Association between *LAPTM4B* gene polymorphism and susceptibility to and prognosis of diffuse large B-cell lymphoma

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Abstract. Lysosomal protein transmembrane 4β (*LAPTM4B*) is an oncogene that is overexpressed in a number of various types of human cancer. There are two known alleles of *LAPTM4B*: *LAPTM4B*1* and *LAPTM4B*2*. The present study assessed the association between *LAPTM4B* polymorphisms and the susceptibility to diffuse large B-cell lymphoma (DLBCL) and its prognosis. *LAPTM4B* genotypes were determined using polymerase chain reaction analysis in 164 DLBCL and 350 healthy control cases. The association between *LAPTM4B* polymorphisms and the risk of DLBCL was analyzed using unconditional logistic regression. Differences in patient survival were calculated using Kaplan-Meier analysis. The present study indicated no significant differences (P>0.05) in the frequency of *LAPTM4B*2* alleles between DLBCL cases (26.5%) and controls (24.1%). The risk of DLBCL was slightly increased in cases with the *LAPTM4B*1/2* genotype [odds ratio (OR)=1.160; 95% confidence interval (CI)=0.781-1.724] or the *LAPTM4B*2/2* genotype (OR=1.446; 95% CI=0.648-3.227) compared with those with the *LAPTM4B*1/1* genotype. There was no significant association between the presence of the *LAPTM4B*2* allele and overall survival (OS) and disease-free survival (DFS) in patients with DLBCL (P=0.399 and 0.520, respectively). However, there was a tendency for patients with *LAPTM4B*2* and International Prognostic Index (IPI) score 3-5 to have longer OS and DFS (P=0.126 and 0.109, respectively). These findings suggest that genetic polymorphisms of *LAPTM4B* is not a risk factor for the development of DLBCL, but the *LAPTM4B*2* allele may a better prognostic indicator in patients with IPI score 3-5 in DLBCL.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), constituting up to 40% of all cases globally (1). DLBCL is a highly heterogeneous disease. The standard front-line therapy for DLBCL, which includes rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), has improved the survival rate of DLBCL patients (2). However, ~33% of DLBCL patients have relapsed or refractory type of disease, which was reported by Sehn *et al* (2) in the province of British Columbia in 2005, and the molecular mechanism underlying DLBCL development remains to be fully understood (2-4). Although certain indicators may assist in predicting prognosis in patients with DLBCL, including the International Prognostic Index (IPI) score, MYC proto-oncogene, and tumor location (5-7), the development of novel biomarkers for estimating the efficacy of therapeutic strategies and prognosis is required.

LAPTM4B exists as two alleles: *LAPTM4B*1* with one 19 bp segment (GenBank accession no. AY219176) and *LAPTM4B*2* with two tandem repeat segments (GenBank accession no. AY219177) in the 5' untranslated region of exon 1 (8). Previous studies have demonstrated that *LAPTM4B* polymorphisms were associated with susceptibility to multiple types of cancer, including lung, breast, gastric, colon, ovarian and primary liver cancer (9-16), which suggested that *LAPTM4B*2* may be associated with a significantly increased risk of developing these types of cancer. *LAPTM4B*2* was also associated with poor prognosis in patients with hepatocellular,

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lung or endometrial cancer (17-19). To the best of our knowledge, no study has previously reported on the association between *LAPTM4B* polymorphisms and clinical data on DLBCL. The present study evaluated whether *LAPTM4B* polymorphisms were associated with the susceptibility to and prognosis of DLBCL.

Materials and methods

Patients and control cases. A total of 164 patients with DLBCL were enrolled (for the overall survival analysis, 35 cases were not included because of loss to follow up or accepting non first-line therapy), which included 81 males and 83 females, mean age 53.08 years, with 2 individuals belonging to the *LAPTM4B*1/3* genotype. The diagnosis of the patients was confirmed by the Department of Pathology (Peking University Cancer Hospital and Institute, Beijing, China) according to the World Health Organization classification. Final diagnosis of all patients was confirmed by pathological assessment at the Beijing Cancer Hospital, Peking University School of Oncology (Beijing, China), and all cases were collected between June 2007 and December 2010. The Ann Arbor staging classification system were used to determine the stage of these patients (20). The data for the 350 healthy control cases were quoted from the data of Cheng *et al* (12), which included 225 males and 125 females, mean age 49.75 years. The clinical research protocol of the present study was approved by the Institutional Review Board (Peking University Cancer Hospital and Institute). The present study was approved by the Research and Ethics Committee of Peking University School of Oncology. Each patient enrolled in the present study provided written informed consent for participation.

