

Research Article

Genetic polymorphism and transcriptional regulation of *CREBBP* gene in patient with diffuse large B-cell lymphoma

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In the present study, we aim to examine the relationship between genetic polymorphism and transcriptional expression of cyclic AMP response element binding protein (*CREBBP*) and the risk of diffuse large B-cell lymphoma (DLBCL). Two hundred and fifty healthy individuals and 248 DLBCL patients participated in the present study. The *CREBBP* rs3025684 polymorphism was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The mRNA expression of *CREBBP* was tested by the real-time quantitative PCR (RT-qPCR). The allele A frequency of *CREBBP* rs3025684 in DLBCL patients was obviously higher than that of controls ($P=0.01$). No significant difference was detected between *CREBBP* rs3025684 polymorphism and clinical characteristics of DLBCL patients when subgrouped according to different parameters. The results demonstrated that the allele A of *CREBBP* rs3025684 increased the susceptibility to DLBCL ($P=0.004$), with a worse overall survival (OS) rate ($P=0.002$), a worse progression-free survival (PFS) rate ($P=0.033$) and poor prognosis ($P=0.003$) in DLBCL patients. Furthermore, the expression of *CREBBP* mRNA was considerably decreased in DLBCL patients as compared with controls ($P<0.001$), and the expression in patients with GG genotype was up-regulated in comparison with patients with GA and AA genotype ($P=0.016$ and $P=0.001$, respectively). However, no statistical differences were found in OS ($P=0.201$) and PFS ($P=0.353$) between the lower *CREBBP* mRNA level subgroup and higher *CREBBP* mRNA level subgroup. These data suggested that the *CREBBP* gene may be an important prognostic factor in DLBCL patients and perform an essential function in the development of DLBCL.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma with extreme heterogeneity, accounting for 30–40% of newly diagnosed lymphomas [1]. Although the standard R-CHOP regimen has extremely good therapeutic effect on DLBCL patients, approximately 30–40% of patients show relapse and 10% have refractory disease [2]. In the past decades, accumulating evidences have shown the genetic, microenvironment, autoimmune diseases and occupational exposure participated in the pathogenesis of DLBCL [3–5]. With gene-expression profiling and next-generation sequencing, some common genetic loci are found to enmesh in the lymphomagenesis of DLBCL [6]. However, the pathogenesis of DLBCL is still not fully understood.

Single nucleotide polymorphism (SNP) is the most abundant type of genetic variation that occurs at a specific position in the human genome. Accumulating evidence indicated that SNPs have shown the

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ability to influence the activity and expression of the genes, and affect the pathogenesis and risk of an extensive range of cancer [7–10]. Previous studies have demonstrated that SNPs in *TP53*, *XRCC1* and *A20* are related to the risk of DLBCL [11–13]. Genome-wide association studies have recognized genetic susceptibility locus for DLBCL [14]. The contribution of SNP in histone-modifying enzymes to DLBCL pathogenesis is a research hotspot.

Somatic mutations in cyclic AMP response element binding protein (*CREBBP*) and *EP300*, and removal or inactivation of the HAT coding domain affect approximately 39% of DLBCL patients [15], and are also associated with Rubinstein Tyabi Syndrome (RTS) [16,17]. *CREBBP* belongs to the KAT3 family of histone/protein lysine acetyltransferases, which is a highly conserved and universally expressed nuclear phosphoprotein [18,19]. *CREBBP* inactivation expedites GC-derived pathogenesis of lymphoma [20]. Down-regulation of *CREBBP* is related to worse overall survival (OS) rate in pediatric acute lymphoblastic leukemia and may affect the response to chemotherapy [21]. *Crebbp*^{+/-} mice had blemish in the development of B-cell lymphoid and an increased incidence of hematopoietic malignancy [22]. The rs3025684 (A/G) is an SNP of *CREBBP* located in intron 21. This SNP was shown to be a possible risk factor for developing autism in the Netherlands, U.K. and Denmark, as well as among Bengali-Hindus [23,24].

However, the status of *CREBBP* rs3025684 SNP and the gene expression in DLBCL in a Chinese Han population is not completely understood. It was hypothesized that *CREBBP* rs3025684 polymorphism and expression may be related to the susceptibility and pathogenesis of DLBCL, and the results found that it may be a prognostic factor for DLBCL patients.

