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Transcription Factor 21 (TCF21) rs12190287 Polymorphism is Associated with Osteosarcoma Risk and Outcomes in East Chinese Population

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Background: The transcription factor 21 (TCF21) gene is believed to be a tumor suppressor gene. TCF21 gene polymorphisms were found to play a role in the tumorigenesis of some solid malignancies. We raised a hypothesis that genetic polymorphisms of TCF21 were correlated with risk and prognosis of osteosarcoma.

Material/Methods: We recruited 225 young osteosarcoma individuals and 250 cancer-free controls. Five tagging SNPs (TCF21 rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, rs12190287 C>G, and rs4896011 T>A) were genotyped. Preserved DNA samples from blood underwent PCR analysis for genotyping.

Results: rs12190287 C>G is a good predictor of osteosarcoma risk and outcomes. The CG and GG genotypes of rs12190287 predict elevated risk of osteosarcoma. Besides, rs12190287 CG and GG genotypes are associated with Enneking stage and potential in forming metastasis of osteosarcoma.

Conclusions: Genetic polymorphisms of TCF21 are potentially predictive for osteosarcoma risk and outcomes.

MeSH Keywords: Osteosarcoma • Polymorphism, Single Nucleotide • Prognosis

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Background

Osteosarcoma is regarded as the most common primary malignancy originated from the bone, characterized by early metastasis potential and poor prognosis [1]. Osteosarcoma is threatening the health of adolescents; hence, finding out a predictor to evaluate the risk of osteosarcoma will be valuable. Besides, current therapeutic strategies are composed of neo-adjuvant chemotherapy, surgical resection, postoperational chemotherapy and/or radiotherapy [2]. However, once the tumor is resistant to chemotherapy, the outcome is very poor. Clinicians are trying to employ some second-line chemotherapy agents, such as etoposide and ifosfamide, for poor response individuals [2]. Thus, finding reliable biomarkers to evaluate the risk and prognosis of osteosarcoma will allow physicians to use more aggressive regimens for high-risk cases.

Single nucleotide polymorphisms (SNPs) of different genes are associated with cancer risk and progression. Emerging studies have revealed the predictive role that SNPs serve in solid malignancies. But SNPs in osteosarcoma are still poorly understood, because of the low morbidity of the disease. Thus, SNPs are good candidates for researchers to identify prognostic markers and consequently utilize them in evaluating the risk and outcome of osteosarcoma [3].

Transcription factor 21 (TCF21), a member of the basic helix-loop-helix transcription factor family, plays an important role in controlling cell development and differentiation [4,5]. In the past, TCF21 was believed to be related to coronary artery diseases [6,7]. Recently, it was also shown to work as a tumor suppressor [8,9]. However, the expression and activation status of TCF21 is frequently altered in quite a few types of malignancies. Several studies reported that the expression of TCF21 was downregulated in breast cancer, bladder cancer, and lung cancer [10–12]. In addition, TCF21 genetic polymorphisms were found to be correlated with the risk of breast cancer, bladder cancer, and renal cell cancer. Thus, it is rational to hypothesize that genetic polymorphism of TCF21 is correlated with osteosarcoma risk and prognosis.

Our study on TCF21 polymorphisms in osteosarcoma included collecting blood samples from 225 osteosarcoma patients and 230 cancer-free controls from east China. In this case-control study, we analyzed five TCF21 tagging SNPs (rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, rs12190287 C>G, and rs4896011 T>A) to determine if TCF21 polymorphism may be correlated with osteosarcoma risk and outcomes.

Material and Methods

Osteosarcoma individuals and controls

A total of 225 patients (age <25 years), who were diagnosed with primary osteosarcoma and 230 tumor-free normal controls were recruited for this study. All of the osteosarcoma individuals were previously diagnosed by pathological examining during April 2007 and April 2012. Peripheral blood samples for research use were collected at the first diagnosis, and consequently preserved in the department of epidemiology of Fudan University for the further DNA extraction. All osteosarcoma patients received tumor resection by experienced orthopedic surgeons and had follow-up for at least five years. Tumor-free normal controls were selected from ordinary fracture individuals, and they were matched to osteosarcoma patients by age and sex. All the clinical information from the osteosarcoma patients were reviewed from previously saved medical records provided by the Department of Epidemiology of Fudan University, and information from the fracture control cases were obtained from the medical records collected by the Department of Orthopedics, The First People's Hospital of Wenling.