DNA extraction. Blood samples were obtained from all patients with DLBCL prior to genetic analysis. Genomic DNA was extracted from peripheral-blood mononuclear cells using a blood genomic DNA extraction kit according to the manufacturer's protocol (BioTeke Corporation, Beijing, China). The genomic DNA was subsequently dissolved in Tris-EDTA buffer and stored at -80˚C.

Polymerase chain reaction (PCR) analysis. The genomic DNA (30 ng/20 µl) was amplified using GoTaq DNA polymerase (Promega Corporation, Madison, WI, USA) and primers forward, 5'-GCCGACTAGGGGACTGGCGGA-3' and reverse, 5'-CGAGAGCTCCGAGCTTCTGCC-3' which correspond to the 72-92 and 255-275 bp of LAPTM4B, respectively (8). GAPDH was used as the positive internal control in the present study, with the following primers: Forward, 5'-GTCTGCCCTAATTATCAGGTCCA-3' and reverse, 5'-CCTGGCTCCTGGCATCTCT-3'. PCR reaction conditions were set using a thermo cycler (Gene Cycler™; Bio-Rad Laboratories, Inc., Hercules, CA, USA) as follows: Denaturation at 94˚C for 2 min, followed by 35 cycles at 94˚C for 30 sec, at 65˚C for 30 sec, and at 72˚C for 30 sec. The last cycle was followed by auto-extension at 72˚C for 7 min. The amplified products were subsequently analyzed using electrophoresis on a 10% polyacrylamide or 2% agarose gel. Visualization was performed using GelRed (Biotium,

Hayward, CA, USA). All samples are repeated by two independent PCR analysis.

The DNA fragments were purified using the AxyPrep DNA Gel Extraction kit according to the manufacturer's protocol (Axygen Scientific, Inc., Union City, CA, USA). The purified products were sequenced using an ABI 3730XL Avant Genetic analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA), according the manufacturer's protocol. The sequences were subsequently analyzed using Seqman software DNASTAR version 5.2 (DNASTAR Inc., Madison, WI, USA).

Statistical analysis. Statistical analysis was performed using SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA). The χ^2 test or the Fisher's exact test was used to calculate genotype frequency (including Hardy-Weinberg equilibrium) and other clinical parametric distributions between DLBCL and control cases. Unconditional logistic regression analysis models were used to assess the association, adjusted by age and sex, between different genotypes and cancer risks.

The clinical characteristics and response rate of the patients were compared using the χ^2 test or the Fisher's exact test according to the different genotypes. The association between *LAPTM4B* gene polymorphism and overall survival (OS) and disease-free survival (DFS) was evaluated using Kaplan-Meier curves and the log-rank test. All statistical tests were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

LAPTM4B genotypes in patients with DLBCL. Using PCR analysis, the present study identified four different *LAPTM4B* polymorphisms: *LAPTM4B*1/1*, *LAPTM4B*2/2*, *LAPTM4B*1/2* and *LATPM4B*1/3*. As indicated in Fig. 1, a 204 bp fragment is encoded by *LAPTM4B*1/1*, and a 223-bp fragment is encoded by *LAPTM4B*2/2*. *LAPTM4B*1/2 and *LAPTM4B*1/3* are heterozygous. The 204 bp and 223-bp fragments were both detected in *LAPTM4B*1/2*. The 204 and 242 bp fragments were observed in two individuals with *LAPTM4B*1/3*.

The present study detected a significant difference in the distribution of DLBCL between male and female patients (P<0.002; Table I). No significant differences in allele frequency were identified between the DLBCL and control cases (Table II). In the 350 controls, the frequency of the *LAPTM4B*2* allele was 24.1%, whereas the frequency in patients with DLBCL was 26.5%.

