RESEARCH ARTICLE

Polymorphisms of TERT and CLPTM1L and the Risk of Hepatocellular Carcinoma in Chinese Males

Ling-Yan Su[1,2], Xue-Lian Li[1,2], Li Shen[1,2], Yue Zhang[1,2], Meng-Meng Zhao[1,2], Zhi-Hua Yin[1,2], Hong-Ying Su[3], Bao-Sen Zhou[1,2]*

Abstract

Background: Telomerase reverse transcriptase (TERT) and cleft lip and palate trans-membrane 1 like (CLPTM1L) genes located on chromosome 5p15.33 are known to influence the susceptibility to various cancers. Here, we examined the association of TERT and CLPTM1L single nucleotide polymorphisms (SNPs) with hepatocellular carcinoma (HCC). Materials and Methods: Genotyping of TERT SNP rs2736098 and CLPTM1L SNP rs401681 was performed using TaqMan allelic discrimination assays in a case-control study of 201 HCC cases and 210 controls in a Chinese male population. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression analyses. Results: Both the rs2736098 T allele of TERT and the rs401681 T allele of CLPTM1L were associated with a significantly increased risk of HCC (adjusted odds ratio [OR]=1.605, 95% confidence interval [CI]=1.164-2.213; adjusted OR=1.399, 95%CI=1.002-1.955, respectively). Individuals carrying both TERT and CLPTM1L risk genotypes had an even higher risk of HCC (adjusted OR=4.420, 95%CI= 2.319-8.425). The TERT rs2736098 T allele was also significantly associated with the level of the HCC clinical indicator alpha-fetoprotein (*P*=0.026). Conclusions: Our results show that genetic variants of TERT and CLPTM1L may contribute to HCC susceptibility in Chinese males.

Keywords: Telomerase reverse transcriptase - cleft lip and palate transmembrane 1-like - SNPs - HCC risk

Asian Pac J Cancer Prev, **15 (19)**, 8197-8201

Introduction

Primary liver cancer is the fifth most commonly diagnosed cancer worldwide but the second most frequent cause of death in men. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. The highest reported primary liver cancer rates are found in East and South-East Asia. Hepatocellular carcinoma (HCC) represents the major histological subtype of primary liver cancers, accounting for 85-90% of the total liver cancer burden worldwide (Hashem et al., 2007; Global cancer statistics 2011). Meanwhile, liver cancer incidence rates are increasing in many parts of the world. The occurrence of HCC is a multi-factor and multi-stage process, including both hereditary and environmental factors. Long-term carcinogenic effects give rise to genetic changes, which can lead to tumor formation (Tanabe et al., 2008). In recent years, several studies have investigated the correlation of genetic polymorphisms and HCC.

The chromosome 5p15.33 region including telomerase reverse transcriptase (*TERT*) and cleft lip and palate trans-membrane 1-like (CLPTM1L) genes is known to be associated with the development of many cancers (Rafnar et al., 2009). Telomerase is a ribonucleoprotein complex composed of RNA and proteins that plays an important role in maintaining telomere stability, long-term cellular activity, and potential proliferation ability (Cong et al., 1999, Young 2010, Luis et al., 2011). Human *TERT* at the core of telomerase can synthesize DNA from an RNA template using catalytic activity. Recent studies have shown that the reactivation of *TERT* is likely to promote tumor progression and regulate cancer-promoting pathways (Artandi et al., 2010). *CLPTM1L* encodes a predicted transmembrane protein that was shown to induce apoptosis in cisplatin-resistant cell lines, although the function of *CLPTM1L* and its role in tumor genesis remains unclear (Yamamoto et al., 2001).

To date, many studies have demonstrated that single nucleotide polymorphisms (SNPs) of *TERT* and *CLPTM1L* are associated with cancer risks. Two variants in this 5p15.33 region (rs401681 and rs2736098) are correlated with bladder cancer, lung cancer, glioma, breast cancer, and other tumors (Rafnar et al., 2009). However, the relationships between these SNPs and HCC have not been investigated. Therefore, we performed a case-control study consisting of 201 HCC cases and 211 controls to further research any correlation.

