Association between Long noncoding RNA rs944289 and rs7990916 polymorphisms and the risk of colorectal cancer in a Chinese population

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Abstract

Long non-coding RNAs (lncRNAs) play vital roles in the tumorigenesis of many cancers. Single nucleotide polymorphisms (SNPs) of the lncRNA also play vital roles in tumorigenesis. We explored lncRNA rs944289 and rs7990916 polymorphisms and analyzed the relationship between these lncRNA polymorphisms with the colorectal cancer (CRC) risk in a Chinese population. We recruited 1,003 CRC patients from the Affiliated People's Hospital of Jiangsu University and the Fujian Medical University Union Hospital from October 2014 to August 2017. Genomic DNA was extracted using a DNA Kit from lymphocytes of peripheral blood and the genotyping was performed with a SNPscan method. We found that the rs944289 TT homozygote was associated with the decreased CRC risk. However, there was no statistically significant association between lncRNA rs7990916 polymorphism and the CRC risk. lncRNA rs944289 TT decreased the CRC risk in the subgroup of female by logistic regression, male, age $\geq$ 61, without alcohol intake, smoking and BMI $\geq$ 24. The subgroup analysis revealed that lncRNA rs7990916 was not associated with the CRC risk except for age $<$ 61. Logistic regression analysis revealed that the lncRNA rs944289 TT homozygote was associated with the increased risk of rectum cancer (TT vs. CC+CT: adjusted OR=1.29, 95% CI: 1.10-1.66, $P=0.041$) or colon cancer. In summary, we proved that the lncRNA rs944289 might be significantly related to the decreased CRC risk in the Chinese Han populations and lncRNA rs7990916 was not associated with the CRC risk except for patients of age $<$ 61. In the future, studies with larger samples should be conducted to validate our results.

Introduction

Colorectal cancer (CRC) has ranked third in terms of incidence but second in terms of mortality in the world [1]. In China, CRC have ranked both fifth in terms of incidence and mortality [2]. The incidence of CRC has been increasing, mostly due to unhealthy lifestyle, aging and environmental factors [3], but accumulating evidences have shown that an individual's inherited factors also contribute to the development of CRC.

Long noncoding RNAs (lncRNAs) are a sort of noncoding RNA molecules with more than 200 nucleotides in length, and are disease- or tissue-specific expression patterns [4, 5]. lncRNAs play crucial roles in chromatin dynamics, genome packaging, gene regulation, cellular pathways and biological processes⁶. lncRNAs also play pivotal roles in the oncogenesis and metastasis of CRC [7, 8]. Yu et al found that linc-UFC1 participated in the progression of CRC, and overexpression of linc-UFC1 in CRC patients was positively associated with tumor grade and stage [7]. Zhao et al also reported overexpression of Linc-A was correlated with poor survival in CRC patients [8].

Single nucleotide polymorphisms (SNPs) occurring in the functional region of lncRNAs can influence disease susceptibility and can also promote cancer development [9]. For example, lncRNAs rs7990916 TT genotype was found to increase Alzheimer's disease (AD) susceptibility [10]. Papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) rs944289 polymorphism increased susceptibility of papillary thyroid cancer (PTC) [11]. These data indicate SNPs in lncRNAs play important roles in tumorigenesis.

Although lncRNA rs944289 and rs7990916 polymorphisms have a risk effect on some diseases, there are no studies concerning the relationship of these two variants with the CRC risk. To clarify this issue, we explored lncRNAs rs944289 and rs7990916 polymorphisms in CRC patients and analyzed the relationship between these lncRNA polymorphisms and the CRC risk.

Materials And Methods

Patients and samples.

We recruited 1,003 CRC patients from the Affiliated People's Hospital of Jiangsu University and the Fujian Medical University Union Hospital from October 2014 to August 2017. One thousand three hundred and three healthy subjects were selected as controls from the departments of physical examination in those two hospitals. All subjects were unrelated Chinese Han populations. The demographic characteristics were recorded, including body mass index (BMI), age, gender, alcohol intake and smoking. The Ethics Committee of the Affiliated People's Hospital of Jiangsu University approved the protocol of the study (K-20200107-W), and all participants signed an informed consent before enrolled in this research.