The distribution of *LAPTM4B* genotypes in control and DLBCL cases are displayed in Table III. The genotype frequencies for the polymorphism were in agreement with the Hardy-Weinberg equilibrium (P=0.898). No significant differences in the distribution of *LAPTM4B*1/2* and *LAPTM4B*2/2* genotypes when compared with *LATPM4B*1/1* were detected between the DLBCL and control cases (P=0.462 and P=0.368, respectively). The odds ratios of *LATPM4B*1/2* and *LATPM4B*2/2* genotypes in patients with DLBCL compared with patients with *LATPM4B*1/1* is 1.160-fold (95% CI=0.781-1.724) and 1.446-fold (95% CI=0.648-3.227), respectively.
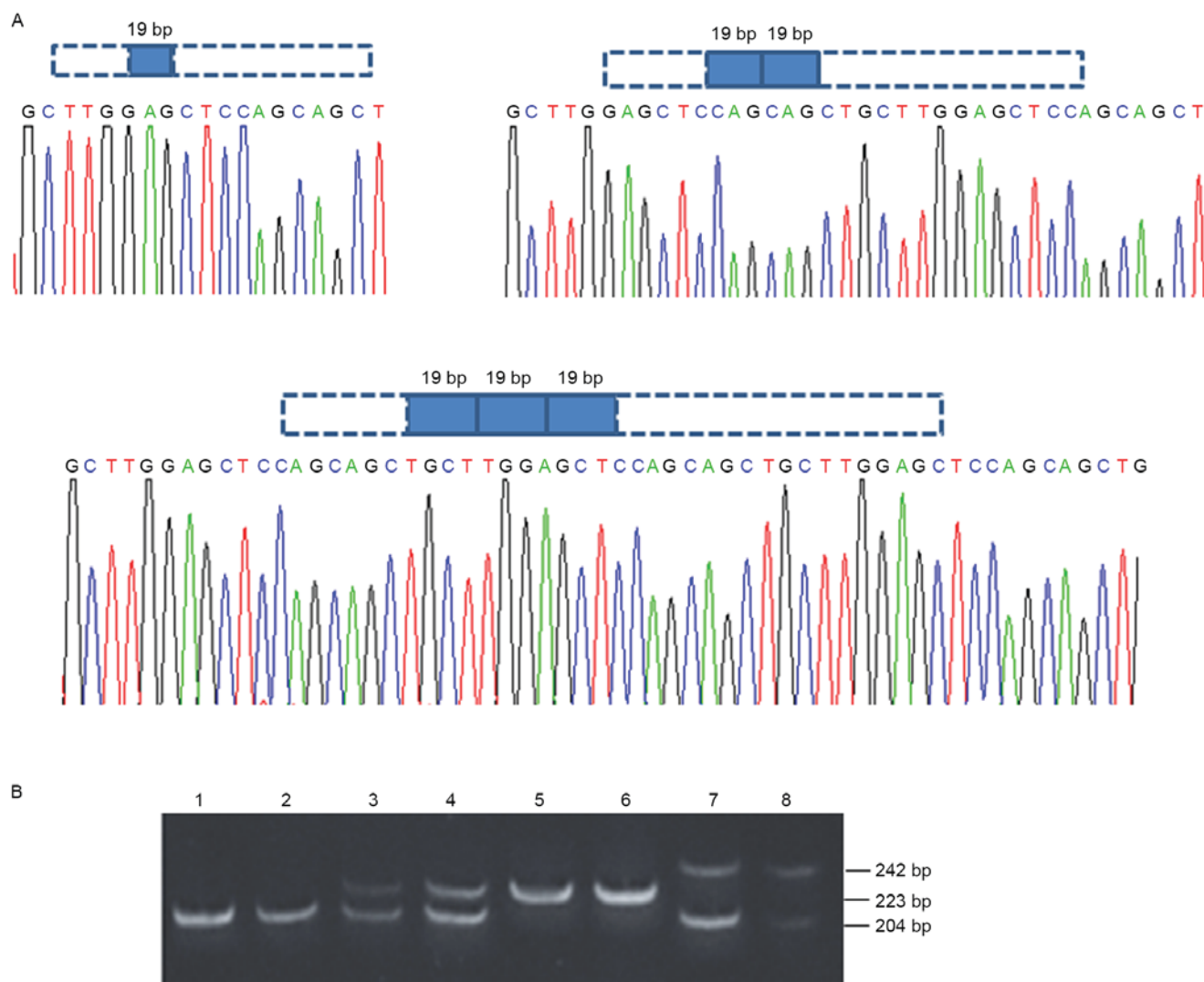
Figure 1. Schematic diagram showing *LAPTM4B* alleles. (A) Sequencing chromatograms of *LAPTM4B* alleles. *LAPTM4B**1 contains one copy of the 19 bp sequence. *LAPTM4B**2 contains two tandem repeats of the 19 bp sequence, and *LAPTM4B**3 contains three tandem repeats of the 19 bp sequence. (B) *LAPTM4B* polymorphisms as verified by polymerase chain reaction analysis. Lanes 1-2, *LAPTM4B**1/1; lanes 3-4, *LAPTM4B**1/2; lanes 5-6, *LAPTM4B**2/2; lanes 7-8, *LAPTM4B**1/3 genotype. LAPTM4B, lysosomal protein transmembrane 4β.