*[1]Department of Epidemiology, School of Public Health, China Medical University, [3]Department of Radiology, The First Affiliated Hospital of China Medical University, [2]Key Laboratory of Cancer Etiology and Intervention, University of Liaoning Province, Shenyang, China *For correspondence: bszhou@mail.cmu.edu.cn*

Materials and Methods

Our case-control study recruited 217 HCC patients aged 30-87 years from the first affiliated Hospital of China Medical University between 2008 and 2013. There were no restrictions on age or tumor stage. Controls were 210 non-cancer patients from the same hospital that were matched according to age (±5 years), gender (male), and ethnicity (Han Chinese). The diagnosis of HCC was confirmed by positive diagnostic imaging such as CT and angiography. The following HCC Characteristics were investigated from questionnaire interviews. A total of 201 cases of 217 selected HCC patients achieved a response rate of 93%. All participants were unrelated, ethnic Han Chinese individuals. Informed consent forms were obtained from all study individuals, and the China Medical University Ethics Committee approved this study.

DNA was extracted from peripheral blood using phenol-chloroform and ethanol precipitation as previously described (Sambrook 1989). rs2736098 and rs401681 genotyping was performed using Taqman allelic discrimination assays, and primers and probes were obtained from Applied Biosystems (Foster City, CA, USA). Polymerase chain reaction (PCR) conditions were 95°C for 10 min followed by 47 cycles of 92°C for 30 s and 60°C for 1 min. Results were read using Sequence Detection Software on an Applied Bio-systems 7500 FAST Real-Time PCR System according to the manufacturer's instructions. For each SNP, genotypic frequencies were tested for deviation from Hardy-Weinberg Equilibrium using Pearson's χ^2 test. There was no deviation in the control group. Distributions of demographic variables, risk factors, and genotypes between the cases and controls were evaluated using the two-sided χ^2 test. The associations of these two variant genotypes with risk of HCC were estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) from both univariate and multivariate logistic regression analyses. Statistical analysis was carried out using two-sided tests with Statistical Product and Service Solutions software (v.16.0; SPSS Institute Cary, Chicago, IL, USA). $p<0.05$ was considered as the level of statistical significance.

Results

Patient and control characteristics are shown in Table 1. There were no significant differences in age distribution between the cases and controls ($p=0.559$), with a similar mean age in both groups (57.36±10.50 years for cases, and 58.04±12.18 years for controls). All individuals were male with different smoking statuses. However, the smoking status was not significantly different between cases and controls ($p=0.229$).

Both SNPs (*TERT* rs2736098 and *CLPTM1L* rs401681) were in Hardy-Weinberg Equilibrium ($p=0.055$ and 0.325, respectively). Detailed information about the genotype and allele distributions in cases and controls for the two SNPs is shown in Table 2. For the rs2736098 polymorphism, a significantly increased risk of HCC was associated with the CT genotype in a co-dominant model (CT *vs* CC: adjusted OR=1.840, 95%CI=1.148-2.948) and variant genotypes CT+TT in a dominant model (CT+TT *vs* CC: adjusted OR= 1.946, 95%CI=1.244-3.043). We also found a significant association between the *CLPTM1L* rs401681 polymorphism and HCC risk for the CT genotype in a co-dominant model (CT *vs* CC:

Table 1. Characteristics of HCC Cases and Controls

Characteristics	Cases (n=201)	Controls (n=211)	*p* values[a]
Mean age	57.36±10.50	58.04±12.21	0.522
Gender(male)	201	210	
Smoker	57(28.4%)	71(34.1%)	0.207
Non-smoker	84(41.8%)	139(65.9%)	
HBV(Positive)	161(80.1%)		
HBV(Negative)	40(19.9%)		
AFP <20	74(36.8%)		
AFP≥20	127(63.2%)		
TNMI+II	93(46.3%)		
TNM III+IV	108(53.7%)		
lymph nod metastasis (N)	177(88.1%)		
lymph nod metastasis (Y)	24(11.9%)		
Tumor number =1	104(51.7%)		
Tumor number≥2	97(48.3%)		