Materials and methods

Subjects

The present study recruited 250 healthy individuals and 248 DLBCL patients, diagnosed according to the World Health Organization classification [25] at Tianjin Medical University Cancer Institute and Hospital from 2011 to 2013. Peripheral blood and lymphoid specimens were collected before initial therapy. All participants signed the informed consent, and the approval of the study was obtained from the Tianjin Cancer Institute Institutional Review Board. The clinical and pathological characteristics of the patients and controls are presented in Table 1.

Extraction of DNA and genotyping of *CREBBP* rs3025684

The TIANamp genomic DNA kit (TIANGEN Biotech, Beijing, China) was used to extract the genomic DNA according to the manufacturer's protocol. Genotypes were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The reaction system contained 60 ng DNA template, 2 μ l of each primer, 25 μ l Premix Taq (Takara, Dalian, China) and sterilized water up to 50 μ l. The PCR protocol was as follows: initial denaturation at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 58°C for 30 s, extension at 72°C for 30 s, followed by 72°C for 7 min. The primers for rs3025684 were: forward 5'-AGGGGAAACAACCTCACCCCTG-3' and reverse 5'-CTGGTCTTGTGGTTCCTGT-3'. The PCR product was digested by MnlI (New England Biolabs, Beverly, MA) and analyzed by gel electrophoresis on 2.5% agarose gels. Randomly selected DNA samples were detected by direct sequencing to verify the results (Supplementary Figure S1).

Isolation of RNA and reverse-transcription quantitative PCR

Total RNA was isolated using TRIzol reagent (Invitrogen). We normalized the levels of expression of *CREBBP* relative to glyceraldehyde phosphate dehydrogenase (GAPDH), and $2^{-\Delta\Delta C_t}$ indicated the quantification of gene expression. The primers for *CREBBP* were: forward 5'-CGGCTCTAGTATCAACCCAGG-3' and reverse 5'-TTTTGTGCTTGCGGATTCAGT-3'. The primers for (i:italic)GAPDH(/0:italic) were: forward 5'-CCACATCGCTCAGACACCAT-3' and reverse 5'-CCAGGCGCCAATACG-3'.

Statistical analysis

A goodness-of-fit Chi-square test was used to analyze the Hardy–Weinberg equilibrium. The Chi-square test was used to detect the allelic frequency and genotypic distribution in all subjects. We estimated the relationship between *CREBBP* rs3025684 and the susceptibility to DLBCL by unconditional logistic regression. The prognostic factors were explored by univariate Cox regression analysis. The *CREBBP* mRNA expression levels were investigated by the independent Student's *t* test. The survival curves were computed by Kaplan–Meier method with log-rank tests. All the statistical analyses mentioned above were executed by IBM SPSS Statistics version 20.0. $P < 0.05$ was considered to be statistically significant. The false-positive report probability (FPRP) was calculated as previously described [26], we set an FPRP value of 0.2 and assigned a prior probability of 0.1.

Table 1 Clinical characteristics of DLBCL patients

Characteristics	Number (n=248) n (%)	Control (n=250) n (%)
Gender		
Male	112 (45.16)	109 (43.60)
Female	136 (54.84)	141 (56.40)
Age		
≤60	165 (66.53)	184 (73.60)
>60	83 (33.47)	66 (26.40)
Subtype		
GCB	75 (30.24)	
nGCB	173 (69.76)	
Ann-arbor stage		
I-II	152 (61.29)	
III-IV	96 (38.71)	
IPI score		
0-1	133 (53.63)	
2-5	115 (46.37)	
ECOG		
0-1	230 (92.74)	
2-5	18 (7.26)	
B symptom		
+	79 (31.85)	
-	169 (68.15)	
Extra nodal sites		
+	156 (62.90)	
-	92 (37.10)	
Bone marrow involvement		
+	21 (8.47)	
-	227 (91.53)	
HBV infection		
+	74 (29.84)	
-	174 (70.16)	
Bulky tumor (> 10 cm)		
+	55 (22.18)	
-	193 (77.82)	
Elevated LDH		
+	98 (39.52)	
-	150 (60.48)	
Elevated β2-MG		
+	86 (34.68)	
-	162 (65.32)	
KI-67		
≤75%	93 (37.50)	
>75%	155 (62.50)	
Source		
Gastrointestinal	116 (46.77)	
Others	132 (53.23)	
Response rate		
PR+CR	215 (86.69)	

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PR, partial response; β2-MG, β2 macroglobulin.