Table I. Distribution of age and sex in control and DLBCL cases.

Characteristic	Control cases, n (n=350)	DLBCL cases, n (n=162)	P-value[a]
Age			0.732
≤50	165	79	
>50	185	83	
Sex			0.002
Male	225	81	
Female	125	81	

[a]Analyzed using χ^2 test. DLBCL, diffuse large B-cell lymphoma.

Table II. Distribution of *LAPTM4B* alleles in controls (n=350) and DLBCL cases (n=162).

Alleles	Controls, n (%)	DLBCL cases, n (%)	OR (95% CI)[a]
LAPTM4B*1	531 (75.9)	238 (73.5)	
LAPTM4B*2	169 (24.1)	86 (26.5)	1.175 (0.866-1.596)

[a]Analyzed by logistic regression and analysis, and adjusted for age and sex. CI, confidence interval; LAPTM4B, lysosomal protein transmembrane 4β; DLBCL, diffuse large B-cell lymphoma; OR, Odds ratio.

LAPTM4B genotypes and clinicopathological parameters in DLBCL. The present study also assessed the distribution of clinical parameters, including age and sex, among different LAPTM4B genotypes in patients with DLBCL (Table IV). There were no statistically significant associations between the genotype distribution of *LAPTM4B* in patients with DLBCL and clinicopathological parameters (Table IV).

Table III. Distribution of *LAPTM4B* genotypes in controls (n=350) and DLBCL cases (n=162).

Genotypes	Controls, n (%)	DLBC cases, n (%)	P-value[a]	OR (95% CI)
LAPTM4B*1/1	199 (56.9)	87 (53.7)		
LAPTM4B*1/2	133 (38.0)	64 (39.5)	0.462	1.160 (0.781-1.724)
LAPTM4B*2/2	18 (5.1)	11 (6.8)	0.368	1.446 (0.648-3.227)

[a]Analyzed by logistic regression and analysis and adjusted for age and sex. CI, confidence interval; LAPTM4B, lysosomal protein transmembrane 4β; DLBCL, diffuse large B-cell lymphoma; OR, Odds ratio.

Table IV. Association between the distribution of *LAPTM4B* genotypes and clinicopathological parameters in DLBCL cases.

Parameters	*LAPTM4B* genotypes			P-value[a]
	*1/1	*1/2	*2/2	
Sex				
Male	43	31	7	0.64
Female	44	33	4	
Age				
≤50	46	29	4	0.456
>50	41	35	7	
B symptoms[b]				
Positive	36	21	5	0.494
Negative	51	43	6	
LDH				
Positive	45	37	4	0.392
Negative	42	27	7	
β₂-MG				
Positive	23	19	5	0.532
Negative	58	42	6	
Stage				
I-II	40	31	4	0.757
III-IV	47	33	7	
Bulky mass				
≥10 cm	9	7	2	0.766
<10 cm	78	57	9	
Localized				
Yes	13	10	2	0.961
No	74	54	9	
No extra nodal[c]				
≤1	68	46	7	0.474
>1	19	18	4	
Incidence site				
Lymph node	50	36	6	0.977
Extra lymph	37	28	5	
IPI score				
0-2	66	43	5	0.102
3-5	21	21	6	

Table IV. Continued.

Parameters	*LAPTM4B* genotypes			P-value[a]
	*1/1	*1/2	*2/2	
Molecular subtypes				
GCB	12	16	0	0.102
Non-GCB	61	41	9	
Other	14	7	2	

[a]Analyzed using χ² test or Fisher's exact test. [b]B symptom includes unexplained fever/chills/weight loss, fatigue and drenching night sweats. [c]No extra nodal: the number and type of extra nodal will influence DLBCL patient prognosis. LAPTM4B, lysosomal protein transmembrane 4β; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; MG, macroglobulin; IPI, International Prognostic Index; GCB, germinal center B cell.

