (Leuratti et al., 2002). Especially for men, a heavy drinking habit has been reported to increase risks for rectal cancer and colorectal adenomatous polyps among J- and US-Japanese (Kono et al., 1970; Pollack et al., 1984; Stemmermann et al., 1988; Hirayama, 1989). Alcohol consumption and the activity of metabolic enzymes among both J- and US-Japanese are much lower than those among US-Whites, because Asian people have higher frequencies (20-50%) with regard to the Lys (low-activity) allele of the aldehyde dehydrogenase 2 (ALDH2) gene Glu487Lys polymorphism (Goedde, et al., 1979; Yoshida et al., 1984).

We are interested in interactions between colorectal cancer, drinking habit and the gene polymorphisms of CD36 and ALDH2 among Japanese, and our consideration has led to alternative theories for risks of colorectal cancer as follows; 1) for men and women with high-activity and low-activity genotypes, respectively, of the Glu487Lys polymorphism of ALDH2, the A52 polymorphism can not be expected to demonstrate associations with the risk of colorectal cancer; 2) for men, the combination of high frequency of drinking habit and the A52C polymorphism would be expected to have a positive association, whereas, for women, the risk might be unable to be estimated or would be unlikely to have any associations given the low munbers of individuals with a pronounced drinking habit. In the present case-control study we therefore explored whether gene-gene and gene-environmental interactions with the A52C polymorphism might increase the risk of colorectal cancer, with especial reference to the Glu487Lys polymorphism and the drinking habit.

Subjects and Methods

Study Subjects

The case-control study was conducted as a part of series in a major project on genetic polymorphisms and cancer risk in Aichi Cancer Center (Tajima et al., 2000; Hamajima et al., 2001a). We recruited the subjects from patients aged 40-79 years old who visited the outpatient services at Aichi Cancer Center Hospital between March 1999 and July 2000, and who were excluded to have host-related factors such as familial adenomatous polyposis, as described elsewhere (Hamajima et al, 2001b; Kuriki et al, in press). In brief, 74 male and 54 female cases comprised incident (within 1 year before the study) and prevalent cases which had been histopatholosical diagnosed as having colon and rectal cancer. The incident cases accounted for 49.6%. Totals of 116 male and 122 female controls were confirmed to be cancer free, but most of them had some gastrointestinal disorders. All subjects were Japanese, and lived in Tokai area including Aichi prefecture, in the central region of Japan. They were provided with an explanatory document and all gave their written informed consent for participation in this study. We then collected information on lifestyle and medical histories from self-administrated questionnaires, and performed 7ml blood sampling from a peripheral vein. This study was approved by the Ethics Committee of the Aichi Cancer Center.

Lifestyle Assessment

For the drinking habit regarding the frequency, subjects were divided into three groups, i.e., less than once a week "low", one to four times/week "moderate", and five or more times/week "high". For habitual exercise, which was other than work for more than 15 min, subjects were classified into three groups, i.e., less than once a week, one to two times/week, and three or more times/week. For smoking status, subjects were classified into current, former, and never-smokers. We defined former smokers as those who quit smoking more than 2 years before the questionnaire study. Regarding dietary habits, the frequency for five food items (whole meat, fish, raw vegetables, fruits and tofu), three beverages (Japanese tea, coffee and milk), and preference for salt were assessed. We asked the cases to provide information about their lifestyle before the onset of disease, and the controls at the study enrolment.

Laboratory Methods

DNA was extracted from buffy coat fractions with a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA). Genotyping of the A to C substitution at position +52 (A52C) from the first nucleotide on 5'-proximal promoter region of the CD36 gene exon 1 (accession no. L06849, A1160C) was conducted by the polymerase chain reaction with confronting two-pair primers (PCR-CTPP)(Hamajima et al., 2000), as previously described (Kuriki et al., in press). The ALDH2 gene Glu487Lys polymorphism (accession no. NM_000690, G1543A) was also genotyped by a PCR-CTPP

method established in our laboratory (Matsuo et al, 2001).