Results

Characteristics of study subjects

The genotypic distributions in both patients and controls were under the Hardy–Weinberg equilibrium ($P > 0.05$). The genotypic distribution and allelic frequencies showed significant difference between the DLBCL patients and

Table 2 Genotype distribution and allele frequencies of *CREBBP* rs3025684 polymorphism in DLBCL patients and the controls

	Control (n=250) n (%)	DLBCL patients (n=248) n (%)	P
Genotype frequency			
GG	153 (61.20)	121 (48.79)	0.021
GA	86 (34.40)	113 (45.56)	
AA	11 (4.40)	14 (5.65)	
Allele frequency			
G	392 (78.40)	355 (71.57)	0.013
A	108 (21.60)	141 (28.43)	

healthy individuals for *CREBBP* rs3025684 ($P=0.021$ and $P=0.013$, respectively, shown in Table 2). Furthermore, the association between the genotype and the clinical parameters of DLBCL patients was explored, which showed no statistical differences as shown in Table 3.

Relationship between the *CREBBP* rs3025684 and the susceptibility to DLBCL

The GA genotype was correlated with the risk of DLBCL (odds ratio (OR) = 1.692, 95% confidence interval (95% CI) = 1.170–2.446, $P=0.005$) (Table 4). However, the AA genotype displayed a slightly increased susceptibility to DLBCL with no statistical significance (OR = 1.620, 95% CI = 0.710–3.696, $P=0.252$, $P=0.252$) (Table 4). The combined AA and GA genotype was significantly related to increased susceptibility to DLBCL (OR = 1.684, 95% CI = 1.179–2.404, $P=0.004$) (Table 4). The results for dominant and recessive models are shown in Table 4. As no statistical significance was shown in the dominant model, we did not calculate the FPRP values and statistical power for the dominant model. Positive association was observed in the recessive model and GA genotype as their FPRP value was less than 0.2 (shown in Table 4).

Survival analysis of DLBCL patients according to the *CREBBP* rs3025684

The survival analysis of all 248 DLBCL patients showed that the patients with genotype GA/AA ($P=0.006$, Figure 1A) and the combined GA and AA group ($P=0.002$, Figure 1B) had a worse OS than patients with GG genotype. Furthermore, the patients with GA/AA genotype had a worse progression-free survival (PFS) in comparison with the GG patients with no statistical significance ($P=0.058$, Figure 1C), however, the combined GA and AA group showed worse PFS rate compared with the GG group with statistically significant ($P=0.033$, Figure 1D). Furthermore, it was also indicated that patients with A allele showed poor prognosis ($P=0.003$, HR = 1.944, 95% CI = 1.247–3.029).

Analysis of the *CREBBP* mRNA expression levels

CREBBP expression was detected in 63 patients and 32 controls. The results showed that the *CREBBP* expression was remarkably down-regulated in patients as compared with controls ($P<0.001$, Figure 2A). The *CREBBP* expression of patients with GG genotype was down-regulated as compared with the patients with GA and AA genotype ($P=0.016$ and 0.001, respectively, Figure 2B). However, no significant difference was detected between the GA and AA subgroups ($P=0.134$, Figure 2B). The *CREBBP* expression was down-regulated in the GA/AA subgroup as compared with the GG subgroup ($P=0.002$, Figure 2C).

Survival analysis based on the *CREBBP* mRNA levels of DLBCL patients

Based on the median of *CREBBP* mRNA expression value, 63 DLBCL patients were partitioned into two subgroups, the low *CREBBP* expression subgroup and the high *CREBBP* expression subgroup. The results indicated no significant differences between the patients with lower *CREBBP* mRNA level and those with high *CREBBP* mRNA level in OS ($P=0.201$, Figure 3A) and PFS ($P=0.353$, Figure 3B).