Associations between LATPM4B genotypes and prognosis of patients with DLBCL. In the present study, follow-up data ranging from 3.9-94.8 months (mean, 50.5 months) was obtained for 129 patients with DLBCL. At the end date of the follow-up, a total of 93 patients survived and 36 succumbed to disease. Survival analysis was conducted in the 129 patients to examine the effect of *LATPM4B* polymorphism on the prognosis of patients with DLBCL. Kaplan-Meier analysis and log-rank test indicated that *LAPTM4B**2 was not associated with decreased OS and DFS (P=0.399 and P=0.520, respectively). However, patients with the *LAPTM4B**2 genotype and IPI score 3-5 (n=40) tend to exhibit longer durations of OS and DFS compared with patients with the *LAPTM4B**1 genotype (P=0.126 and 0.109, respectively; Fig. 2).

Discussion

The present study demonstrated that the presence of the *LAPTM4B**2 allele was not associated with a markedly increased risk of developing DLBCL compared with *LAPTM4B**1. However, in patients with IPI score 3-5, a significantly increased risk of developing DLBCL was identified in patients with the *LAPTM4B**2/2 genotype compared with those that exhibited the *LAPTM4B**1/1 genotype. A total of three tandem repeats comprising 19 bp segments were detected in 2/164 of the patients with DLBCL. Furthermore, patients with DLBCL that exhibited *LAPTM4B**2 had a tendency to
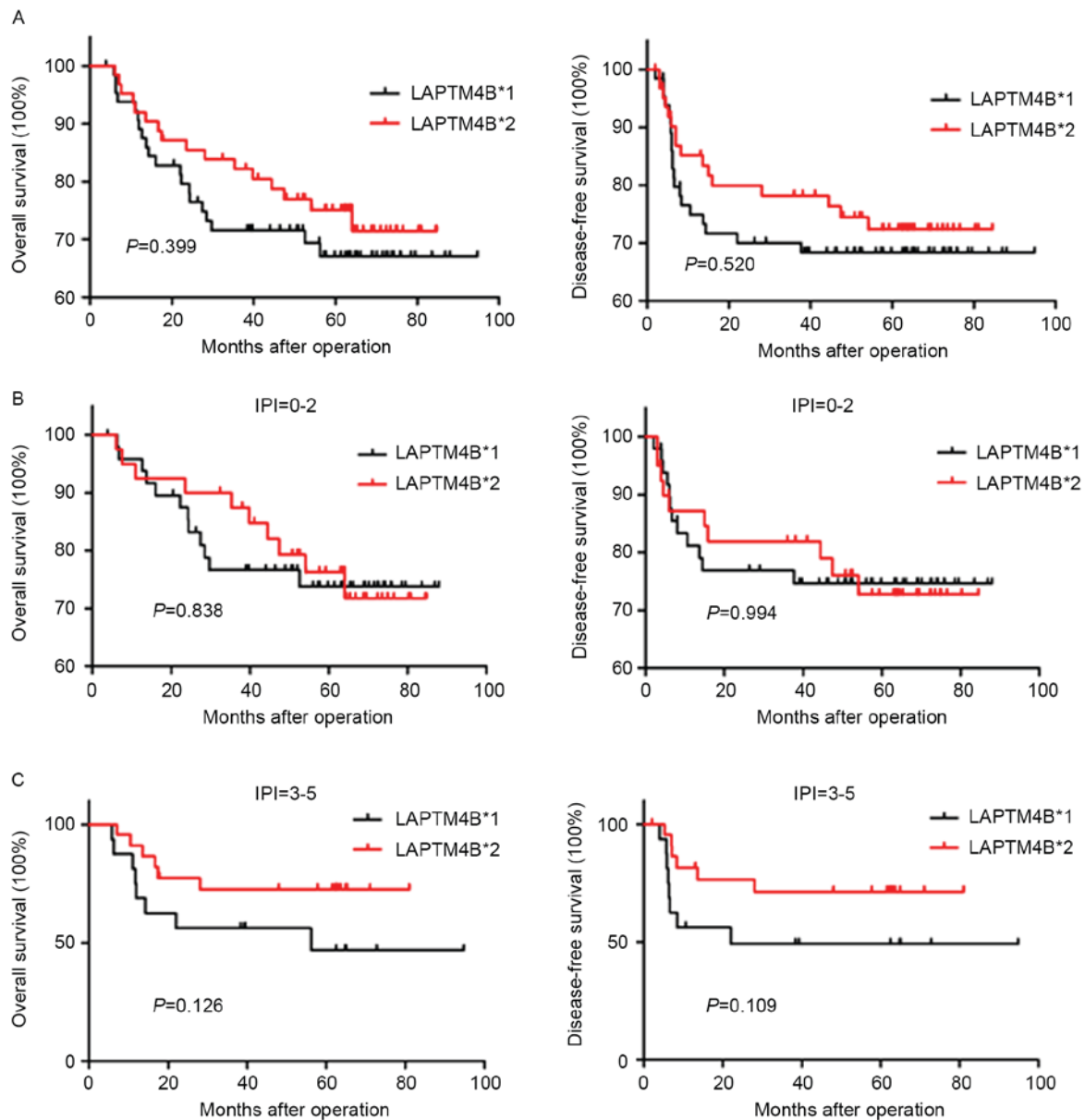
Figure 2. Kaplan-Meier survival analysis of patients with DLBCL with *LAPTM4B*1* and *LAPTM4B*2* alleles. (A) Kaplan-Meier survival curves indicating OS and DFS in patients with DLBCL and *LAPTM4B*1* or *LAPTM4B*2* alleles. OS and DFS were stratified by IPI scores: (B) 0-2 and (C) 3-5. LAPTM4B, lysosomal protein transmembrane 4β; OS, overall survival; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index.