[a]Two-sided test

Table 2. TERT (rs2736098) and CLPTM1L (rs401681) Genotype Frequencies in HCC Cases and Controls and their Associations with HCC Risk

rs2736098	Cases N(%)	Controls N(%)	*p* values	Adjusted ORa(95%CI)
CC	75(37.3)	111(52.8)		1
CT	97(48.3)	76(36.2)	0.011	1.840(1.148-2.948)
TT	29(14.4)	23(11.0)	0.018	2.406(1.160-4.989)
CT+TT	126(62.7)	99(47.2)	0.004	1.946(1.244-3.043)
T allele			0.004	1.605(1.164-2.213)
rs401681				
CC	86(42.8)	120(57.2)		1
CT	98(48.7)	74(35.2)	0.016	1.786(1.115-2.863)
TT	17(8.5)	16(7.6)	0.333	1.520(0.651-3.546)
CT+TT	115(57.2)	90(42.7)	0.016	1.739(1.110-2.723)
T allele			0.049	1.399(1.002-1.955)

a Adjusted by age

Table 3. Association between Joint Analysis of rs2736098 and rs401681 and HCC Risk

TERT rs2736098	CLPTM1L rs401681	Cases (N)	Controls (N)	P values	Adjusted OR[a](95%CI)
CC	CC	25	51		
CC	CT+TT	50	60	0.086	1.700(0.925-3.123)
CT+TT	CC	61	69	0.049	1.803(1.000-3.252)
CT+TT	CT+TT	65	30	0.000	4.420(2.319-8.425)

*[a]Adjusted by age

Table 4. Interaction Analysis between Polymorphisms and Smoking with HCC Risk

	Genotypes	Cases (N)	Controls (N)	*P* values	Adjusted OR(95%CI)
Smoking status TERT rs2736098					
Non-smokers	CC	35	68		1
Non-smokers	CT+TT	49	71	0.55	1.211(0.647-2.269)
Smokers	CC	23	43	0.754	0.888(0.422-1.868)
Smokers	CT+TT	34	28	0.022	2.353(1.133-4.887)
CLPTM1L rs401681					
Non-smokers	CC	37	75		1
Non-smokers	CT+TT	47	64	0.177	1.545(0.822-2.904)
Smokers	CC	26	45	0.891	1.051(0.518-2.130)
Smokers	CT+TT	31	26	0.009	2.790(1.296-6.008)

[a]Adjusted by age

adjusted OR=1.786, 95%CI=1.115-2.863) and variant genotypes CT+TT in a dominant model (CT+TT *vs* CC: adjusted OR=1.739, 95%CI=1.110-2.723).

Table 3 shows the association between the joint effect of *TERT* and *CLPTM1L* genotypes and HCC risk. We used the *TERT* CC genotype and *CLPTM1L* CC genotype as references to determine high-risk genotypes and found that CT+TT of *TERT* and CT+TT of CLMPT1L had a significantly increased risk of HCC with an adjusted OR of 4.420 (95%CI= 2.319-8.425, p≤0.001). The results of the analysis into the interaction between *TERT* rs2736098, *CLPTM1L* rs401681, and smoking with the risk of HCC are shown in Table 4. Smokers carrying both *TERT* and *CLPTM1L* risk genotypes had a higher risk of HCC (adjusted OR=2.353, 95%CI=1.133-4.887; adjusted OR=2.790, 95%CI=1.296-6.008).

The association of the two SNPs with clinical indicators hepatitis B virus (HBV) and alfa-fetoprotein (AFP) was next analyzed in HCC patients (Tables 5 and 6). There was no significant association in the genotype frequency between HBV and non-HBV HCC patients, but the *TERT* rs2736098 T allele was associated with an increased level of AFP (co-dominant model CC *vs* TT: OR=3.354, 95%CI= 1.226-9.177; dominant model: OR=1.952,

Table 5. Association of rs2736098 Genotypes with Relative Factors in HCC Patients

Genotype	Cases (N)	Co-dominant		Dominant		Recessive	
rs2736098	Non-HBV/ HBV	OR(95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
CC	18/57			1.493(0.740-3.011)	0.263	1.226(0.437-3.444)	0.699
CT	17/80	1.486(0.706-3.130)	0.297				
TT	5/24	1.516(0.505-4.552)	0.458				
AFP<20 /AFP≥20							
CC	35/40			1.952 (1.082-3.522)	0.026	2.506 (0.970-6.475)	0.058
CT	33/64	1.697(0.914-3.149)	0.094				
TT	21/3	3.354(1.226-9.177)	0.018				

