Polymorphisms in the promoter region of the CASP8 *gene are not associated with non-Hodgkin's lymphoma in Chinese patients*

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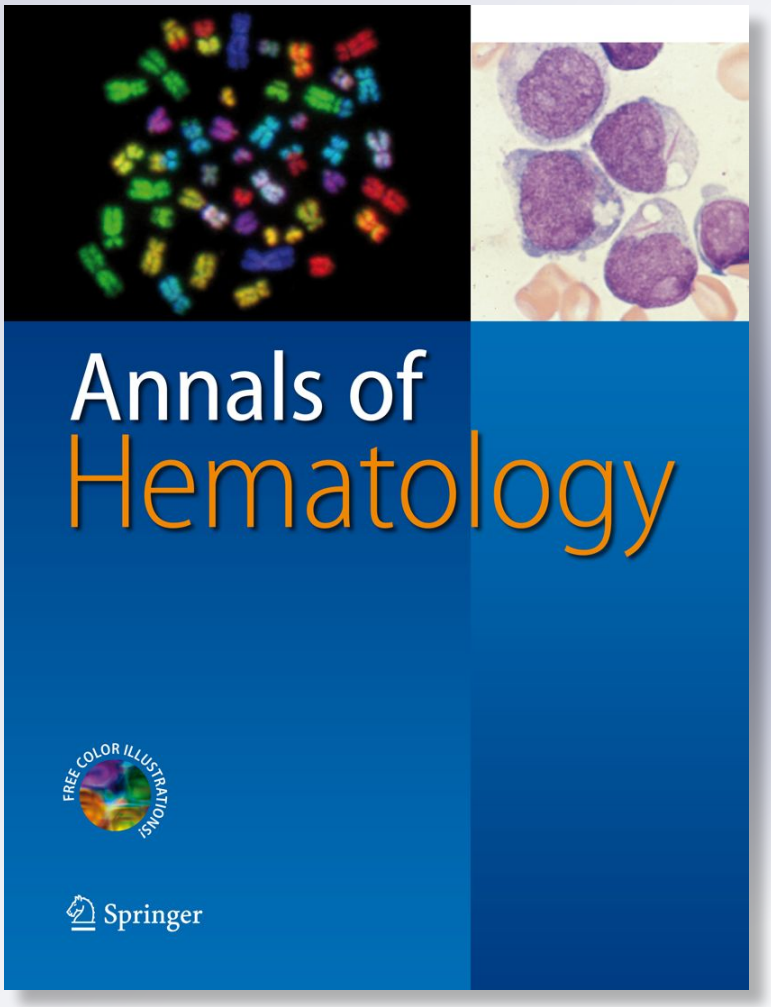

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ORIGINAL ARTICLE

Polymorphisms in the promoter region of the *CASP8* gene are not associated with non-Hodgkin's lymphoma in Chinese patients

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Abstract Caspase-8 (CASP8) involved in apoptosis plays an important role in mediating the normal regulation of cell proliferation, differentiation, inflammation, and homeostasis of multicellular organisms. Genetic polymorphisms, rs3834129 (−/CTTACT) and rs3769821 (T/C), in the promoter region of different *CASP8* transcripts, were reported to be associated with genetic susceptibility of multiple cancers and non-Hodgkin's lymphoma (NHL), respectively. To investigate whether these two genetic variants, together with rs113686495 (−/CTGTCATT) which is 50 bp downstream of rs3769821, were associated with NHL in Chinese patients, we genotyped two cohorts of case and control samples from Kunming (case n=64, control n=133) and Shanghai (case n=75, control n=107). Luciferase assays were further performed to characterize the potential role of different alleles in the promoter region of the *CASP8* gene. In contrast to previous studies, we found no difference regarding the genotypes and haplotypes of rs3834129, rs3769821, and rs113686495 between the case and control samples. Luciferase assays of the promoter regions harboring different alleles of these three variants also showed no difference. Our negative results gave no support for an active role for these genetic variants in conferring NHL in Chinese patients.