have increased durations of OS and DFS compared with those with *LAPTM4B*1*, particularly those that also exhibited IPI score 3-5. To the best of our knowledge, the present study is the first to demonstrate, albeit not statistically, that *LAPTM4B*2* is a more useful prognostic indicator for DLBCL compared with *LAPTM4B*1*. However, this finding is not consistent with the results of previous studies, including those assessing hepatocellular carcinoma, lung and breast cancer (17,18,21).

LAPTM4B has two known protein isoforms: LAPTM4B-24 (226 aa) and LAPTM4B-35 (317 aa) (22). Previous studies have indicated that LAPTM4B-35 is able to activate the binding of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) to p85α subunits, and thereby facilitate cancer cell multidrug resistance and inhibit apoptosis (23). Liu *et al* (22,24) used a polyclonal antibody to demonstrate that LAPTM4B-35 and LAPTM4B-24 may differ in expression and function in

tissues and multiple cell lines of hepatocellular carcinoma. The balance of LAPTM4B-35 and LAPTM4B-24 may affect malignant transformation. Multiple studies have revealed that LAPTM4B-35 may participate in malignant transformation and tumor invasion (25-28). However, a recent report demonstrated that the LAPTM4B-24 isoform was able to stimulate mechanistic target of rapamycin complex (mTORC)1 through vacuolar-type H^+-ATPase via the influx of leucine resulting from the binding of LAT1-4F2hc to lysosomes (29). LAPTM4B-24 may also promote cell growth and proliferation and regulate immune responses by decreasing transforming growth factor β1 production in human regulatory T cells (29,30).

Although as aforementioned there are two known isoforms of LAPTM4B, the present study suggested that another isoform may exist due to the *LAPTM4B*2* allele. The 19 bp difference in the first exon of *LAPTM4B* between *LAPTM4B*1*

and *LAPTM4B*2* may alter the open reading frame, thereby resulting in two different protein isoforms: LAPTM4B-35 and LAPTM4B-40 (8,17). Previous studies have demonstrated that LAPTM4B polymorphisms were associated with an increased risk of multiple types of cancer, including ovarian, breast and gallbladder cancer (13,31,32). These findings suggest that the 19 bp sequence may serve an important function in transcriptional regulation, or a different protein isoform encoded by *LAPTM4B*2* may affect cancer cell function (8). Yang *et al* (17) indicated that *LAPTM4B*2* was associated with tumor recurrence and poor histopathological differentiation, and is an independent prognostic factor in hepatocellular carcinoma. Other studies have reported similar results for lung cancer, and endometrial and gallbladder carcinoma (18,19,32).

In the present study, the *LAPTM4B*2* allele was not associated with a significantly increased risk of developing DLBCL, and there was no significant association with survival in patients with DLBCL. However, there was a tendency for patients with *LAPTM4B*2* to have improved OS and DFS compared with patients with *LAPTM4B*1* in DLBCL, and this pattern was more evident in cases with IPI score 3-5.

The 19 bp sequence may serve a crucial role in transcriptional regulation, including binding with transcription factors, microRNAs or non-coding linker RNA in patients with DLBCL, which discriminates its function with that of other types of cancer, including hepatocellular carcinoma (15,17). Therefore, the different LAPTM4B protein isoforms may have diverse functions in patients with *LAPTM4B*2* compared with those with *LAPTM4B*1* in DLBCL. The results of the present study on *LAPTM4B* alleles in patients with DLBCL may provide additional evidence that different LAPTM4B protein isoforms could serve multiple functions. For example, it was previously reported that LAPTM4B-35 may activate the PI3 K/Akt signaling pathway, and LAPTM4B-24 may activate mTORC1 (23,29). Identifying the isoform that predominates in the induction of the 19 bp sequence in various types of cancer should be investigated in further studies.