Statistical Analysis

Analyses were conducted separately for men and women. The chi-square test was performed for nonparametric comparisons of data. Accordance with the Hardy-Weinberg equilibrium, which indicates an absence of discrepancies between genotype and allele frequencies, was checked for controls. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated, using the unconditional logistic regression model. To control for the effects of potential lifestyle confounding factors, ORs were calculated after adjustment for age (continuous), habitual exercise, smoking habit and drinking habit. Meat consumption was not available for analyses as a confounding factor, because there were no individuals with the C/C genotype with high meat consumption in either colorectal cancer cases or controls (Kuriki et al, in press). The probability of the Hardy-Weinberg equilibrium was assessed with the STATA statistical package (STATA, College Station, TX, USA). Logistic procedures from the PC-SAS statistical package version 8.0 were employed for the other calculations (SAS Institute Inc., Cary, NC, USA).

Results

The mean age of female colorectal cancer cases was older than that in female controls (Table 1). In men, the rate of high drinking habit in colorectal cancer cases was significantly higher than that in controls (64.9% and 44.8%,resepctively, $p<0.05$). In women, rates of low drinking habit in both colorectal cancer cases and controls were over 80%. Although proportions of exercisers and smokers in both genders did not differ between colorectal cancer cases and controls, rates for smokers were much higher in men than in women.

No differences in frequencies of both genotypes and alleles for the A52C polymorphism were evident between colorectal cancer cases and controls in either gender (Table 2). The frequencies of those for the Glu487Lys polymorphism also demonstrated no differences. In men and women, the allelic distributions of the A52C and Glu487Lys polymorphisms in controls were in the Hardy-Weinberg equilibrium (p values, 0.16 and 0.91 for men and 0.31 and 0.88 for women, respectively). In men, rates of high drinking habit in colorectal cancer cases and controls were 73.3% and 59.4% for the Glu/Glu genotype and 48.1% and 26.9% for the Glu/Lys + Lys/Lys genotype (not significant for either genotype group), respectively.

On subgroup analyses with reference to the Glu487Lys polymorphism for the risk of colorectal cancer, ORs with the C/C genotype relative to the A/A genotype were 1.70 (95% CI, 0.76-4.11) for men with the low-activity (Glu/Lys + Lys/Lys) genotype, but 4.24 (95% CI, 1.42-22.66) for women (Table 3). There were no associations for men and women with the high-activity (Glu/Glu) genotype.

Regarding the risk of colorectal cancer with cross-classification of subjects for drinking habit and the A52C polymorphism, the OR for the combination of high drinking habit and the C/C genotype compared with that of low drinking habit and the A/A genotype in men was 3.63 (95% CI, 1.29-13.15) (Table 4). The number of high drinking habit women was too small for any corresponding analysis.

Discussion

In the present study, most of the men had a high frequency drinking habit, while the majority of women had a low

Table 1. Background Characteristics of Colorectal Cancer Cases and Controls by Gender

	Men		Women	
	Controls (n=116)	Cases (n=74)	Controls (n=122)	Cases (n=54)
Age (year)(Mean ± SD)	57.9 ± 8.1	59.6 ± 8.8	56.0 ± 7.4	60.1 ± 9.2
p value for t-test		NS		<0.01
Drinking habit				
Low (<1 time/week)	34 (29.3)[a]	12 (16.4)	101 (82.8)	45 (83.3)
Moderate (1-4 times/week)	30 (25.9)	14 (19.2)	15 (12.3)	3 (5.6)
High (>=5 times/week)	52 (44.8)	48 (64.4)	6 (4.9)	6 (11.1)
p value for χ^2-test		<0.05		NS
Habitual exercise				
Low (<1 time/week)	57 (49.1)	49 (66.2)	67 (54.9)	35 (64.8)
Moderate (1-2 times/week)	25 (21.6)	9 (12.2)	21 (17.2)	10 (18.5)
High (>=3 times/wkee)	34 (29.3)	16 (21.6)	34 (27.9)	9 (16.7)
p value for χ^2-test		NS		NS
Smoking habit				
Non-smokers	34 (29.3)	12 (16.2)	105 (86.1)	47 (87.0)
Ex-smokers	38 (32.8)	33 (44.6)	5 (4.1)	1 (1.9)
Smokers	44 (37.9)	29 (39.2)	12 (9.8)	6 (11.1)
p value for χ^2-test		NS		NS

a: Values in parentheses are percentages NS: Not significant

Table 2. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Colorectal Cancer According to the *CD36* Gene *A52C* Polymorphism and the *ALDH2* Gene *Glu487Lys* Polymorphism in Colorectal Cancer Cases and Controls by Gender