Keywords *CASP8* · Chinese · Non-Hodgkin's lymphoma · SNP · Genetic susceptibility

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Introduction

Apoptosis, also named programmed cell death, is involved in maintaining the homeostasis and development of multicellular organisms [1]. Aberrant regulations of apoptosis result in a great number of human diseases including cancers, autoimmune diseases, dysfunction of development, and neurodegenerative diseases [1–3]. Apoptotic cell death is mediated by a family of highly conserved intracellular caspases (cystein-dependent aspartate-specific proteases), which can be divided into "initiator" caspases and "effector" caspases [4, 5]. Genetic variants of the caspase genes, including single nucleotide polymorphisms (SNPs) and insertion/deletions (indels), have been widely documented to be associated with various types of human diseases [6–10].

Accumulating evidence suggested that caspase genes were altered in non-Hodgkin's lymphoma (NHL) [11, 12]. Somatic mutations in *CASP3* and *CASP10* have been reported in patients with NHL [13, 14]. A large number of SNPs in the caspase genes were also reported to be associated with the risk of NHL and/or its clinical subtypes [13–16]. In particular, somatic mutations and genetic

Table 1 Information of the studied samples

Variables	Case (n=139)		Control (n=240)	
	KM (n=64)	SH (n=75)	KM (n=133)	SH (n=107)
Age (mean±SD)	52.0±16.5	51.5±15.2	53.1±17.3	50.0±13.1
Gender				
Male (%)	39 (60.9)	38 (50.7)	81 (60.9)	62 (57.9)
Female (%)	25 (39.1)	37 (49.3)	52 (39.1)	45 (42.1)

KM Kunming samples, *SH* Shanghai samples

polymorphisms in the *CASP8* gene have been reported in patients with breast cancer, glioma, lung cancers, and multiple myeloma [6, 17–20]. The indel polymorphism, rs3834129 (−/CTTACT, written as 6 bp/del in the following text), in the promoter region of the *CASP8* gene, was suggested to remove the stimulatory protein 1 binding site and to be associated with reduced susceptibility to many cancers, including lung, esophageal, gastric, colorectal, cervical, and breast cancers in Chinese population [21]. However, this finding was not replicated in subsequent case–control studies that were based on European populations and American populations [22, 23]. Single nucleotide polymorphism (SNP) rs3769821 (T/C), which was located in the promoter of *CASP8* gene, was investigated in a pooled analysis of three populations from the United States of America and Australia, and the result showed that the carrier of genotype TC or CC would have an increased risk of NHL in a dose-dependent manner [15].

To discern whether the *CASP8* gene promoter polymorphisms contributed to genetic susceptibility to NHL in Chinese patients, we genotyped three genetic variants (rs3834129, rs3769821, and rs113686495) in two cohorts of NHL cases and healthy controls. We also constructed a variety of luciferase plasmids containing the promoter regions of the *CASP8* gene with different alleles, to further characterize the potential role of these alleles. Our results showed no active role of the *CASP8* gene promoter variants in conferring NHL in Chinese patients.

Materials and methods

Samples

Two cohorts of NHL case and control samples from Kunming (case n=64, control n=133) and Shanghai (case n=75, control n=107) were analyzed in this study. These subjects were collected with informed consent. Some of the patients were previously reported by Zou et al. [24]. Demographic information of the cases and controls are shown in Table 1. This study was approved by the institutional review board of the Kunming Institute of Zoology, Chinese Academic of Sciences.

CASP8 genotyping

Genomic DNA was extracted from peripheral blood cells or bone marrow by standard phenol/chloroform method.