Discussion

DLBCL is an example of a translocation-based cancer, in which key genes are dysregulated by active lineage-specific promoters or enhancers due to characteristic equilibrium translocations [6]. The evolution of DLBCL was a multi-step procedure that requires the cumulation of multiple genetic pathological changes [14,27]. By the modern genome-wide

Table 3 Characteristics of DLBCL patients and their association with CREBBP rs3025684

Characteristics	Number (n=248) n (%)	Genotype		P
		GA+AA, n (%)	GG, n (%)	
Gender				
Male	112 (45.16)	61 (24.60)	51 (20.56)	0.352
Female	136 (54.84)	66 (26.61)	70 (28.23)	
Age				
≤60	165 (66.53)	87 (35.08)	78 (31.45)	0.500
>60	83 (33.47)	40 (16.13)	43 (17.34)	
Subtype				
GCB	75 (30.24)	38 (15.32)	37 (14.92)	0.910
nGCB	173 (69.76)	89 (35.89)	84 (33.87)	
Ann-arbor stage				
I-II	152 (61.29)	73 (29.44)	79 (31.85)	0.207
III-IV	96 (38.71)	54 (21.77)	42 (16.94)	
IPI score				
0-1	133 (53.63)	62 (25.00)	71 (28.63)	0.120
2-5	115 (46.37)	65 (26.21)	50 (20.16)	
ECOG				
0-1	230 (92.74)	114 (45.97)	116 (46.77)	0.064
2-5	18 (7.26)	13 (5.24)	5 (2.02)	
B symptom				
+	79 (31.85)	43 (17.34)	36 (14.52)	0.488
-	169 (68.15)	84 (33.87)	85 (34.27)	
Bone marrow involvement				
+	21 (8.47)	11 (4.44)	10 (4.03)	0.911
-	227 (91.53)	116 (46.77)	111 (44.76)	
HBV infection				
+	74 (29.84)	39 (15.73)	35 (14.11)	0.759
-	174 (70.16)	88 (35.48)	86 (34.68)	
Bulky tumor (> 10 cm)				
+	55 (22.18)	31 (12.50)	24 (9.68)	0.386
-	193 (77.82)	96 (38.71)	97 (39.11)	
Elevated LDH				
+	98 (39.52)	57 (22.98)	41 (16.53)	0.077
-	150 (60.48)	70 (28.23)	80 (32.26)	
Elevated β2-MG				
+	86 (34.68)	41 (16.53)	43 (17.34)	0.588
-	162 (65.32)	86 (34.68)	78 (31.45)	
KI-67				
≤75%	93 (37.50)	50 (20.16)	43 (17.34)	0.533
>75%	155 (62.50)	77 (31.05)	78 (31.45)	
Source				
Gastrointestinal	116 (46.77)	55 (22.18)	61 (24.60)	0.262
Others	132 (53.23)	72 (29.03)	60 (24.19)	

Abbreviations: LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; β2-MG, β2 macroglobulin.

Table 4 Association between CREBBP rs3025684 polymorphism and the risk of DLBCL

Genotype	OR (95% CI)	P	Statistical power	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
AA vs. GG	1.620 (0.710–3.696)	0.252						
GA vs. GG	1.692 (1.170–2.446)	0.005	0.500	0.030	0.085	0.505	0.0912	0.990
GA/AA vs. GG	1.684 (1.179–2.404)	0.004	0.500	0.024	0.069	0.449	0.891	0.988
GA/GG vs. AA	0.769 (0.342–1.729)	0.526						

