Translational Oncology
www.transonc.com

Volume 7 Number 5 October 2014 pp. 638–643 638

Relationship Between *LAPTM4B* Gene Polymorphism and Susceptibility of Malignant Melanoma in Chinese Patients

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Abstract

Lysosomal-associated protein transmembrane 4 beta (*LAPTM4B*) is known as an oncogene associated with many human malignant tumors. There are two alleles of the gene, *LAPTM4B**1 and *LAPTM4B**2. Previous studies have shown that *LAPTM4B* polymorphism contributes to the risk of many cancers. This case-control study was to investigate the relationship between *LAPTM4B* gene polymorphism and susceptibility of malignant melanoma. The genotypes of *LAPTM4B* were determined in 617 control subjects and 220 patients with malignant melanoma by utilizing polymerase chain reaction based on specific primers. The genotypic distribution of *LAPTM4B* and Hardy–Weinberg equilibrium were analyzed by χ^2 test. Odds ratio and 95% confidence interval was calculated by unconditional logistic regression. The distributions of *LAPTM4B* genotypes were significantly different between melanoma patients (45.9% for *1/1, 46.4% for *1/2 and 7.7 for *2/2) and controls (54.5% for *1/1, 39.9% for *1/2 and 5.7 for *2/2). *LAPTM4B* *1/2 and *LAPTM4B* *2/2 had a 1.396-fold and 1.619-fold higher risk for melanoma occurrence than *1/1, and subjects with *LAPTM4B**2 have a 1.308-fold higher risk than *LAPTM4B**1 carriers. No association between *LAPTM4B* genotypes and gender, age, subtype, Clark level of invasion, Breslow thickness, ulceration, clinical stage, and *C-KIT*, *BRAF* gene mutation status was observed. *LAPTM4B**2 is associated with the high risk of malignant melanoma and carrying *LAPTM4B* *2 may be a susceptible factor to Chinese melanoma patients.

Translational Oncology (2014) 7, 638–643

Introduction

Melanoma is a malignant tumor of melanocytes, with a high potential to develop metastases. In the last few decades, the incidence of melanoma has increased substantially worldwide [1,2]. The annual growth rate of incidence is approximately 3% to 5%. Genetic, phenotypical, and environmental factors are involved in melanoma developing [3]. The manifestation and prognosis are significantly different between Asian and white populations. The subtype of superficial spreading melanoma is common in white patients, which is clearly associated with sunlight exposure [4]. Studies have confirmed that mutations of p16 located in the chromosome 9 or CDKN2A is the main genetic susceptibility of melanoma [5]. However, the most frequent subtypes of melanoma in Asian patients are acral lentiginous melanoma (AM) and mucosal melanoma (MM) [6,7]. The primary lesions were not always exposed to the ultraviolet, so the specific causative factor for increasing melanoma incidence in China was still unclear [6].

Lysosome-associated protein transmembrane 4 beta (LAPTM4B), is a new gene first cloned in hepatocellular carcinoma [8]. It was mapped to chromosome 8q22.1, spanning at least 50 kb, and is composed of six introns. The full length of mRNA is 2245-bp, encoding a type III transmembrane protein with four transmembrane regions. It has been reported that LAPTM4B is expressed fairly low in normal adult tissue

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Received 12 July 2014; Accepted 17 July 2014