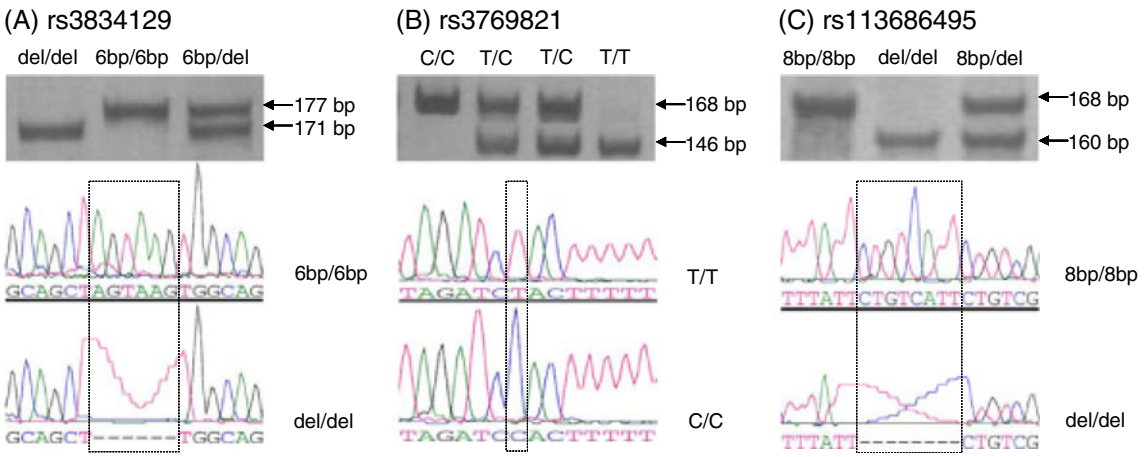

Fig. 1 Different genotypes of rs3834129 (**a**), rs3769821 (**b**), and rs113686495 (**c**) in the promoter region of *CASP8* gene. For rs3834129 and rs113686495, PCR products were separated by 12% polyacrylamide gel to show the 6 bp deletion and 8 bp deletion, respectively. For rs3769821, PCR products were digested by *Bgl*II and were separated by 10% polyacrylamide gel

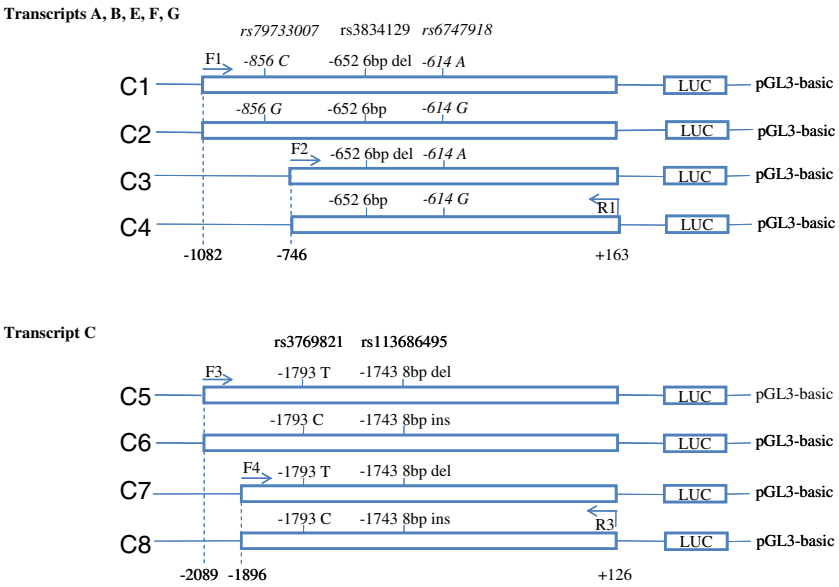

Fig. 2 Schematic structure of eight luciferase reporter vectors containing different promoter region of the *CASP8* gene. The *CASP8* gene has six transcripts. Transcripts A, B, E, F, and G share the same promoter region. The promoter region of transcript C is located in the first intron of the *CASP8* gene. Transcripts F and C encode the same isoform C. The locations of each variant and the primers were numbered according to the first nucleotide of the 5' - untranslated region (5'-UTR) of respective transcripts

Variant rs3834129 was determined by polymerase chain reaction (PCR) and polyacrylamide gel electrophoresis (PAGE). In brief, the PCR reactions were performed in a total volume of 25 μL containing about 10 ng of genomic DNA, 0.7 U of Takara rTaq DNA polymerase (TaKaRa Bio Inc., Dalian, China), 1× PCR buffer (1.5 mM $MgCl_2$), 5% DMSO, 250 μM for each dNTP, and 250 nM for each primer (forward primer, 5′-CTGCATGCCAGGAGCTAAGT-3′; reverse primer, 5′-GCCATAGTAATTCTTGCTCTGC-3′ [21]). The reactions were performed on the GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA, USA) with the following condition: an initial denaturation at 94°C for 3 min, followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, 72°C for 20 s; and a final extension at 72°C for 5 min. PCR products were separated by 12% polyacrylamide gel at 200 V for 3.5 h to discern the indel polymorphisms of rs3834129 (Fig. 1).