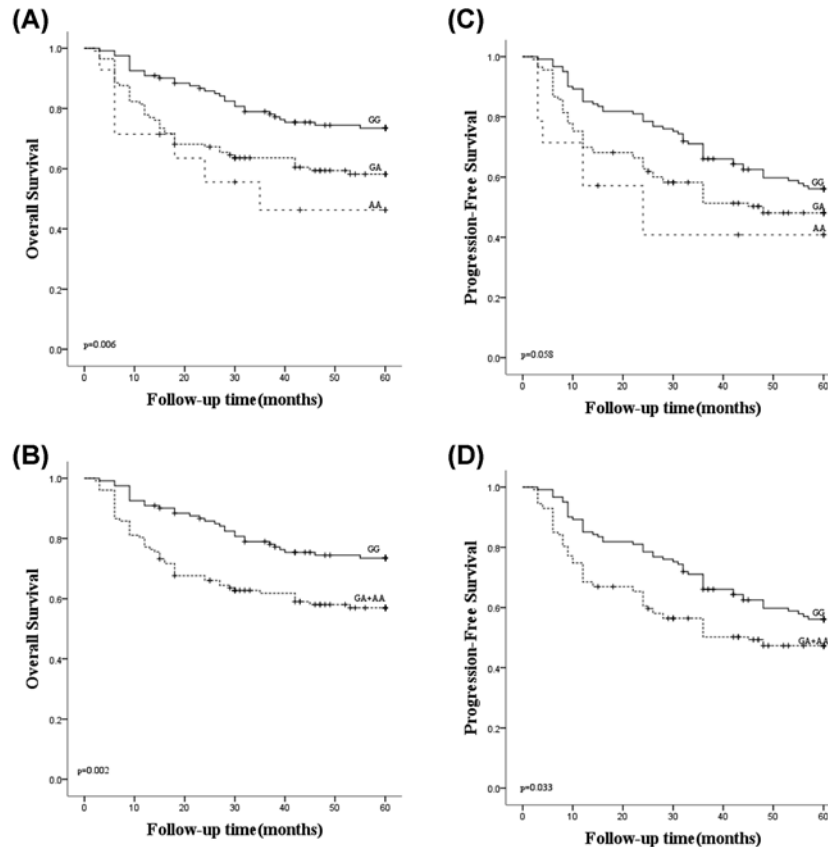


Figure 1. Survival analyses of DLBCL patients under the genotype of *CREBBP* rs3025684

(A) OS analysis compared among the GG, GA and AA subgroups ($P=0.006$). (B) OS analysis compared between the GG subgroup and the combined GA/AA subgroup ($P=0.002$). (C) PFS analysis compared among the GG, GA and AA subgroups ($P=0.058$). (D) PFS analysis compared between the GG subgroup and the combined GA/AA subgroup ($P=0.033$). A check mark indicates that the data is censored.

molecular analysis, an abundance of altered cellular pathways that perform vital functions in the development of DLBCL and the sensitivity of cancer cells to therapy was detected. However, the notable heterogeneity of this disease partly limits the effective treatment. Therefore, it is necessary to seek ameliorated special biomarkers, permitting the devising of more efficient and accurate medical methods to specific cancer-causing addictions.

CREBBP, one of the most frequently mutated genes in DLBCL [15,28–30], acts as a tumor repressor of GC-derived pathogenesis of lymphoma [31]. Most of the *CREBBP*-binding regions in GC B cells displayed characteristics of transcriptionally active (or suspended) enhancers [32], which control the cell type-specific transcription [33]. *CREBBP* acetylates H3K27 on the promoter or enhancer sequence of the *BCL6* target genes, promoting transcription to counteracting the inhibition of *BCL6*, which leads to the opposition of proto-oncogene activity of *BCL6* [20,31]. Therefore, *CREBBP* may be considered as a tumor therapeutic target in DLBCL patients.

Gene expression-based categorization of DLBCL has been established [34,35], and the relevance to prognosis has been illustrated [36]. It has been demonstrated that certain genetic defects and distinct signal transduction pathways occur in specific subtypes [37,38]. In this study, the association between *CREBBP* rs3025684 polymorphism and its expression with the susceptibility and survival of DLBCL patients was investigated. The results showed that the A allele carriers were related to increased risk of DLBCL and had worse OS rate and PFS rate. Hence, *CREBBP* rs3025684 polymorphism may be used as a hallmark for the prediction of risk and prognosis of DLBCL.

In East Asians, the frequency of A allele of *CREBBP* rs3025684 was reported to be 19.3% in the HapMap Project. However, the present study showed that the frequency of allele A in controls and DLBCL patients was 21.60 and 28.43%, respectively. This difference in allele frequency may owe to the risk effects of allele A and the small sample