1936-5233/14
http://dx.doi.org/10.1016/j.tranon.2014.07.001

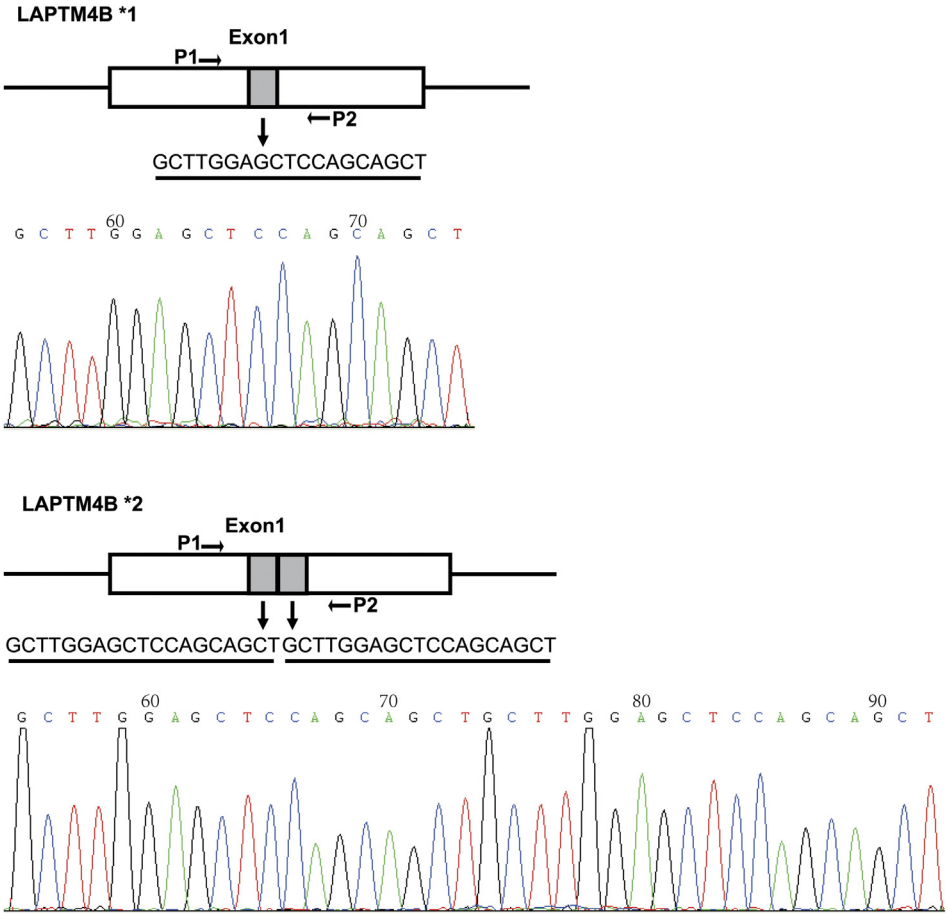

Figure 1. Schematic diagram showing LAPTM4B promoter and exon 1.Promoter region is depicted as horizontal bar. The closed box is referred to the exon, and the gray box indicates the 19-bp sequence. Allele *1 contains only one copy of a 19-bp sequence in the first exon, whereas this sequence is duplicated and tandemly arranged in allele *2. Primers loci are shown as P1 and P2. The nucleotide sequence is numbered with transcriptional start site as +1. Partial sequences in the first exon from both alleles were shown.

but high in various types of carcinomas [9]. The overexpression of LAPTM4B is associated with unfavorable biological behaviors and poor prognosis of many carcinomas, such as hepatocellular carcinoma [10], gallbladder carcinoma [11], colorectal carcinoma [12], epithelial ovarian carcinoma [13] and endometrial carcinoma [14]. LAPTM4B could active PI3K/AKT signaling pathway, which motivates multi-drug resistance [15] and also involved in drug resistance of melanoma targeted therapy [16]. LAPTM4B is also crucial for autophagy maturation that associated with chemotherapy resistance and enhances tumor survival in metabolic and genotoxic stress [17,18].