SNP genotyping

Genomic DNA was extracted using a DNA Kit (Promega, Madison, USA) from lymphocytes of peripheral blood. The DNA was quantified by a measurement of OD₂₆₀ and then was stored at -80°C. SNPs of lncRNA rs944289 and rs7990916 were analyzed by a SNPscan Kit (Genesky Biotechnologies Inc., Shanghai, China) [12]. 4% DNA samples were selected randomly and another technician reconfirmed the genotypes for quality control.

Statistical analysis

All data were analyzed by using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). The chi-square or Fisher's exact test was applied to compare the categorical variables, whereas the continuous variables were evaluated by the student's t-test. The relationship between the lncRNA rs944289/7990916 polymorphisms and the CRC risk was assessed by odds ratios (OR) and 95% confidence intervals (CIs). Logistic regression model was conducted to analyze the associations among lncRNA rs944289 and 7990916 polymorphisms, the clinical characteristics and the CRC risk. Hardy–Weinberg equilibrium (HWE) was used to analyze the genotype distributions of lncRNA rs944289/7990916. A $P < 0.05$ (two-tailed) was adopted as the statistically significant level.

Results

Characteristics of CRC patients

In our study, 1,003 CRC cases (431 colon cancer and 572 rectum cancer patients) and 1,303 normal controls were enrolled to investigate the correlation of the two SNPs (rs944289 and rs7990916) with the CRC risk. Table 1 listed detailed demographics data. The mean age of CRC patients and controls were 61.10 ± 12.17 years and 61.40 ± 9.61 years, respectively. There were no statistically significant differences in age and gender between the CRC patients and the controls (both $P > 0.05$). However, smoking, alcohol intake and BMI increased the risk of CRC (both $P < 0.05$), so we adjusted these factors by multiple logistic regression analyses.

Primary information for lncRNA rs944289 and rs7990916

The genotypic frequencies of lncRNA rs944289 and rs7990916 meet the HWE ($P=0.105$ and $P=0.359$, respectively). Minor allele frequency (MAF) of lncRNA rs944289 polymorphism was 0.28, which was similar to SNP database for Chinese populations (MAF=0.24). MAF of lncRNA rs7990916 polymorphism was 0.23, which was similar to SNP database for Chinese populations. Table 2 summarizes the corresponding information of lncRNA rs944289 and rs7990916.

Association of lncRNA polymorphisms with CRC risk in the overall population

The genotypes and allele distributions of lncRNA rs944289 and rs7990916 in the CRC patients and the controls were presented in Table 3. lncRNA rs944289 frequencies were 29.55% (CC), 46.73% (CT) and 23.72% (TT) in CRC patients, whereas in controls, the distributions of those genotypes were 29.69%, 51.62%, and 18.69%, respectively. We found that the rs944289 TT homozygote was associated with decreased CRC risk when compared with the CC or CC+CT (TT vs. CC: adjusted OR= 0.88, 95% CI: 0.78-0.99, $P=0.037$; TT vs. CC+CT: adjusted OR=0.86, 95% CI: 0.78-0.95, $P=0.004$). lncRNA rs7990916 frequencies were 79.69% (CC), 19.49% (CT) and 0.82% (TT) in CRC patients, and 77.31% (CC), 20.92% (CT) and 1.77% (TT) in controls. There was no significant difference between lncRNA rs7990916 and the susceptibility of CRC (all $P>0.05$).