Table 6. Association of rs401681 Genotypes with Relative Factors in HCC Patients

Genotype	Cases (N)	Co-dominant		Dominant		Recessive	
rs401681	Non-HBV/ HBV	OR(95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
CC	18/68			1.119 (0.557-2.247)	0.752	4.303(0.553-33.462)	0.163
CT	21/77	0.971(0.487-1.972)	0.934				
TT	16-Jan	4.235(0.526-34.106)	0.175				
	AFP<20 /AFP≥20						
CC	35/51			1.337(0.750-2.384)	0.324	2.932 (0.814-10.565)	0.100
CT	36/62	1.182(0.652-2.142)	0.582				
TT	14-Mar	3.203(0.856-11.978)	0.086				

Table 7. Association between *TERTrs2736098* and Cancer Progress

Genotype	Cases (N)	Co-dominant		Dominant		Recessive	
	I+II / III+IV[a]	OR (95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
CC	30/45			0.667(0.374-1.190)	0.170	1.070 (0.485-2.360)	0.866
CT	50/47	0.627(0.341-1.153)	0.133				
TT	13/16	0.821(0.345-1.950)	0.654				
	n=0[b] / n=1[c]						
CC	64/11			0.669 (0.283-1.581)	0.360	1.216(0.384-3.855)	0.740
CT	88/9	0.595(0.233-1.520)	0.278				
TT	25/4	0.931(0.271-3.198)	0.909				
	Nod=1 / No≥2						
CC	31/44			0.512 (0.286-0.914)	0.023	0.611(0.273-1.370)	0.232
CT	55/42	0.538(0.292-0.991)	0.047				
TT	18/11	0.431(0.179-1.038)	0.060				

[a]TNM; [b]No lymph node metastasis; [c]Lymph node metastasis; [d]The number of tumors

Table 8. Association between *CLPTM1Lrs401681* and Cancer Progress

Genotype	Cases (N)	Co-dominant		Dominant		Recessive	
	I+II / III+IV[a]	OR (95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
CC	38/48			0.667(0.374-1.190)	0.170	1.070 (0.485-2.360)	0.866
CT	49/49	0.792(0.443-1.416)	0.431				
TT	11-Jun	1.451(0.492-4.282)	0.500				
	n=0b / n=1c						
CC	77/9			0.864 (0.493-1.514)	0.609	2.523 (0.750-8.486)	0.135
CT	87/11	1.082(0.426-2.749)	0.869				
TT	13/4	2.632(0.706-9.818)	0.150				
	Nod=1 / No≥2						
CC	49/37			1.445(0.823-2.535)	0.200	1.227(0.454-3.321)	0.687
CT	47/51	1.437(0.803-2.573)	0.222				
TT	9-Aug	1.490(0.525-4.231)	0.454				

[a]TNM; [b]No lymph node metastasis; [c]Lymph node metastasis; [d]The number of tumors.

95%CI= 1.082-3.522). Table 7, 8 show the association between polymorphisms and HCC progress. Individuals carrying the rs2736098 T allele were associated with a significantly association with tumor number (p=0.023). No other significant associations were observed between the two SNPs and cancer progress.

Discussion

This case-control study explored the association of the *TERT-CLPTM1L* region with risk of HCC. Both *TERT* rs2736098 and *CLPTM1L* rs401681 polymorphisms showed a significant association with risk of HCC in a Chinese male population, and significant multiplicative interactions were observed between the two SNPs in the development of HCC.

Telomerase is composed of three parts: telomerase mRNA (hTR), telomerase-related protein (TP1), and telomerase reverse transcriptase (h TRET) (Takakura et al., 1999; Artandi et al., 2010). It is a specialized DNA polymerase responsible for telomere maintenance and is expressed at high levels in most human cancer cells such as lung cancer, skin cancer, and Glioma (Harley et al., 1990; Iwama et al., 1998; Rudolph et al., 2001). The *TERT* gene spans 35 kb of genomic DNA, and consists of 16 exons and 15 introns. The rs2736098 polymorphism is located within the second exon (Wick et al., 1999); however, its function is unclear and its effect on the molecular mechanism of HCC risk has not been ascertained. Our data provide strong evidence from a Chinese population that the rs2736098 [T] polymorphism increases susceptibility to HCC, which supports a previous study carried out in Tianjin (Zhang et al., 2012).