SNP rs3769821 was genotyped by PCR-RFLP assay using the *Bgl*II enzyme and PAGE. In addition, the 8-bp indel polymorphism (rs113686495, −/CTGTCATT, written as 8 bp/del in the following text) in the 50 bp downstream of rs3769821 was also screened by PAGE. We used primers 5′-GGAGAGTCCAGAAGACTTTATAGATC-3′ (forward, a mismatched primer created by changing CA to AG and introducing a *Bgl*II restriction site [A^GATCT] for allele T at rs3769821) and 5′-GGGTGGAGAGATAAAAG-GAAAC-3′ (reverse). We used same PCR condition as that of rs3834129. The enzyme digestion reaction was performed in a total volume of 10 μL containing 0.1 μg PCR products, 1× buffer 1 μL, 5 μL H_2O, 1 U *Bgl*II (Fermentas), and the mixture was incubated at 37°C overnight. Different genotypes of rs3769821 and rs113686495 were resolved by 10% and 12% polyacrylamide gels, respectively (Fig. 1). All the gels were stained by ethidium bromide and were visualized by the BioDoc-It Systems (UVP, CA, USA). We

Table 2 Primers and restriction enzymes used for constructing luciferase reporter vectors for the promoter region of the *CASP8* gene

Primer	Sequence (5′–3′)	Restriction enzyme
F1[a]	GTAG*CTCGAG*AATCCAGTCCTCTGCTAGG	*XhoI*
F2	GTAG*CTCGAG*ATAACCTTCACATGCAGGAATC	*XhoI*
R1[a]	GTAG*AAGCTT*AGACAGCAGATGCTCCAGAAAT	*HindIII*
F3	CTA*GCTAGC*TCAACAGGAAACCACAAT	*NheI*
F4	CTA*GCTAGC*TCTGCTACCTTTTTGTCC	*NheI*
R3	CCG*CTCGAG*TAACTCGTGTAGTAAGTG	*XhoI*

The restriction enzyme recognition sites are marked in italic and are underlined. The relative primer location is marked in Fig. 2

[a] These primers are from Sun et al. [21]

Table 3 Allele frequencies of the *CASP8* rs3834129, rs3769821, and rs113686495 in Chinese patients with non-Hodgkin's lymphoma and healthy controls

Sample		*N*	rs3834129		*P*[a]	rs3769821		*P*[a]	rs113686495		*P*[a]
			6 bp, *n* (%)	del, *n* (%)		T, *n* (%)	C, *n* (%)		del, *n* (%)	8 bp, *n* (%)	
KM	Case	64	103 (80.47)	25 (19.53)		86 (67.19)	42 (32.81)		88 (68.75)	40 (31.25)	
	Control	133	216 (81.20)	50 (18.80)	0.971	194 (72.93)	72 (27.07)	0.290	206 (77.44)	60 (22.56)	0.083
	Control[b]		7,373 (74.94)	2,465 (25.06)	0.183	–	–	–	–	–	–
SH	Case	75	121 (80.67)	29 (19.33)		98 (65.33)	52 (34.67)		100 (66.67)	50 (33.33)	
	Control	107	166 (77.57)	48 (22.43)	0.561	138 (64.49)	76 (35.51)	0.956	142 (66.36)	72(33.64)	1.000
	Control[b]		7,373 (74.94)	2,465 (25.06)	0.131	–	–	–	–	–	–

KM Kunming samples, *SH* Shanghai samples

[a] Two-sided χ^2 test

[b] General controls from Sun et al. [21]

validated the genotyping results by sequencing two randomly selected individuals with the different genotypes of each variant.

Plasmids construction

The *CASP8* gene can undergo alternative splicing and has six transcripts. We constructed eight luciferase reporter plasmids by cloning different promoter regions of these transcripts into pGL3-Basic vector (Promega, Madison City, WI, USA), which contain different alleles of rs3834129, rs3769821, and rs113686495 (Fig. 2). The primers used for amplification of the promoter regions were shown in Table 2. PCR fragments with different alleles of rs3834129 (6 bp/del) were digested by *XhoI-HindIII*, whereas PCR fragments containing different alleles of rs3769821 (T/C) and rs113686495 (8 bp/del) were digested by and *NheI-XhoI*. After gel purification, the digested fragments were ligated into pGL3-basic luciferase vector. All the inserts were confirmed by sequencing. Note that there are additional SNPs (rs79733007 and rs6747918) in these inserts (Fig. 2).