Stratified analyses between lncRNA rs944289 polymorphism and CRC risk

Stratified analysis was performed and revealed that rs944289 TT genotype was associated with the decreased CRC risk in the subgroup of male (adjusted OR=0.88, 95% CI: 0.77-0.99, $P=0.045$), female (adjusted OR=0.81, 95% CI: 0.68-0.99, $P=0.097$), age $\geq$ 61 (adjusted OR=0.86, 95% CI: 0.74-0.99, $P=0.035$), smoking (adjusted OR=0.66, 95% CI: 0.53-0.81, $P<0.001$), never alcohol intake (adjusted OR=0.88, 95% CI: 0.78-0.98, $P=0.021$) and BMI $\geq$ 24 (adjusted OR=0.82, 95% CI: 0.696-0.94, $P=0.0016$) (Table 4).

Stratified analyses between lincRNA rs7990916 polymorphism and CRC risk

We further analyzed stratified effects of lncRNA rs7990916 on CRC risk by logistic regression model. Genotype distributions of rs7990916 were evaluated with age, sex, BMI, drinking and smoking. Results show that there was no significant association between the CRC patients and the control group except for age $<$ 61 (CT vs. CC: adjusted OR = 0.67, 95% CI: 0.48–0.93, $P=0.018$) (Table 5).

lncRNA rs944289/rs7990916 polymorphisms and CRC risk by site of tumor

Logistic regression analysis revealed that lncRNA rs944289 was associated with the increased risk of colon cancer (TT vs. CC+CT: adjusted OR=1.44, 95% CI: 1.11-1.88, $P=0.007$) or rectum cancer (TT vs. CC+CT: adjusted OR=1.29, 95% CI: 1.10-1.66, $P=0.041$) when compared with CC+CT (Table 6). We also found lncRNA rs7990916 did not alter the risk of colon cancer (CT vs. CC: adjusted $P=0.18$, TT vs. CC: adjusted $P=0.21$, CT+TT vs. CC: adjusted $P=0.11$, and TT vs. CC+CT: adjusted $P=0.24$) or rectal cancer (CT vs. CC: adjusted $P=0.58$, TT vs. CC: adjusted $P=0.11$, CT+TT vs. CC: adjusted $P=0.37$, and TT vs. CC+CT: adjusted $P=0.12$) (Table 6).

Discussion

lncRNAs play an essential role in various biological processes, including cell proliferation, apoptosis, genomic imprinting, transcriptional interference and other critical processes [13]. Recently, numerous investigations have suggested lncRNA polymorphisms as one of the contributors to the risk of CRC. For example, Yang et al reported lncRNA PCAT1 rs2632159 polymorphism increased the CRC risk in a Chinese population [14]. Wang et al also reported H19 rs2839698 polymorphism was associated with an increased CRC risk [15]. On the other hand, lncRNA PRNCR1 rs13252298/rs1456315 and MALAT1 rs1194338 polymorphisms decreased the CRC risk significantly [16, 17]. Considering this background, we performed a case-control study to determine the relationship between lncRNA rs944289/rs7990916 polymorphisms and the CRC risk.

In this study, we found that lncRNA rs944289 TT homozygote could decrease CRC risk. After adjustment by multiple logistic regression, the TT genotype of lncRNA rs944289 was associated with the decreased CRC risk in the subgroups of female, male, age ≥ 61 , BMI ≥ 24 , smoking and never alcohol intake populations. lncRNA rs944289 have been confirmed to increase the risk of PTC, and rs944289 predisposes to PTC by inhibiting the expression of PTCSC3 (a tumor suppressor) [18, 19]. Cao et al also found that lncRNA rs944289 may increase the risk of esophagogastric junction adenocarcinoma (EGJA) in the smoking and age < 60 years populations [20]. However, in a Chinese population, Xu et al discovered that lncRNA rs944289 have no significant effect on the risk of breast cancer (BC), which might be due to the specific tumorigenesis of BC [21].

Our results also revealed that there was no significant difference between lncRNA rs7990916 polymorphism and the CRC risk. But when stratified by age < 61 years, lncRNA rs7990916 polymorphism decreased the risk of CRC. Jendrzewski et al found significant relationship between lncRNAs rs7990916 and the susceptibility for AD in the Europe populations. But the etiology of CRC are primarily different from that of AD [19]. Thus, these distinct conclusions on the lncRNA rs7990916 polymorphism may be mainly attributed to the heterogeneity of ethnics and disease types.