Ethics approval

Written informed consent was obtained from all recruited participants or their current guardians. The research protocol was approved by the Ethics Committees of both involved institutions (The First People's Hospital of Wenling, and Fudan University).

DNA isolation

Total genomic DNA was extracted using a standard salting-out method from peripheral blood and then preserved in liquid nitrogen for further study. A DNA Blood Mini Kit (Qiagen, Berlin, Germany) was used following the manufacturer's instructions.

Genotyping

Five selected SNPs (rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, rs12190287 C>G, and rs4896011 T>A) were tested in this study. Genotypes were determined by ligase detection reaction of polymerase chain reaction (PCR-LDR) method. PCR primers, and LDR probes which include two allele specific probes and one common labeled probe, were synthesized by Shenggong Biotechnology, Shanghai. The fluorescent products of LDR were analyzed by sequence detection software on ABI 3730xl DNA Analyzer (ThermoFisher Scientific, Waltham, MA, USA).

Haplotype analysis

The online SHEsis system, provided by the Bio-X lab of Shanghai Jiaotong University, was used to perform haplotype analysis.

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Table 1. General characteristics of the subjects.

Variables		Osteosarcoma Cases [n (%)]	Control n (%)]	*P*
Age	Mean ±SD (year)	17.76±3.25	18.24±2.90	0.351
Gender	Male	117 (52.00)	138 (55.20)	0.265
	Female	108 (48.00)	112 (44.80)	
Location	Trunk	38 (12.44)		
	Limbs	197 (57.56)		
Ennecking Stages	IA or IB	32 (14.22)		
	IIA or IIB or III	193 (85.78)		
Operation	Amputation	38 (16.89)		
	Limb salvage	187 (83.11)		
Metastasis	Yes	40 (17.78)		
	No	185 (82.22)		

Computational haplotyping method was used, and the five chosen SNPs were analyzed online to look for possible frequent haplotypes.

Statistical analysis

All data were analyzed by a two-sided method performed by SPSS (v19.0; IBM, NY, USA). The chi-square (χ^2) test was used to detect the differences in the distributions of participant characteristics, variables, and genotypes of TCF21 between the cases and controls. The Hardy-Weinberg equilibrium (HWE) was calculated by using goodness-of-fit χ^2 test. Odds ratios (ORs) and 95% confidential intervals (95% CIs) were calculated to evaluate the associations between the five selected SNPs and the morbidity or clinical outcome of osteosarcoma in these tested blood samples. Logistic regression analysis was preformed to calculate crude ORs, and consequently adjusted for age and sex. A *p* value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics

The clinical characteristics of all recruited osteosarcoma individuals, as well as tumor-free normal controls are shown in Table 1. Of the cases, 117 osteosarcoma cases were male and 108 were female. The tumors were clinically graded according to the widely used Enneking GTM System (a commonly accepted grading system for musculoskeletal tumors). The medium ages and the age ranges of osteosarcoma individuals and tumor-free normal controls were 17.76 years and 18.24 years, respectively. No significant statistical difference was found in age and sex between the two examined groups (p=0.351 and 0.265, respectively).

TCF21 genomic SNPs were correlated with osteosarcoma risk

The pooled data of five studied SNPs (rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, rs12190287 C>G, and rs4896011 T>A) in this report are illustrated in Table 2. In tumor-free normal control individuals, the distributions of genotype of the five chosen SNPs were found all within HWE (p=0.128, 0.710, 0.129, 0.128, and 0.251, respectively). Genotyping results revealed an association of TCF21 polymorphism and osteosarcoma. In rs12190287 C>G, when the CC homozygote genotype was set as the reference for further comparison with the other genotypes, the CG genotype showed statistically significant elevated risk of osteosarcoma. The statistic results showed a strong correlation between CG genotype and osteosarcoma (crude OR=1.75, 95% CI=1.21–2.41, p=0.002; adjusted OR=1.77, 95% CI=1.20–2.39, p=0.002). Furthermore, the GG genotype was also shown to be correlated with the risk of osteosarcoma (crude OR=1.32, 95% CI=1.05–1.99, p=0.048; adjusted OR=1.35, 95% CI=1.07–2.01, p=0.043). When analyzing the G dominant model (CG+GG), a greater statistical difference was found (CG/GG versus CC: crude OR=1.70, 95% CI=1.29–2.31, p=0.003; adjusted OR=1.72, 95% CI=1.30–2.32, p=0.003). No statistically significant difference was found in the recessive model.