Cell culture, transient transfection, and luciferase activity detection

To discern the potential effect of the *CASP8* promoter region with different alleles, three cell lines (Hela, HEK293, and MT-4) were used for transient transfection. Hela cells and HEK293 cells were cultured in Dulbecco's modified Eagle's medium (Invitrogen, Carlsbad City, CA, USA) supplemented with 10% fetal bovine serum (FBS). MT-4 cells were cultured in RPIM 1640 medium (Invitrogen) with 10% FBS. Cells were seeded in a 24-well plate at a density of 1×10^5 per well for Hela or HEK293 cells and 2×10^5 per well for MT-4 cells. After overnight culture, cells were co-transfected with 500 ng of each reporter vector (C1-C8) and 50 ng of *Renilla* luciferase pRL-TK plasmid (Promega). Hela and HEK293 cells were transfected with the FuGENE HD Transfection Reagent (Roche, Indianapolis City, IN, USA) and the MT-4 cells were transfected by using the TransIT-2020 Transfection Reagent (Mirus Bio, Madison City, WI, USA). All transfection assays were performed in triplicate wells. After 24 h, cells were harvested in 150 μL passive lysis buffer (Promega) for 1 h and were stored at −80° C or were immediately detected for luciferase activity by using the Dual-Luciferase Reporter Assay System (Promega) on GloMax 96 Luminometer (Promega).

Statistical analysis

Statistical analysis was undertaken by using the R program (Version 2.11.1, Vienna, Austria) and *P* value

Table 4 Association of *CASP8* promoter genotypes with non-Hodgkin's lymphoma in Chinese

Sample	Genotype	rs3834129				Genotype	rs3769821				Genotype	rs113686495			
		Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	P^a		Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	P^a		Cases, *n* (%)	Controls, *n* (%)	OR (95% CI)	P^a
KM		*n*=64	*n*=133				*n*=64	*n*=133				*n*=4	*n*=133		
	6 bp/6 bp	43 (67.19)	89 (66.92)	reference		TT	28 (43.75)	69 (51.88)	reference		del/del	29 (45.31)	71 (53.38)	reference	
	6 bp/del	17 (26.56)	38 (28.57)	0.94 (0.47–1.86)	0.87	TC	30 (46.88)	56 (42.11)	1.30 (0.69–2.45)	0.42	del/8 bp	30 (46.88)	54 (40.60)	1.35 (0.72–2.53)	0.35
	del/del	4 (6.25)	6 (4.51)	1.29 (0.31–4.86)	0.71	CC	6 (9.38)	8 (6.01)	1.78 (0.53–5.71)	0.33	8 bp/8 bp	5 (7.81)	8 (6.02)	1.47 (0.40–4.92)	0.54
	~/del[b]	21 (32.81)	44 (33.08)	0.99 (0.52–1.88)	0.98	~/C[c]	36 (56.25)	64 (48.12)	1.36 (0.74–2.50)	0.32	~/ins[d]	35 (54.69)	64 (46.62)	1.36 (0.74–2.51)	0.32
SH		*n*=75	*n*=107				*n*=75	*n*=107				*n*=75	*n*=107		
	6 bp/6 bp	49 (65.33)	63 (58.88)	reference		TT	30 (40.00)	45 (42.06)	reference		del/del	32 (42.67)	48 (44.86)	reference	
	6 bp/del	23 (30.67)	40 (37.38)	0.71 (0.36–1.35)	0.30	TC	38 (50.67)	48 (44.86)	1.11 (0.57–2.18)	0.76	del/8 bp	36 (48.00)	46 (43.00)	1.08 (0.55–2.10)	0.83
	del/del	3 (4.00)	4 (3.74)	0.72 (0.12–3.76)	0.70	CC	7 (9.33)	14 (13.08)	0.78 (0.26–2.18)	0.65	8 bp/8 bp	7 (9.33)	13 (12.14)	0.86 (0.29–2.40)	0.77
	~/del[b]	26 (34.67)	44 (41.12)	0.71 (0.37–1.33)	0.29	~/C[c]	45 (60)	62 (57.94)	1.04 (0.55–1.97)	0.91	~/ins[d]	43 (57.33)	59 (55.14)	1.03 (0.55–1.94)	0.93