Limited knowledge is available regarding the function of CLPTM1L, although it is thought to contribute to the accumulation of DNA damage and cell apoptosis (Myneni et al., 2013). CLMPT1L over-expression is also reported in many human cancers, such as lung cancer (Wang et al., 2008; Ni et al., 2012). However, study findings are controversial. According to HapMap data, these discrepancies could reflect different allele frequencies in different ethnicities, or might be affected by cancer types, hereditary factors, and environmental factors (Choi et al., 2009). No report has previously determined whether the *CLPTM1L* rs401681 polymorphism influences HCC susceptibility, but we found that the *CLPTM1L* rs401681 CT genotype increased the HCC risk in a Chinese male population. The dominant model also indicated that any T (CT+TT) genotypes of rs401681 were associated with HCC in male individuals.

Our analysis found that carrying the *TERT* rs2736098 T allele and *CLPTM1L* rs401681 T allele increased the odds of developing HCC. One explanation for this derives from a previous study that speculated that *CLPTM1L* might be in strong linkage disequilibrium with other potential functional SNPs (Yamamoto et al., 2001; Zhao et al., 2012). In addition, *CLPTM1L* was reported to be involved in cellular responses to genotoxic stress and cisplatin resistance (James et al., 2012). Many factors can induce genotoxic stress and DNA damage, which would lead to the malignant transformation of cells. Smoking is considered to be a major factor (Myneni et al., 2013), and, indeed, our data showed that individuals carrying *TERT* rs2736098 or *CLPTM1L* rs401681 risk genotypes and who smoked had a significant association with HCC (p=0.022 and 0.009, for respective heterogeneity) .

The association of the two SNPs with clinical indicators HBV and AFP and HCC progress was analyzed in HCC patients, but only a significant association between the *TERT* T allele and AFP was identified. The rearrangement and instability of genomic DNA could occur through the integration of HBV DNA and hepatocyte chromosomal DNA (Zhang et al., 2012). Indeed, recent reports showed that the telomerase gene was targeted for integration in independent HCCs and HCC-derived cell lines (Brechot, 2004). However, we did not obtain significant results regarding HBV and SNP associations. This discrepancy could reflect the analysis of only the male gender in the present study and its small sample size. AFP is regarded as the most useful serum biomarker for HCC patients, with a critical value of 20 serum proteins being commonly used in the early diagnosis of HCC (Shen et al., 2012). Our results showed that patients carrying the rs2736098 T allele were associated with a significantly increased AFP level.

To our knowledge, this is the first study to investigate the effects of *TERT* rs2736098 and *CLPTM1L* rs401681 SNPs in a Chinese Han population on HCC susceptibility. Although our study was limited regarding its small sample size and lack of associated risk factors such as alcohol use, we nevertheless identified prominent associations with HCC and *TERT* and *CLPTM1L* polymorphisms, gene-gene interactions, and gene-risk factor interaction. The *TERT* rs2736098 T allele and *CLPTM1L* rs401681 T allele increased the risk of HCC, and the association of *TERT* and *CLPTM1L* with HCC was stronger in smokers. The *TERT* rs2736098 T allele was also associated with increased AFP levels. Neither of the two SNPs had an association with HCC progress. Further work will be necessary to confirm these findings and to investigate more HCC risk factors in larger sample sizes and in different ethnicities.

Acknowledgements

Conceived and designed the experiments: LYS. Performed the experiments:LYS XLL LS YZ MMZ. Analyzed the data: LYS LS YZ. Contributed reagents/materials/analysis tools: LYS ZHY HYS BSZ. Wrote the paper: LYS.

References

Artandi SE, DePinho RA (2010). Telomeres and telomerase in cancer. *Carcinogenesis*, **31**, 9-18

Brechot C (2004). Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms. *Gastroenterology*, **127**, 56-61.