Taken together, lncRNAs could induce the occurrence of cancer by binding transcription factors in the promoter of gene, deregulating signal pathways, binding to miRNA and so on. However, these mechanisms of lncRNA rs944289/rs7990916 should be addressed by further investigations.

To the best of our knowledge, our research focused on the possible association of lncRNA rs944289 and rs7990916 polymorphisms with the CRC risk for the first time. There still existed several limitations in the study. Firstly, this case-control study only focused on Chinese Han populations. Secondly, the two lncRNAs selected in our study may not be comprehensive because there may be other genetic polymorphisms that affected the risk of CRC. Thirdly, we did not perform the association of lncRNA rs944289 and rs7990916 polymorphisms with

tumor stages, patients' prognosis, or other associated risk factors, which might affect the precision of estimating the effect of these two polymorphisms on the CRC risk. Finally, we did not investigate the mechanism of the two polymorphisms during the tumorigenesis of CRC. Nevertheless, our study provides clues for a further mechanism study and provides possible biomarkers for CRC diagnosis.

Conclusions

In summary, we proved that the lncRNA rs944289 might be significantly related to the decreased risk of CRC in the Chinese Han populations. However, there was no significant difference between lncRNA rs7990916 polymorphism and the CRC risk except for the subgroup of age<61. In the future studies, larger samples including detailed clinical information and different ethnic populations should be conducted to validate our findings.

Declarations

Disclosure of Potential Conflicts of Interests:

The authors have no potential financial conflicts of interest.

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Tables

Table 1 The demographic variables of CRC patients and controls

Variable	Cases (n=1,003)		Controls (n=1,303)		<i>P</i> ^a
	n	%	n	%	
Age (years)					0.61
< 61	451	44.97	600	46.05	
≥61	552	55.03	703	53.95	
Sex					0.87
Male	620	61.81	801	61.47	
Female	383	38.19	502	38.53	
BMI (kg/m ²)					<0.001
< 24	670	66.80	688	52.80	
≥ 24	333	33.20	615	47.20	
alcohol intake					<0.001
Never	829	82.65	1,167	89.56	
Ever	174	17.35	136	10.44	
Smoking					0.002
Never	744	74.18	1038	79.66	
Ever	259	25.82	265	20.34	
Site of tumor					
Colon cancer	431	42.97			
Rectum cancer	572	57.03			

^a Bold values are statistically significant ($P<0.05$); BMI, body mass index.

Table 2 Primary information for LncRNA rs 944289 C>T and rs7990916 C>T polymorphisms

Genotyped SNPs	Chromosome	Chr Pos (NCBI Build 38)	Region	MAF ^a for Chinese in database	MAF in our controls (n = 1,303)	<i>P</i> value for HWE ^b test in our controls	Genotyping value (%)
rs944289 C> T	14	36180040	nc transcript variant	0.24	0.28	0.11	98.66
rs7990916 C> T	13	80065389	nc transcript variant	0.21	0.23	0.36	98.87

^a MAF: minor allele frequency;

^b HWE: Hardy-Weinberg equilibrium.

Table 3 Genotype Frequencies of LncRNA rs944289 C>T and rs7990916 C>T Polymorphisms and the CRC Risk