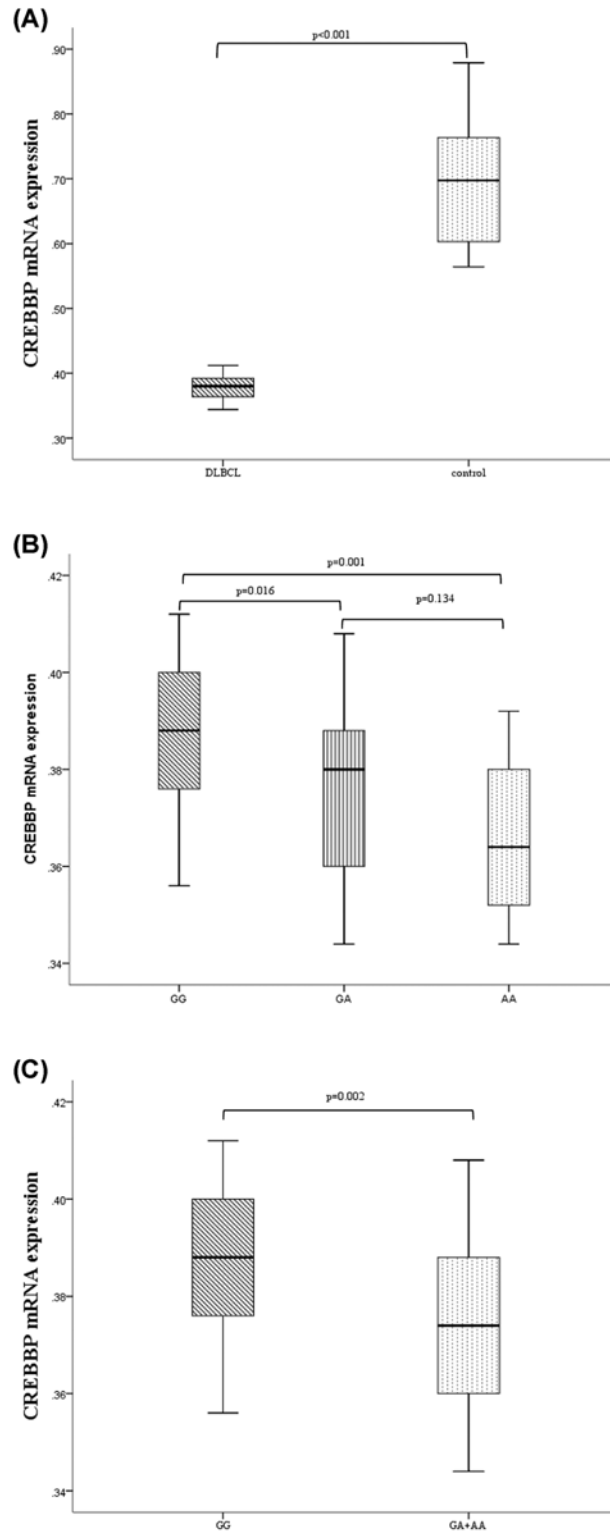


Figure 2. The expression of CREBBP mRNA in DLBCL patients

(A) The expression of CREBBP mRNA in DLBCL patients was down-regulated as compared with the controls ($P < 0.001$). (B) The expression of CREBBP mRNA in DLBCL patients with GG genotype was significantly up-regulated than those with GA and AA genotypes ($P = 0.016$ and 0.001 , respectively). (C) The expression of CREBBP mRNA in DLBCL patients with GA/AA genotype was significantly down-regulated than those with GG genotype ($P = 0.002$).