The other four tested SNPs (rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, and rs4896011 T>A) did not show any correlation with osteosarcoma risk.

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Table 2. Logistic regression analyses of associations between TCF21 rs2327429 T>C, rs2327433 A>G, rs2327433 A>G, rs12190287 C>G, and rs4896011 T>A polymorphisms and risk of osteosarcoma.

TCF21 Genotype	Cases (n=225)		Controls (n=250)		Crude OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*
	n	%	n	%				
rs2327429 T>C								
TT	10	4.44	9	3.60	1.00		1.00	
TC	41	18.22	49	19.60	0.93 (0.51–1.23)	0.880	0.95 (0.52–1.24)	0.901
CC	174	77.33	192	76.80	1.20 (0.80–1.76)	0.765	1.19 (0.80–1.76)	0.780
TC+CC	215	95.56	241	96.40	1.17 (0.55–1.64)	0.755	1.18 (0.55–1.72)	0.759
TT+TC	51	22.67	60	23.2	1.00		1.00	
CC	174	77.33	226	76.8	1.01 (0.57–1.25)	0.498	0.99 (0.55–1.20)	0.169
rs2327433 A>G								
AA	20	8.89	27	10.80	1.00		1.00	
AG	101	44.89	118	47.20	0.95 (0.51–1.63)	0.682	0.98 (0.54–1.67)	0.805
GG	104	46.22	105	42.00	1.17 (0.76–2.21)	0.614	1.18 (0.19–2.31)	0.542
AG+GG	205	91.11	249	89.20	1.09 (0.64–1.80)	0.719	1.08 (0.64–1.79)	0.798
AA+AG	121	53.78	165	58.00	1.00		1.00	
GG	104	46.22	121	42.00	1.29 (0.89–1.70)	0.266	1.20 (0.87–1.73)	0.268
rs2327433 A>G								
AA	101	44.89	110	44.00	1.00		1.00	
AG	82	36.44	96	38.40	0.95 (0.78–1.20)	0.520	0.89 (0.68–1.21)	0.526
GG	42	18.67	44	17.60	1.05 (0.72–1.43)	0.571	1.15 (0.73–1.54)	0.627
AG+GG	124	55.11	168	56.00	0.92 (0.66–1.26)	0.893	0.93 (0.67–1.29)	0.880
AA+AG	183	81.33	240	82.40	1.00		1.00	
GG	42	18.67	46	17.60	1.05 (0.71–1.63)	0.309	1.09 (0.81–1.74)	0.310
rs12190287 C>G								
CC	89	39.56	139	55.70	1.00		1.00	
CG	113	50.22	84	33.60	1.75 (1.21–2.41)	0.002*	1.77 (1.20–2.39)	0.002*
GG	23	10.22	27	10.80	1.32 (1.05–1.99)	0.048*	1.35 (1.07–2.01)	0.043*
CG+GG	136	60.44	111	44.40	1.70 (1.29–2.31)	0.003*	1.72 (1.30–2.32)	0.003*
CC+CG	202	89.78	223	89.30	1.00		1.00	
GG	23	10.22	27	10.80	1.17 (0.63–2.04)	0.205	1.17 (0.62–2.05)	0.205
rs4896011 T>A								
TT	28	12.44	30	12.00	1.00		1.00	
TA	83	36.89	101	40.40	0.71 (0.31–1.23)	0.369	0.70 (0.38–1.20)	0.393
AA	114	50.67	119	47.60	0.86 (0.55–1.57)	0.491	0.92 (0.55–1.55)	0.503
TA+AA	197	86.38	230	88.00	0.73 (0.50–1.35)	0.756	0.72 (0.50–1.31)	0.733
TT+TA	111	47.31	131	52.40	1.00		1.00	
AA	114	50.67	119	47.60	1.11 (0.87–1.49)	0.205	1.20 (0.86–1.68)	0.276

* Statistically significant (P<0.05).