	Controls	Cases	ORs (95% CI)[a]	ORs (95% CI)[b]
Men[c, d]				
CD36				
Genotype				
A/A	57 (49.6)[e]	36 (50.7)	1.00	1.00
A/C	51 (44.3)	26 (36.6)	0.81 (0.43-1.53)	0.73 (0.37-1.40)
C/C	7 (6.1)	9 (12.7)	1.50 (0.87-2.65)	1.56 (0.88-2.82)
Allele frequency				
A	165 (71.7)	98 (69.0)		
C	65 (28.3)	44 (31.0)		
ALDH2				
Genotype				
Glu/Glu	64 (55.2)	45 (62.5)	1.00	1.00
Glu/Lys + Lys/Lys	52 (44.8)	27 (37.5)	0.74 (0.40-1.35)	1.04 (0.53-2.06)
Allele frequency				
Glu	172 (74.1)	114 (79.2)		
Lys	60 (25.9)	30 (20.8)		
Women				
CD36				
Genotype				
A/A	65 (53.3)	26 (48.1)	1.00	1.00
A/C	51 (41.8)	23 (42.6)	1.07 0.53-2.14)	1.11 (0.54-2.27)
C/C	6 (4.9)	5 (9.3)	1.47 (0.75-2.83)	1.50 (0.75-2.94)
Allele frequency				
A	181 (74.2)	75 (69.4)		
C	63 (25.8)	33 (30.6)		
ALDH2				
Genotype				
Glu/Glu	61 (50.0)	28 (51.9)	1.00	1.00
Glu/Lys + Lys/Lys	61 (50.0)	26 (48.1)	0.88 (0.44-1.78)	0.87 (0.45-1.68)
Allele frequency				
Glu	173 (70.9)	80 (74.1)		
Lys	71 (29.1)	28 (25.9)		

a: Model 1: adjusted for age.
b: Model 2: adjusted for age, habitual exercise, smoking and drinking habits.
c: The *CD36* genotypes and the allele frequencies in three male colorectal cancer cases and one male control were unknown because DNA was not amplified by PCR-CTPP.
d: The *ALDH2* genotypes and allele frequencies in two male colorectal cancer case were unknown because DNA was not amplified by PCR-CTPP.
e: Values in parentheses are percentages.

frequency of drinking . For men, the C/C genotype of the A52C polymorphism had a positive interaction with high drinking habit for the risk of colorectal cancer. For women, a positive interaction between the C/C and the Gly/Lys + Lys/Lys genotypes may indicate individuals at high risk of colorectal cancer.

Many epidemiological studies have provided evidence that red meat is a probable risk factor of colorectal cancer, with processed meat, total fat and animal fat/SFA as possible risk factors (WCRF/AICR, 1997). Heavy consumption of alcohol is a convincing risk factor for colorectal cancer, whereas alcohol consumption has been reported to demonstrate a J- or U-sharp dose response relationship with mortality from all causes, including cancer, because low to moderate consumption of alcohol is related to decrease in LDL-cholesterol and elevation of high density lipoprotein cholesterol (Marmot and Brunner, 1991; Kune and Vitetta, 1992; Doll et al., 1994; Potter, 1996; WCRF/AICR, 1997; Nagaya et al., 1999). Serum LDL-cholesterol levels have been shown to be negatively associated with the risk of colorectal cancer, but this point remains controversial (Tornberg et al., 1986; Cowan et al., 1990; Kreger et al., 1992; Bayerdorffer et al., 1993; Kono et al., 1993; Bird, et al., 1996; Gaard 1997; Schoen et al., 1999). Alcohol metabolism is linked not only with decreased beta-oxidation of long-chain fatty acids in the liver and transient increase of serum triacylglycerols, but also with generation of acetaldehyde and the production of oxygen radicals that promote lipid peroxidation (Grunnet and Kondrup, 1986; Lieber, 1997). Consumption of alcohol beverages, except for red wine rich in polyphenols, has been suggested to enhance oxidizability of LDL-cholesterol (Puddey et al., 1998). Chronic alcohol consumption in excess of energy needs favors fat storage, although any association between

Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Colorectal Cancer According to the CD36 Genotype by Gender, with Reference to the ALDH2 Genotype

The *CD36* genotype	The *ALDH2* genotype (*Glu/Glu*)		The *ALDH2* genotype (*Glu/Lys + Lys/Lys*)	
	No. of Cases/Controls	OR (95% CI)[b]	No. of Cases/Controls	OR (95% CI)[b]
Men[a]				
A/A	20/30	1.00	16/27	1.00
A/C	20/29	0.92 (0.39-2.15)	6/22	0.40 (0.11-1.28)
C/C	4/4	1.38 (0.59-3.24)	5/3	1.70 (0.76-4.11)
Women				
A/A	15/28	1.00	11/37	1.00
A/C	12/28	0.95 (0.34-2.66)	11/23	1.40 (0.49-4.03)
C/C	1/5	0.72 (0.16-2.05)	4/1	4.24 (1.42-22.66)

a: The subjects with unknown the CD36 or the ALDH2 genotypes in Table 2 were excluded from analyses.
b: Adjusted for age, habitual exercise, smoking and drinking habits.

Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Colorectal Cancer According to the *CD36* Genotype by Gender, with Reference to Drinking Habit

The CD36 genotype	No. of cases/controls on drinking habit			OR (95%CI)[b]		
	Low (<1time/week)	Moderate (1-4times/week)	High (>=5times/week)	Low (<1time/week)	Moderate (1-4times/week)	High (>=5times/week)
Men[a]						
A/A	5/19	9/14	22/24	1.00	2.79 (0.68-12.99)	1.91 (1.07-3.69)
A/C	5/13	3/13	18/25	1.43 (0.30-7.02)	0.94 (0.15-5.34)	2.43 (0.74-9.06)
C/C	2/2	2/2	5/3	2.85 (0.74-13.61)	2.58 (0.75-9.89)	3.63 (1.29-13.15)
Women						
A/A	19/56	2/6	5/3	1.00	1.55 (0.19-8.20)	1.37 (0.48-3.73)
A/C	22/40	0/8	1/3	1.49 (0.70-3.22)	NE[c]	1.79 (0.08-19.14)
C/C	4/5	1/1	0/0	1.45 (0.67-2.95)	2.37 (0.42-13.04)	NE[c]

a: The subjects with unknown the *CD36* genotype in Table 2 were excluded from analyses.
b: Adjusted for age, habitual exercise and smoking habit.
c: NE indicates not estimated because case and/or control were absent in this category.

ethanol intake and body weight is controversial (Suter et al., 1992).

In a previous study, the Lys/Glu + Lys/Lys genotype was found to elevate the risk of colorectal cancer, dependent on alcohol consumption, as compared with subjects with the Glu/Glu genotype (Matuso et al., 2002). Regarding consumption of meat as one food rich in SFAs, we have demonstrated that the C/C genotype with moderate meat intake relative to the A/A genotype with low meat intake had an increased risk of colorectal cancer, and that there were no individuals with the C/C genotype and high meat intake (Kuriki et al., in press). From the results of the present study, moreover, we consider that the A52C polymorphism might be linked to the function as not only a long-chain fatty acid translocase but also a scavenger of oxidized LDL, which has been suggested to be mitogenic and/or cytotoxic factor, and cell proliferation stimulator under some conditions (Zettler et al., 2003).