The present study assessed the association between *LAPTM4B* polymorphisms and prognosis of patients with DLBCL. It was indicated that *LAPTM4B*2* may be a more useful prognostic indicator for DLBCL compared with *LAPTM4B*1*, particularly in cases with IPI score 3-5 compared with IPI score 0-2 (although this trend was not statistically significant). IPI is a crucial indicator for selecting the appropriate therapeutic strategies in DLBCL. In DLBCL, patients with IPI score 0-2 have good prognosis with the rate of 5-year survival reaching 80% (33). In the present study, the lack of association between *LAPTM4B*2* allele and survival of patients with IPI score 0-2 may be due to the small number of cases in the present study. However, there is a poor rate of 5-year survival (<50%) following the standard R-CHOP treatment in patients with IPI score 3-5 (33). *LAPTM4B*2* allele may be a good indicator for patients with IPI score 3-5 and may be used to guide clinical therapy to reduce unnecessary drug treatment.

Acknowledgements

References

1. International Agency for Research on Cancer: World Cancer Report 2014. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014. Accessed July, 2014.
2. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, MacPherson N, O'Reilly S, Spinelli JJ, Sutherland J, *et al*: Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 23: 5027-5033, 2005.
3. Perry AR and Goldstone AH: High-dose therapy for diffuse large-cell lymphoma in first remission. Ann Oncol 9 (Suppl 1): S9-S14, 1998.
4. Fisher RL, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, Glick JH, Coltman CA Jr and Miller TP: Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328: 1002-1006, 1993.
5. International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329: 987-994, 1993.
6. Ruzinova MB, Caron T and Rodig SJ: Altered subcellular localization of c-Myc protein identifies aggressive B-cell lymphomas harboring a c-MYC translocation. Am J Surg Pathol 34: 882-891, 2010.
7. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, Vanderplas A, Zelenetz AD, Abel GA, Rodriguez MA, *et al*: An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 123: 837-842, 2014.
8. Shao GZ, Zhou RL, Zhang QY, Zhang Y, Liu JJ, Rui JA, Wei X and Ye DX: Molecular cloning and characterization of LAPTM4B, a novel gene unregulated in hepatocellular carcinoma. Oncogene 22: 5060-5069, 2003.
9. Deng LJ, Zhang QY, Liu B and Zhou RL: Relationship between LAPTM4B gene polymorphism and susceptibility of lung cancer. Beijing Da Xue Xue Bao 37: 302-505, 2005 (In Chinese).
10. Fan M, Liu Y, Zhou R and Zhang Q: Association of LAPTM4B gene polymorphism with breast cancer susceptibility. Cancer Epidemiol 36: 364-368, 2012.
11. Liu Y, Zhang QY, Qian N and Zhou RL: Relationship between LAPTM4B gene polymorphism and susceptibility of gastric cancer. Ann Oncol 18: 311-316, 2007.
12. Cheng XJ, Xu W, Zhang QY and Zhou RL: Relationship between LAPTM4B gene polymorphism and susceptibility of colorectal and esophageal cancers. Ann Oncol 19: 527-532, 2008.
13. Xu Y, Liu Y, Zhou R, Meng F, Gao Y, Yang S, Li X, Yang M and Lou G: LAPTM4B polymorphisms is associated with ovarian cancer susceptibility and its prognosis. Jpn J Clin Oncol 42: 413-419, 2012.
14. Li C, Zhou Q, Wang Y, Chen X, Yang X and Zhu D: Relationship between LAPTM4B gene polymorphism and susceptibility of lung cancer. Zhongguo Fei Ai Za Zhi 9: 109-112, 2006 (In Chinese).
15. Wang S, Zhang QY and Zhou RL: Relationship between LAPTM4B gene polymorphism and susceptibility of primary liver cancer. Ann Oncol 23: 1864-1869, 2012.
16. Wang B, Xu J, Zhou R and Zhang Q: Association of LAPTM4B gene polymorphism with nasopharyngeal carcinoma susceptibility in a Chinese population. Med Oncol 30: 470, 2013.
17. Yang H, Zhai G, Ji X, Xiong F, Su J and McNutt MA: LAPTM4B allele *2 is a marker of poor prognosis following hepatic tumor resection for hepatocellular carcinoma. PLoS One 7: e34984, 2012.
18. Tang H, Tian H, Yue W, Li L, Li S, Gao C, Si L, Qi L, Lu M and Hu W: LAPTM4B polymorphism is associated with non-small cell lung cancer susceptibility and prognosis. Oncol Rep 31: 2454-2460, 2014.
19. Meng F, Li H, Zhou R, Luo C, Hu Y and Lou G: LAPTM4B gene polymorphism and endometrial carcinoma risk and prognosis. Biomarkers 18: 136-43, 2013.
20. Narayanan S and Savage KJ: Staging and prognostic factors. In: Non-Hodgkin Lymphomas. Armitage JO, Mauch PM, Harris NL, Coiffier B and Dalla-Favera R (eds). 2nd edition. Lippincott Williams & Wilkins, Philadelphia, PA, pp149-171, 2010
21. Li X, Kong X, Chen X, Zhang N, Jiang L, Ma T and Yang Q: LAPTM4B allele *2 is associated with breast cancer susceptibility and prognosis. PLoS One 7: e44916, 2012.