KM Kunming samples, *SH* Shanghai samples

[a] Data were calculated using unconditional logistic regression, adjusted for age (<40, 40–49, 50–59, 60–69, and ≥70 years) and gender

[b] Including genotypes 6 bp/del and del/del

[c] Including genotypes T/C and C/C

[d] Including genotypes 8 bp/del and 8 bp/8 bp

Table 5 Association of *CASP8* gene haplotypes and non-Hodgkin's lymphoma in Chinese

Haplotype (rs3834129-rs3769821)	KM		OR (95% CI)	P^a	SH		OR (95% CI)	P^a
	Case, *n* (%)	Control, *n* (%)			Case, *n* (%)	Control, *n* (%)		
6 bp-T	63 (49.2)	146 (54.9)	reference		70 (46.7)	90 (42.1)	reference	
6 bp-C	40 (31.3)	70 (26.3)	1.30 (0.79–2.13)	0.29	51 (34.0)	76 (35.5)	0.83 (0.51–0.34)	0.44
del-T+del-C[b]	23+2 (19.5)	48+2 (18.8)	1.14 (0.64–2.01)	0.64	28+1 (19.3)	48+0 (22.4)	0.70 (0.39–1.25)	0.23

KM Kunming samples, *SH* Shanghai samples

[a] Data was calculated using unconditional logistic regression, adjusted for age (<40, 40–49, 50–59, 60–69, and ≥70 years) and gender

[b] Haplotype del-C occurred with very low frequency and was not found in the Shanghai control sample, therefore we pooled haplotypes del-T and del-C together

was considered significant when less than 0.05. The Hardy–Weinberg equilibrium (HWE) was evaluated by comparing observed and expected genotype frequencies using the χ^2 test. Unconditional logistic regression analysis was employed to calculate the odd ratio (OR) and 95% confidence intervals (CI), for estimating the potential association of different genotypes of rs3834129, rs3769821, and rs113686495 with NHL. Genotypes 6 bp/6 bp of rs3834129, TT of rs3769821, and del/del of rs113686495 were used as the reference groups adjusted for age (< 40, 40–49, 50–59, 60–69, and ≥70 years) and gender. Haplotypes and their frequencies were estimated based on the Bayesian method by using Phase 2.1 software [25].

Results and discussion

Genotypes and haplotypes of rs3834129, rs3769821, and rs113686495 were not associated with NHL

Table 3 displayed the allele frequencies of the *CASP8* rs3834129, rs3769821, and rs113686495 polymorphisms in the case and the control groups. All three variants were not deviated from the HWE. There was no statistically significant difference between the cases and controls for allele frequencies of rs3834129, rs3769821, and rs113686495. When we used the general controls from Sun et al. [21] for rs3834129, there was still no significant difference for the allele frequencies between the cases and