Genotype	CRC Cases			Controls		Crude OR (95%CI)	<i>P</i>	Adjusted OR ^a (95%CI)	<i>P</i>
	(n=1,003)			(n=1,303)					
	n	%		n	%				
rs944289 C> T									
CC	289	29.55	-	386	29.69	1.00		1.00	
CT	457	46.73	-	671	51.62	0.91(0.75-1.10)	0.34	1.07(0.88-1.30)	0.53
TT	232	23.72	-	243	18.69	1.27(1.01-1.61)	0.043	0.88(0.78-0.99)	0.037
CT+TT	689	70.45	-	914	70.31	1.01(0.84-1.21)	0.94	0.97(0.81-1.17)	0.75
CC+CT	746	76.28	-	1,057	81.31	1.00		1.00	
TT	232	23.72	-	243	18.69	1.35(1.10-1.66)	0.004	0.86(0.78-0.95)	0.004
T allele	921	47.09	-	1,157	44.50				
rs7990916 C>T									
	-	-	-	-	-				
CC	781	79.69	-	1005	77.31	1.00		1.00	
CT	191	19.49	-	272	20.92	0.90(0.73-1.14)	0.34	0.89(0.72-1.10)	0.27
TT	8	0.82	-	23	1.77	0.45(0.20-1.01)	0.066	0.45(0.20-1.03)	0.059
CT+TT	199	20.31	-	295	22.69	0.87(0.71-1.06)	0.18	0.85(0.70-1.05)	0.13
CC+CT	972	99.18	-	1,277	98.23	1.00		1.00	
TT	8	0.82	-	23	1.77	0.46(0.20-1.03)	0.067	0.47(0.21-1.06)	0.067
T allele	207	10.56		318	12.23				

^a Adjusted for age, gender, smoking, alcohol use and BMI status.

Bold values are statistically significant ($P < 0.05$)

Table 4 Stratified analyses between LincRNA rs944289 C>T polymorphism and CRC risk by gender, age, BMI, smoking and alcohol intake

Variable	LincRNA rs944289 C> T (case/control) ^a			Adjusted OR ^b (95% CI); <i>P</i>						
	CC	CT	TT	CC	CT	TT	CT /TT	TT vs. (CT/CC)		
Sex										
Male	176/231	276/407	150/161	1.00	1.08(0.84-1.39); <i>P</i> : 0.56	0.91(0.78-1.05); <i>P</i> : 0.20	0.99(0.78-1.26); <i>P</i> : 0.94	0.88(0.77-0.99); <i>P</i> : 0.045		
Female	113/155	181/264	82/82	1.00	1.04(0.76-1.43); <i>P</i> : 0.79	0.82(0.67-1.00); <i>P</i> : 0.053	0.93(0.69-1.25); <i>P</i> : 0.62	0.81(0.68-0.97); <i>P</i> : 0.019		
Age	-	-	-							
<61	115/168	216/312	111/118	1.00	0.96(0.71-1.30); <i>P</i> : 0.80	0.87(0.72-1.03); <i>P</i> : 0.13	0.89(0.67-1.19); <i>P</i> : 0.43	0.87(0.75-1.02); <i>P</i> : 0.082		
≥61	174/218	241/359	121/125	1.00	1.15 (0.88-1.49); <i>P</i> : 0.30	0.90(0.77-1.06); <i>P</i> : 0.22	1.04(0.81-1.33); <i>P</i> : 0.76	0.86(0.74-0.99); <i>P</i> : 0.035		
Smoking	-	-	-							
Never	223/314	351/520	154/201	1.00	1.02(0.82-1.27); <i>P</i> : 0.88	0.93(0.81-1.06); <i>P</i> : 0.28	0.91(0.71-1.78); <i>P</i> : 0.49	0.93(0.83-1.05); <i>P</i> : 0.25		
Ever	66/72	106/151	78/42	1.00	1.26(0.82-1.93); <i>P</i> : 0.29	0.70(0.54-0.90); <i>P</i> : 0.006	0.95(0.64-1.41) <i>P</i> : 0.79	0.66(0.53-0.81); <i>P</i> : 0.000		
Alcohol intake	-	-	-							
Never	238/348	387/598	184/218	1.00	1.03(0.83-1.27); <i>P</i> : 0.81	0.88(0.77-1.00); <i>P</i> : 0.056	0.94(0.77-1.15); <i>P</i> : 0.56	0.88(0.78-0.98); <i>P</i> : 0.021		
Ever	51/38	70/73	48/25	1.00	1.33(0.77-2.30); <i>P</i> : 0.30	0.86(0.61-1.20); <i>P</i> : 0.38	1.14(0.69-0.91); <i>P</i> : 0.61	0.77(0.58-1.03); <i>P</i> : 0.074		
BMI (kg/m ²)	-	-	-							
<24	202/216	303/341	150/129	1.00	1.05(0.82-1.34); <i>P</i> : 0.71	0.90(0.77-1.05); <i>P</i> : 0.17	0.97(0.77-1.23); <i>P</i> : 0.80	0.88(0.77-1.01); <i>P</i> : 0.064		
≥24	87/170	154/330	82/114	1.00	1.10(0.80-1.52); <i>P</i> : 0.56	0.84(0.69-1.02); <i>P</i> : 0.085	0.97(0.72-1.32); <i>P</i> : 0.86	0.82(0.696-0.94); <i>P</i> : 0.016		