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Table 3. Correlation between genotype frequencies of TCF21 rs12190287 C>G and clinical features in osteosarcoma individuals.

Variables	n	CC n (%)	CG n (%)	GG n (%)	*P*
Location					
Trunk	28	13 (46.43)	13 (46.43)	2 (7.14)	0.385
Limbs	197	74 (37.56)	98 (49.75)	25 (12.69)	
Ennecking stages					
IA or IB	32	18 (56.25)	11 (34.38)	3 (9.38)	0.032*
IIA or IIB or III	193	64 (33.16)	96 (49.74)	33 (17.10)	
Operation					
Amputation	38	14 (36.84)	19 (50.00)	5 (13.16)	0.328
Limb salvage	187	73 (39.03)	86 (45.99)	28 (14.97)	
Metastasis					
Yes	40	11 (27.50)	18 (45.00)	11 (27.50)	0.037*
No	185	74 (40.00)	90 (48.65)	26 (11.35)	

* Statistically significant (P<0.05)

Table 4. Confounding variables (Ennecking stages).

Confounding variables		IA or IB cases n (%)]	IIA or IIB or III cases n (%)]	*P*
Age	Mean ±SD (year)	15.27±3.19	15.79±2.96	0.233
Gender	Male	17 (53.13)	115 (61.44)	0.226
	Female	15 (46.87)	78 (40.41)	

Table 5. Confounding variables (metastasis).

Confounding variables		Metastasis cases [n (%)]	Non-metastasis cases [n (%)]	*P*
Age	Mean ±SD (year)	15.59±3.65	16.02±3.10	0.096
Gender	Male	21 (52.50)	110 (59.46)	0.401
	Female	19 (47.50)	75 (40.54)	

Genomic SNPs of TCF21 were related to the grade and metastasis of osteosarcoma

Clinical information about the location, grade, operation method (underwent amputation or limb salvage) and remote metastasis of osteosarcoma individuals were analyzed to study the associations between genomic SNPs of TCF21 and osteosarcoma (Table 3). For rs12190287 C>G, the calculated frequencies of CG and GG genotypes at late Enneking stages (49.74% and 17.10%, respectively) were significantly higher when compared with early Enneking stage individuals (34.38% and 9.38%, respectively), and statistical significance in frequency distribution was also revealed (p=0.032). In addition, the investigation regarding metastasis revealed similar results. The genotype GG had higher frequency (27.50%) in tumor metastasized individuals when compared with the other patients who did not form remote metastasis at first diagnosis (11.35%), and further calculations revealed a statistical significance in frequency distribution (p=0.037).

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Table 6. Haplotype analysis.

Haplotype	Cases (n=225)		Controls (n=250)		p	OR (95% CI)	
	n (frequency)		n (frequency)				
CATCT	32.18	(0.057)	31.28	(0.053)	0.583	1.114	(0.692–1.935)
CATTT	23.18	(0.056)	28.45	(0.051)	0.598	0.864	(0.502–1.471)
CACTT	22.89	(0.035)	29.91	(0.070)	0.077	0.629	(0.375–1.025)
CACCG	28.76	(0.049)	26.92	(0.045)	0.514	1.199	(0.696–2.019)
CACCT	20.06	(0.035)	26.12	(0.041)	0.232	0.702	(0.392–1.107)
CCCCG	9.67	(0.016)	11.88	(0.025)	0.041*	0.765	(0.277–0.871)
CCCCT	99.68	(0.181)	95.65	(0.192)	0.135	0.805	(0.606–1.049)
CCCTG	36.73	(0.061)	16.24	(0.022)	<0.001*	2.117	(1.485–4.817)
CCCTT	37.85	(0.073)	41.19	(0.081)	0.690	0.914	(0.587–1.411)
CCTCG	24.73	(0.042)	27.50	(0.048)	0.790	0.910	(0.532–1.610)
CCTCT	29.01	(0.050)	16.11	(0.047)	0.761	0.945	(0.925–1.578)
CCTTT	47.92	(0.079)	30.80	(0.052)	0.032*	1.710	(1.054–2.226)

* Statistically significant (P<0.05).