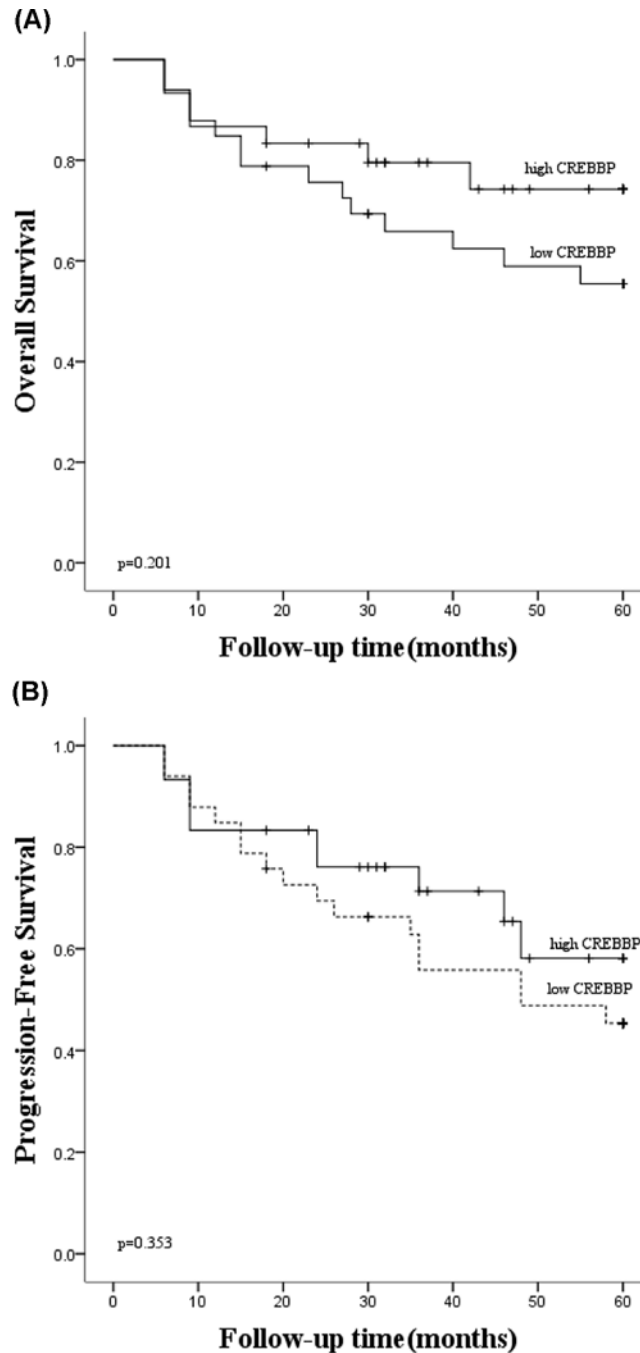


Figure 3. Survival analyses of DLBCL patients according to *CREBBP* mRNA expression

(A) The OS analysis indicated no significant differences between lower *CREBBP* subgroup and high *CREBBP* subgroup ($P=0.201$). (B) The PFS analysis indicated no significant differences between the lower *CREBBP* subgroup and high *CREBBP* subgroup ($P=0.353$). A check mark indicates that the data is censored.

size. In the recessive model, the positive association between the risk of DLBCL and *CREBBP* rs3025684 was observed. However, the statistical power was only 0.5, which may be a result of the small simple size.

The *CREBBP*/EP300 complex participates in numerous life events, such as cell growth, proliferation, apoptosis, metabolism and oncogenesis [18,39,40]. *CREBBP*/EP300 complex also targets many transcriptional factors significantly related to the development of B-cell lymphoma and immune response, such as p53 and c-MYC [41–43]. HAT activity is related to the survival rate of patients with B-cell lymphoma [31,44]. Furthermore, HAT mutations likely

predict treatment efficiency in epigenetically targeted therapy, such as the HDAC3 inhibitors [20,45]. The present study indicated that the expression of *CREBBP* was notably down-regulated in patients as compared with the controls, and was especially down-regulated in the GA/AA genotype subgroup, indicating that *CREBBP* may be used as a therapeutic target for DLBCL.

In conclusion, the polymorphism and expression of *CREBBP* gene may play a vital role as a genetic risk factor and poor prognostic factor among DLBCL Chinese Han patients, indicating that *CREBBP* could be used for the prognosis and treatment of DLBCL. Additional studies with larger sample sizes are necessary to verify the results and further functional analyses are warranted to explore the lymphoma biology.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution

Z.Q. and H.Z. designed the research. Y.K. performed the experiment, analyzed the experimental data and wrote the manuscript. H.Z., P.G. and X.W. helped to analyze the experimental data and collected the samples. L.C. gathered the clinical information. All authors read and approved the final manuscript.

Abbreviations

CREBBP, cyclic AMP response element binding protein; DLBCL, diffuse large B-cell lymphoma; FPRP, false-positive report probability; GAPDH, glyceraldehyde phosphate dehydrogenase; HAT, histone acetyltransferase; HDAC3, histone deacetylase 3; HR, hazard ratio; OR, odds ratio; OS, overall survival; PFS, progression-free survival; SNP, single nucleotide polymorphism; 95% CI, 95% confidence interval.

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