^a For ICAM-1 rs944289 C>T, the genotyping was successful in 980 (97.71%) CRC cases, and 1300 (99.77%) controls;

^b Adjusted for multiple comparisons [age, gender, BMI, smoking status and alcohol intake (besides stratified factors accordingly)] in a logistic regression model

Table 5 Stratified analyses between LincRNA rs7990916 C>T Polymorphism and CRC risk by gender, age, BMI, smoking status and alcohol intake

Variable	LincRNA rs7990916 C>T Polymorphism (case/control) ^a			Adjusted OR ^b (95% CI); <i>P</i>				
	CC	CT	TT	CC	CT	TT	CT /TT	TT vs. (CT/CC)
Sex								
Male	477/619	123/166	4/14	1.00	0.94(0.72-1.22); <i>P</i> : 0.63	0.382(0.12-1.19); <i>P</i> : 0.096	0.90(0.69-1.16); <i>P</i> : 0.40	0.39(0.13-1.20); <i>P</i> : 0.099
Female	304/386	68/106	4/9	1.00	0.83(0.59-1.18); <i>P</i> : 0.30	0.54(0.16-1.79); <i>P</i> : 0.31	0.81(0.58-1.13); <i>P</i> : 0.22	0.56(0.17-1.87); <i>P</i> : 0.35
Age								
<61	370/460	69/127	4/11	1.00	0.67(0.48-0.93); <i>P</i>: 0.018	0.48(0.15-1.53); <i>P</i> : 0.22	0.66(0.47-0.90); <i>P</i>: 0.010	0.51(0.16-1.65); <i>P</i> : 0.26
≥61	411/545	122/145	4/12	1.00	1.08(0.82-1.43); <i>P</i> : 0.57	0.43(0.13-1.37); <i>P</i> : 0.16	1.04(0.79-1.36); <i>P</i> : 0.80	0.42(0.13-1.34); <i>P</i> : 0.14
Smoking status								
Never	585/802	136/216	7/17	1.00	0.87(0.68-1.10); <i>P</i> : 0.24	0.55(0.22-1.36); <i>P</i> : 0.20	0.84(0.66-1.07); <i>P</i> : 0.16	0.57(0.23-1.40); <i>P</i> : 0.22
Ever	196/203	55/56	1/6	1.00	0.98(0.64-1.51); <i>P</i> : 0.94	0.19(0.02-1.58); <i>P</i> : 0.12	0.91(0.60-1.38); <i>P</i> : 0.66	0.18(0.02-1.57); <i>P</i> : 0.12
Alcohol intake								
Never	643/900	160/243	7/21	1.00	0.90(0.71-1.12); <i>P</i> : 0.34	0.47(0.20-1.11); <i>P</i> : 0.085	0.862(0.69-1.08); <i>P</i> : 0.19	0.48(0.20-1.14); <i>P</i> : 0.096
Ever	138/105	31/29	1/2	1.00	0.77(0.44-1.38); <i>P</i> : 0.38	0.39(0.04-4.44); <i>P</i> : 0.45	0.75(0.43-1.32); <i>P</i> : 0.32	0.41(0.04-4.54); <i>P</i> : 0.46
BMI (kg/m ²)								
<24	521/521	130/153	5/12	1.00	0.86(0.66-1.12); <i>P</i> : 0.26	0.42(0.14-1.19); <i>P</i> : 0.10	0.83(0.64-1.07); <i>P</i> : 0.15	0.43 (0.15-1.23); <i>P</i> : 0.12
≥24	260/484	61/119	3/11	1.00	0.96(0.66-1.35); <i>P</i> : 0.79	0.51(0.14-1.87); <i>P</i> : 0.31	0.92(0.66-1.29); <i>P</i> : 0.62	0.51(0.14-1.87); <i>P</i> : 0.31