Prevalence rates of type I CD36 deficiency (neither platelets nor monocytes express) and type II CD36 deficiency (monocytes express but not platelets) are 0.5-1.0% and 3-11% among J-Japanese, respectively, and might be related to elevated serum LDL-cholesterol levels (Yamamoto et al., 1991; Yanai et al., 2000a; 2000b). Compared with the relatively highprevalence rates of type II deficiency among Asians (Koreans, Chinese in Taiwan, and Indonesians), the published rates are only around 0.3% among US-Whites (Greenwalt et al., 1992; Lin et al., 1993; Santoso et al., 1993). The major cause of CD36 deficiency is reported to be the Pro90Ser polymorphism, and the frequency of the Ser allele was found to be 4.2% in Japanese controls (Kashiwagi et al., 1995; Hamajima et al., 2002). The C allele frequency of the A52C polymorphism in our study did not differ from the 26.7% in the general J-Japanese population (http://snp.ims.u-tokyo.ac.jp/). The A52C polymorphism is located within the promoter region at exon 1, where CD36 expression is predicted to be modulated and there is an abundance of transcription-binding sites (Armesilla and Vega, 1994). Other than a regular transcription codon at exon 3, this region at exon 1 has also an upstream transcription codon presented in many protooncogenes (Armesilla and Vega, 199455).

The Lys allele frequency of the Glu487Lys polymorphism is higher among J-Japanese than among US-Whites, and this polymorphism affects the sensitivity to ethanol and drinking behavior (Harada et al., 1981; Yoshida et al., 1984; Takeshita et al., 1994). Regarding cross-cultural comparisons of drinking habit, however, average daily

alcohol consumption as pure ethanol was higher among J-Japanese men than among US-Japanese and US-White men, and J-Japanese may have a higher proportion of heavier drinkers in the middle age group (Higuchi et al., 1994). Alcohol consumption alone, therefore, may not be able to plausibly explain the differences in incident rates of colon and rectal cancer between three ethnical groups. Moreover, there is a greater proportion of heavy drinkers among US-Japanese men than among US-Chinese and US-Korean men (Chi et al., 1989). From cancer registry information it is clear that the incidence rates of colon and rectal cancer are by far the highest among US-Japanese men, whereas the rates are much lower and almost the same between US-Chinese and US-Korean men (Parkin et al., 2002).

Several limitations of the present study should be acknowledged. The results are based on a relative small number of colorectal cancer cases, so our findings are not conclusive. Further studies on larger populations are needed to confirm and extend these observations by site. Serum levels of oxidized LDL and the activity of each genotype with regard to the A52C polymorphism were not clarified here. Although risks for colorectal cancer might be underestimated by modification of drinking habits after the diagnosis of this disease in prevalent cases, we showed positive gene-gene and gene-environmental interactions with the A52C polymorphism for the risk of colorectal cancer, with reference to the Glu487Lys polymorphism and drinking. For most Asian ethnic groups, a population strategy may be more feasible for the near future because their lifestyle gradually has become westernized with economic development and their incident rates of colon and rectal cancers have also steadily increased (Parkin et al., 2002).

Reflecting drinking habit, our findings are consistent with our alternative hypotheses and we showed a positive interaction between high frequency of drinking habit and the C/C genotype in men. Although the frequency of the C/C and the Glu/Lys + Lys/Lys genotypes was very small in men and women, the combined genotype may point to individuals with high risk of colorectal cancer, especially in women. Our results suggested a significant interaction between drinking habit and the metabolism of long-chain fatty acid and oxidized LDL in the etiology of colorectal cancer.

Acknowledgments and Notes

The authors are grateful to Ms. M. Kato, Ms. N. Takeuchi and Ms. M. Yagyu, for genotyping, Ms. H. Fujikura, for the data collection and Dr. Malcolm. Moore, for checking the English language. This work was supported by a Grant-in-Aid for Scientific Research on Special Priority Areas of Cancer from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and by a Grant-in-Aid for a Research Fellow of the Japan Society for the Promotion of Science (JSPS). K. K. was supported by a Research Fellowship of the JSPS for Young Scientists during the performance of this work.

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