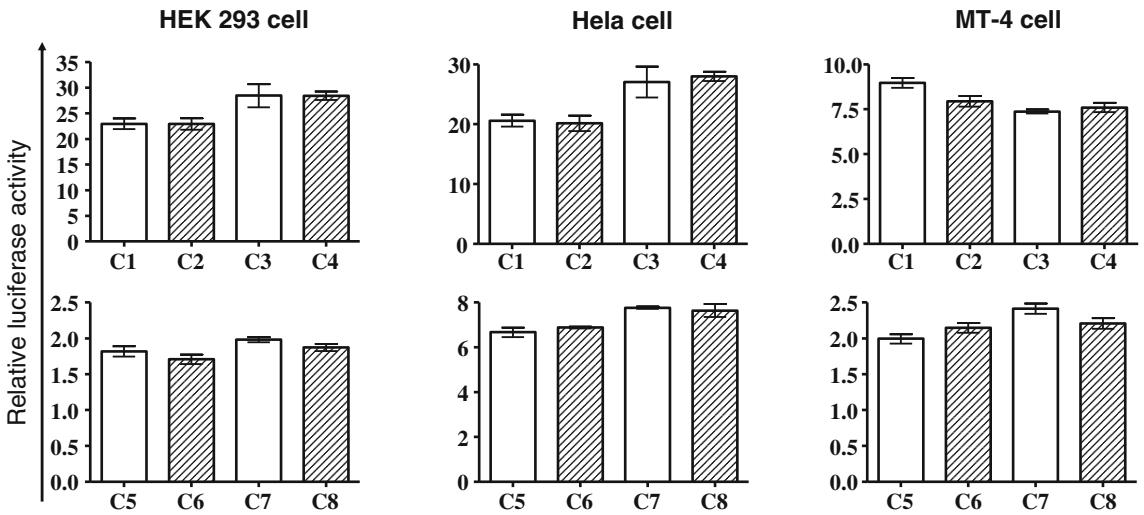

Fig. 3 Luciferase activity of different *CASP8* gene promoter region. Three different cell lines (HEK293, Hela, and MT-4) were used for transfection. Values are shown in mean±SD. Results are representative of at least three different experiments

controls (Table 3). We found no association of different genotypes of these three variants with NHL (Table 4). Because variants rs3769821 and rs113686495 are strongly linked, we only estimated the haplotypes between rs3834129 and rs113686495. There was no association between any of the estimated haplotypes and NHL (Table 5). These negative results were inconsistent with previous studies, in which rs3834129 was reported to be associated with bladder cancer [26], coal workers' pneumoconiosis [27], and multiple solid cancers in Chinese [21].

In a recent study, Lan and coworkers [15] reported that rs3769821 was significantly associated with the risk of NHL. However, this association was not replicated in our current study. The linked rs113686495 was also not associated with the risk of NHL in Chinese patients. Different genetic background might account for this discrepancy, as genotype frequencies of rs3769821 (CC, 22.4%; TC, 39.7%; TT, 39.0%) in CEU are quite different from those of CHB (CC, 6.7%; TC, 40.0%; TT, 53.3%) according to the HapMap Phase I and Phase II data (www.hapmap.org) and our current data. Note that we did not perform an analysis to discern the potential association between NHL subtypes and *CASP8* polymorphisms due to the small sample size. Such an association has been clearly discerned in a large series of NHL patients by Lan and coworkers [13, 15]. Further study with a larger number of NHL patients will be necessary to discern the potential association of rs3834129, rs3769821, and rs113686495 with NHL in Chinese, particular with certain NHL subtype.

The *CASP8* promoter regions with different alleles of rs3834129, rs3769821, and rs113686495 showed no difference on luciferase activity

As all three polymorphisms rs3834129, rs3769821, and rs113686495 were located in the promoter regions of different CASP8 transcripts, we detected the potential effect of different alleles of the *CASP8* gene promoter variants on transcriptional activity, to further characterize their putatively biological significance. We generated eight luciferase reporter vectors with the alleles of rs3834129, rs3769821, and rs113686495 (Fig. 2). Vectors C1–C4 contained different alleles (6 bp and 6 bp del at site −652) of rs3834129 and vectors C5–C8 harbored different alleles (T and C; 8 bp and 8 bp del) of rs3769821 and rs113686495. Although we transfected three cell lines (HEK293, Hela, and MT-4), we failed to observe any statistical difference regarding the luciferase activity induced by different *CASP8* promoter inserts (Fig. 3). This result suggested that these alleles might not play an active role in regulating the transcription of *CASP8* mRNA in our transfected cells. This negative observation was consistent with the lack of association of these alleles with NHL in the above association analysis.

In summary, we investigated three polymorphisms (rs3834129, rs3769821, and rs113686495) in the promoter region of the *CASP8* gene; among them, rs3834129 and rs3769821 were reported to be associated with solid cancer [21, 26, 27] and NHL [13], respectively. However, none of these genetic polymorphisms were confirmed to be associated with NHL in our samples. Functional characterization of the *CASP8* promoter regions with different alleles of rs3834129, rs3769821, and rs113686495 also yielded negative result. All these observations suggested that all the three genetic variants were unlikely to play an active role in conferring genetic susceptibility to NHL in Chinese. Further study with larger number of samples will be essential to verify our conclusion and to discern the potential association between *CASP8* variants and specific NHL subtypes.

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