22. Liu XR, Zhou RL, Zhang QY, Zhang Y, Jin YY, Lin M, Rui JA and Ye DX: Structure analysis and expressions of a novel tetratransmembrane protein, lysosoma-associated protein transmembrane 4 beta associated with hepatocellular carcinoma. World J Gastroenterol 10: 1555-1559, 2004.
23. Li L, Wei XH, Pan YP, Li HC, Yang H, He QH, Pang Y, Shan Y, Xiong FX, Shao GZ and Zhou RL: LAPTM4B: A novel cancer-associated gene motivates multidrug resistance through efflux and activating PI3K/AKT signaling. Oncogene 29: 5785-5795, 2010.
24. Liu X, Zhou R, Zhang Q, Zhang Y, Shao G, Jin Y, Zhang S, Lin M, Rui J and Ye D: Identification and characterization of LAPTM4B encoded by a human hepatocellular carcinoma-associated novel gene. Beijing Da Xue Xue Bao 35: 340-347, 2003 (In Chinese).
25. He J, Shao G and Zhou R: Effects of the novel gene, LAPTM4B, highly expression in hepatocellular carcinoma on cell proliferation and tumorigenesis of NIH3T3 cells. Beijing Da Xue Xue Bao 35: 348-352, 2003 (In Chinese).
26. Yang H, Xiong F, Wei X, Yang Y, McNutt MA and Zhou R: Overexpression of LAPTM4B-35 promotes growth and metastasis of hepatocellular carcinoma in vitro and in vivo. Cancer Lett 294: 236-244, 2010.
27. Zhou L, He XD, Yu JC, Zhou RL, Shan Y and Rui JA: Overexpression of LAPTM4B-35 attenuates epirubucin-induced apoptosis of gallbladder carcinoma GBC-SD cells. Surgery 150: 25-31, 2011.
28. Shao GZ, Zhou RL, Zhang QY, Zhang Y, Liu JJ, Rui JA, Wei X and Ye DX: Molecular cloning and characterization of LAPTM4B, a novel gene upregulated in hepatocellular carcinoma. Oncogene 22: 5060-5069, 2003.
29. Milkereit R, Persaud A, Vanoaica L, Guetg A, Verrey F and Rotin D: LAPTM4b recruits the LAT1-4F2hc Leu transporter to lysosomes and promotes mTORC1 activation. Nat Commun 6: 7250, 2015.
30. Huygens C, Lienart S, Dedobbeleer O, Stockis J, Gauthy E, Coulie PG and Lucas S: Lysosomal-associated Transmembrane Protein 4B (LAPTM4B) Decreases Transforming Growth Factor β1 (TGF-β1) Production in Human Regulatory T Cells. J Biol Chem 290: 20105-20116, 2015.
31. Xiao M, Jia S, Wang H, Wang J, Huang Y and Li Z: Overexpression of LAPTM4B: An independent prognostic marker in breast cancer. J Cancer Res Clin Oncol 139: 661-667, 2013.
32. Zhai G, Yan K, Ji X, Xu W, Yang J, Xiong F, Su J, McNutt MA and Yang H: LAPTM4B allele *2 is a marker of poor prognosis for gallbladder carcinoma. PLoS One 7: e45290, 2012.
33. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J, et al: The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 109: 1857-1861, 2007.