^a For LincRNA rs7990916 C>T, the genotyping was successful in 977 (97.41%) CRC cases, and 1,298 (99.62%) controls;

^b Adjusted for multiple comparisons [age, sex, BMI, smoking status and alcohol intake (besides stratified factors accordingly)] in a logistic regression model.

Table 6 Stratified analyses between LncRNAs rs944289 C>T and rs7990916 C>T polymorphisms and CRC risk by site of tumor

^a Adjusted for age, sex, smoking status, alcohol use and BMI status.

Genotype	Controls (n=1,303)		Colon cancer cases (n=431)		Crude OR (95%CI)	<i>P</i>	Adjusted OR ^a (95%CI)	<i>P</i> ^a	Rectum cancer cases (n=572)	Crude OR (95%CI)	<i>P</i>	Adjusted OR ^a (95%CI)	<i>P</i> ^a		
	n	%	n	%					n	%					
rs944289 C>T															
CC	386	29.69	130	30.73	1.00		1.00		159	28.65	1.00		1.00		
CT	671	51.62	189	44.68	0.84(0.65-1.08)	0.19	0.86(0.67-1.12)	0.27	268	48.29	1.04(0.82-1.30)	0.81	1.00(0.79-1.27)	0.99	
TT	243	18.69	104	24.59	1.27(0.94-1.72)	0.14	1.33(0.97-1.81)	0.073	128	23.06	1.28(0.96-1.70)	0.10	1.27(0.95-1.71)	0.10	
CT+TT	914	70.31	293	69.27	0.95(0.75-1.21)	0.71	0.97(0.77-1.24)	0.84	396	71.35	1.05(0.85-1.31)	0.70	1.07(0.86-1.34)	0.53	
CC+CT	1,057	81.31	319	75.41	1.00		1.00		427	76.94	1.00		1.00		
TT	243	18.69	104	24.59	1.42(0.41-1.24)	0.010	1.44(1.11-1.88)	0.007	128	23.06	1.35(1.06-1.73)	0.015	1.29(1.10-1.66)	0.041	
T allele	1,157	44.50	397	46.93					524	47.21					
rs7990916 C>T															
			-	-	-				-	-					
CC	1,005	77.31	-	342	80.85	1.00		1.00	439	78.81	1.00		1.00		
CT	272	20.92	-	77	18.20	0.83(0.63-1.10)	0.21	0.82(0.62-1.09)	0.18	114	20.47	0.96(0.75-1.23)	0.76	0.931(0.73-1.20)	0.58
TT	23	1.77	-	4	9.46	0.51(0.18-1.49)	0.27	0.50(0.17-1.48)	0.21	4	0.72	0.40(0.14-1.16)	0.092	0.42(0.14-1.22)	0.11
CT+TT	295	22.69	-	81	19.15	0.81(0.61-1.06)	0.14	0.80(0.88-1.36)	0.11	118	21.18	0.92(0.72-1.17)	0.50	0.89(0.70-1.14)	0.37
CC+CT	1,277	98.23	-	419	99.05	1.00		1.00		553	99.28	1.00		1.00	
TT	23	1.77	-	4	9.46	0.53(0.18-1.54)	0.37	0.52(0.18-1.53)	0.24	4	0.72	0.40(0.14-1.17)	0.093	0.42(0.14-1.24)	0.12
T allele	318	12.23	-	85	10.05					222	19.93				