The pooled data on confounding variables was shown in Tables 4 and 5. No statistical difference was found in confounding variables.

Statistical differences were shown in haplotype analyses

Twelve frequent (frequency over 3%) haplotypes were picked out by online analyses of the five candidate SNPs: CATCT, CATTT, CACTT, CACCG, CACCT, CCCTG, CCCCG, CCTCG, CCCCT, CCCTT, CCTTT and CCTCT (shown in Table 6). The 12 haplotypes underwent further analysis to find out possible statistical differences between osteosarcoma cases and tumor-free normal controls. Among the 12 frequent haplotypes, CCTTT, CCCCG, and CCCTG displayed statistical significances between osteosarcoma individuals and tumor-free normal controls (p=0.041, 95% CI=0.277–0.871, p<0.001, 95%=1.485–4.817, and p=0.032, 95% CI=1.054–2.226, respectively).

Discussion

Osteosarcoma is characterized by low morbidity (about three per million people every year) and unfavorable biological behaviors [13]. Although the five-year survival rate for ordinary osteosarcoma cases has reached 65–70% by using chemotherapy and surgery, individuals bearing chemo-resistant tumors or metastasized tumors suffer from poor prognosis, with a five-year survival rate of only 20% or less [13]. Investigators keep looking for possible novel therapeutic regimens for those high-risk cases. However, during the past three decades, barely any new agents or therapeutics have been added to the standard first-line regimen for osteosarcoma [14]. Therefore, exploring reliable biomarkers, especially those easy to detect or examine, will greatly benefit the clinical treatment of osteosarcoma [15].

Genomic factors, especially those easy to be examined by some simple methods such as PCR, are valuable to predict the risk or outcome of malignancies. Once physicians find evidence of a worse prognosis for a cancer, they may consider using more aggressive therapeutic regimens. Recently, accumulating studies have provided the evidence that genomic factors, including SNPs, are correlated with the tumorigenesis and progression of solid malignancies. In osteosarcoma, there are also some reports demonstrating that some gene polymorphisms may be related with outcomes, such as HER2, NAT2, and WWOX [16–18]. However, to more accurately predict the risk and prognosis of osteosarcoma, only using limited number of predictors are far from satisfactory, as there may be some controversies in the given genes or proteins. Using comprehensive biomarkers will profoundly elevated the accuracy of prediction for the risk and outcomes of osteosarcoma.

TCF21 was recently found to be not only associated with coronary artery diseases, but also correlated with tumor risk and outcomes [11,12]. Evidence has been provided for the role TCF21 polymorphism plays in breast cancer, bladder cancer, and kidney cancer. However, up to now, to the best of the authors' knowledge, there is little information on TCF21 polymorphism and osteosarcoma. Herein, we provide the first data on the association between TCF21 polymorphism and osteosarcoma.

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We used preserved DNA samples from peripheral blood of osteosarcoma individuals to analyze TCF21 gene polymorphisms. Although preserved DNA sample is not as good as fresh tissue-extracted DNA, we still successfully performed PCR-LDR assays. We investigated five SNP candidates to resolve the puzzle of whether TCF21 polymorphism is related to osteosarcoma risk and prognosis. We discovered that TCF21 rs12190287 polymorphism was significantly associated with a higher risk of osteosarcoma. In addition, rs12190287 polymorphism was correlated with the clinical Enneking GTM grade and metastasis potential of osteosarcoma, suggesting an important role that rs12190287 polymorphism plays in the carcinogenesis and progression of osteosarcoma. Further studies on TCF21 may reveal more information on its function in osteosarcoma.

There were several limitations in this study. First, inherent bias was unavoidable as all the blood samples were previously collected from different institutions, and all the samples were preserved in one institution. Also, the sample size was not large enough, as the morbidity of osteosarcoma is quite low, and we obtained the blood sample preserved in only one institution. We continue to collect data from osteosarcoma patients to inform future reports on the genomic factors in osteosarcoma.

Conclusions

TCF21 gene polymorphism was associated with the risk and outcome of osteosarcoma in an east Chinese population. In TCF21 rs12190287, the CG and GG genotypes predicted elevated risk of osteosarcoma and worse surgical stage and higher potential to form metastasis.

Conflict of interest

None.

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