Choi JE, Kang HG, Jang JS, et al (2009). Polymorphisms in telomere maintenance genes and risk of lung cancer. *Cancer Epidemiology Biomarkers and Prevention*, **18**, 2773-881.

Cong YS, Wen J, Bacchetti S (1999). The human telomerase catalytic subunit h*TERT*: organization of the gene and characterization of the promoter. *Hum Mol Genet*, **8**, 137-42

Global cancer statistics (2011).
Harley CB, Futcher AB, Greider CW (1990). Telomeres shorten during ageing of human fibroblasts. *Nature*, **345**, 458-60.
Hashem B. EI-Serag, K. Lenhard Rudolph (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*, **132**, 2557-76.
Iwama H, Ohyashiki K, Ohyashiki JH, et al (1998). Telomeric length and telomerase activity vary with age in peripheral blood cells obtained from normal individuals. *Hum Genet*, **102**, 397-402.
James MA, Wen W, Wang Y, et al (2012). Functional characterization of *CLPTM1L* as a lung cancer risk candidate gene in the 5p15.33 locus. *PLOS ONE*, **7**, 36116.
Luis E. Donate and Maria A.Blasco (2011). Telomeres in cancer and ageing. *PhilosT roy Soc B*, **366**, 76-84
Myneni AA, Chang SC, Niu R, et al (2013). Genetic polymorphisms of *TERT* and *CLPTM1L* and risk of lung cancer--a case-control study in a Chinese population. *Lung Cancer*, **80**, 131-7.
Ni Z, Tao K, Chen G, et al (2012). *CLPTM1L* is overexpressed in lung cancer and associated with apoptosis. *PLOS ONE*, **7**, 52598.
Rafnar T, Sulem P, Stacey SN, et al (2009). Sequence variants at the *TERT-CLPTM1L* locus associate with many cancer types. *Nat Genet*, **41**, 221-7.
Rudolph KL, Millard M, Bosenberg MW, DePinho RA (2001). . Telomere dysfunction and evolution of intestinal carcinoma in mice and humans. *Nat Genet,* **28**, 155-9.
Sambrook J (1989). Molecular cloning: a laboratory manual. cold spring harbor laboratory press, New York, NY.
Shen Q, Fan J, Yang XR, et al (2012). Serum DKK1 as a protein biomarker for the diagnosis of hepatocellular carcinoma: a large-scale, multicentre study. *The Lancet Oncology*, **13**, 817-26.
Takakura M, Kyo S, Kanaya T, et al (1999). Cloning of human telomerase catalytic subunit (h*TERT*) gene promoter andidentification of proximal core promoter sequences essential for transcriptional activation in immortalized and cancer cells. *Cancer Res*, **59**, 551-7
Tanabe KK, Lemoine A, Finkelstein DM, et al (2008). Epidermal growth factor gene functional polymorphism and the risk of hepatocellular carcinoma in patients with cirrhosis. *JAMA*, **299**, 53-60.
Wang Y, Broderick P, Webb E, et al (2008). Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nature Genetics*. **40**, 1407-9.
Wick M, Zubov D, Hagen G (1999). Genomic organization and promoter characterization of the gene encoding the human telomerase reverse transcriptase (h*TERT*). *Gene*, **232**, 97-106.
Yamamoto K, Okamoto A, Isonishi S, Ochiai K, Ohtake Y (2001). A novel gene, CRR9, which was up-regulated in CDDP-resistant ovarian tumor cell line, was associated with apoptosis. *Biochem Bioph Res Co*, **280**, 1148-54
YoungNS (2010). Telomere biology and telomere diseases: implications for practice and research. *American Society of Hematology Education Program*, **2010**, 30-35.
Zhang C, Tian YP, Wang Y, et al (2012). h*TERT* rs2736098 genetic variants and susceptibility of hepatocellular carcinoma in the Chinese population: a case-control study. *Hepatobiliary and Pancreatic diseases international: HBPDINT*, **12**, 74-9.
Zhao Y, Chen G, Zhao Y, et al (2012). Fine-mapping of a region of chromosome 5p15.33 (*TERT*-CLPTM1L) suggests a novel locus in *TERT* and a*CLPTM1L* haplotype are associated with glioma susceptibility in a Chinese population. *Int J cancer*, **131**, 1569-76.