There are two alleles of *LAPTM4B* in the 5′ untranslated region, named *1 and *2 (GenBank accession numbers AY219176 and AY219177, respectively) [19]. Allele*1 differs from allele*2 in that it contains only one copy of a 19-bp sequence in the first exon, whereas this sequence is duplicated and tandemly arranged in allele*2 (Figure 1). Previous studies showed that the *LAPTM4B* *2/2-type allele was significantly associated with the susceptibility of adenocarcinoma including lung cancer [20], gastric cancer [21], colorectal cancers [22], cervical cancer [23] and breast cancer [24], but not in squamous cell carcinoma such as esophageal carcinoma, rectum carcinoma [22], and nasopharyngeal carcinoma[25]. However, the origin of melanocytes is unique: derived from the neural crest cells. Whether its malignant tumor associated with *LAPTM4B* gene polymorphism or not is still unclear. Therefore, a case–control study was designed to investigate the relationship between *LAPTM4B* gene polymorphism and melanoma developing in Chinese patients.

Patients and Methods

Cases

Two hundred twenty Chinese melanoma cases who were hospitalized in at Beijing Cancer Hospital were collected. The diagnosis of melanoma was based on the criteria of tumor, node, metastasis (TNM) classification system formulated by American Joint Committee on Cancer (AJCC 7th edition, 2010). Final diagnosis of all patients was confirmed by pathologic investigations. Patient clinicopathologic features include gender, age, tumor primary lesions, microscopic depth of tumor invasion (Clark level or Breslow's depth), ulceration status and gene mutation (C-KIT and BRAF). All patients consented in writing to participate in the study. This study was approved by the medical ethics committee of the Beijing Cancer Hospital and Institute and was conducted according to the Declaration of Helsinki Principles.

Control Subjects

A total of 617 controls were quoted from the healthy adult data of Cheng [22] and Wang [25]. The eligible controls were healthy individuals recruited from employees at the Beijing Cancer Hospital

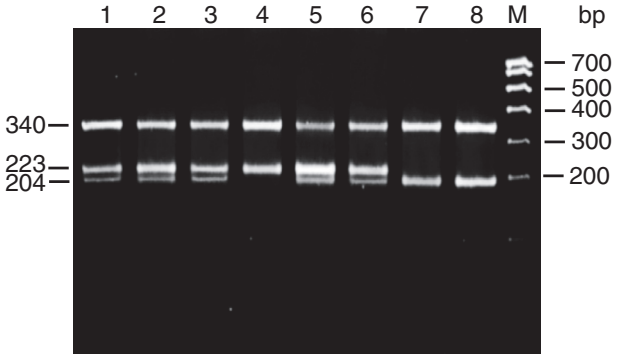

Figure 2. The polymorphism was shown by PCR using specific primers for LAPTM4B.The upper band in each lane was the product of β-actin that served as the positive internal control. The lower band depicted the PCR products of LAPTM4B. The lanes 1 to 3 and 5 to 6 were heterozygous genotype *1/2; lanes 4 were homozygous genotype *2/2; lanes 7 to 8 were homozygous genotype *1/1.

and the Health Science Center in the Peking University, who had no history of cancer. The blood donors from Beijing Cancer Hospital were checked for cancer history through their past medical charts. For the other controls, they were directly asked for their cancer history. The nurse interviewers explained the aims of this study to the blood donors, and ask them to read and sign the informed consent form if they agreed to participate.

Procedures

One milliliter of anticoagulant blood was collected from the vein and kept in a freezer at −20°C. Genomic DNA was isolated using the Relaxgene Blood DNA extraction kit (Tiangen Biotech, China) according manufacturer instructions for polymerase chain reaction (PCR) assay. The specific primers 5′-GCCGACTAGGG GACTGGCGGA-3′ (forward) and 5′-CGAGAGCTCC GAGCTTCTGCC-3′ (reverse) were used for determining the genotypes of *LAPTM4B* (Figure 1). Human β-actin was used as positive internal control, and primers were 5′-TCACCAACTGG GACGACAT-3′ (forward), and 5′-AGGTAGTCAGT CAGGTCCCG-3′(reverse). PCR assay was carried out in a 20 μl reaction mixture containing 200 to 300 ng of DNA template, 10 μmol of each primer, 10 μl 2× EASY Tag mix (TransGen Biotech, China) and 7 μl ddH_2O. The PCR cycle conditions were 94°C denaturation for 5 min, 37 cycles of 30 sec at 94°C, 30 sec at 60°C and 30 sec at 72°C, followed by extension at 72°C for 10 min. The PCR products were analyzed using 3% agarose gel electrophoresis.

Statistical Analysis

The frequency distribution of *LAPTM4B* genotypes and clinicopathological features distributions between groups of cancer cases and controls were examined by χ^2 test or the Fisher's exact test. Genotypic frequencies were tested for Hardy-Weinberg equilibrium using the χ^2 test. The relationships between melanoma and putative risk factors were measured using odds ratios (ORs) and the 95% confidence intervals (CIs) that were derived from unconditional logistical regression analysis and adjusted by the age and gender. A P value <0.05 was used as the significance level. All statistical analysis was carried out with Statistical Product and Service Solutions for Windows (version 16.0; SPSS).

Results

Three different genotypes of 220 melanoma subjects and 617 healthy controls were identified in PCR products using specific primers for *LAPTM4B*. The homozygous *1/1 and *2/2 exhibited a 204-bp band and a 223-bp band, respectively. The heterozygous genotype *1/2 has both 204-bp and 223-bp bands. Amplified products for β-actin existed as a 340-bp band in all positive internal controls (Figure 2).

The *LAPTM4B* gene polymorphism distribution in both the control and patients cases were in agreement with expectation on the basis of the Hardy–Weinberg equilibrium (P values were 0.249 and 0.205, respectively), meaning that the sampling was a good representative of the population. The distribution of patient age was normal ($P = .317$), while the distribution of control was abnormal ($P = .009$). The mean (± standard deviation) age of case group was 51.82 (± 13.15) years and the median age of control was 52 years. Gender ($P = .011$) distribution analysis showed a significant deviation between the cancer cases and control cases (Table 1).

The distribution of *LAPTM4B* genotypes was significantly different between patients and controls. There were more *1/2 and *2/2 genotypes carriers in the case group than control group, while *1/1 carriers were more in the control group (Table 2). Adjusted by gender, unconditional logistic regression analyzes showed that subjects with *LAPTM4B* *1/2 and *LAPTM4B* *2/2 had a 1396-fold (95% CI = 1.011-1.926) and 1.619-fold (95% CI = 0.868-3.020 higher risk for developing melanoma compared with *1/1 carrier.

The allele frequency was also noticed between patients and healthy controls (Table 2). In 617 controls, the *LAPTM4B**2 allele frequency was 25.6%, which is significantly lower than that in the cases (30.9%). Subjects carrying *LAPTM4B**2 have a 1.038-fold higher risk compared with *LAPTM4B**1 carriers (95% CI = 1.028-1.663).

Table 1. Distribution of Gender and Age in Case and Control Groups[a]

	Controls (n=617)	Melanoma (n=220)	P value
Gender n (%)			0.011
Male	345 (55.9)	101 (45.9)	
Female	272 (44.1)	119 (54.1)	
Age n (%)			0.229
≤50	287 (46.5%)	92 (41.8%)	
>50	330 (53.5%)	128 (58.2%)	

[a] Analyzed by χ^2 test.

Table 2. Distribution of Genotypes and Alleles of *LAPTM4B*[a] in Cases and Control Groups

	Control[b] n (%)	Case n (%)	OR[c] (95% CI[d])	P value
Genotypes				
*1/1	336(54.5)	101(45.9)		
*1/2	246(39.9)	102(46.4)	1.396(1.011-1.926)	0.042
*2/2	35(5.7)	17(7.7)	1.619(0.868-3.020)	0.130
Total	617(100.00)	220(100.00)		
Alleles				
*1	918(74.4)	304(69.1)		
*2	316(25.6)	136(30.9)	1.308(1.028-1.663)	0.029
Total	1234(100.00)	440(100.00)		

[a] *LAPTM4B*, lysosome-associated protein transmembrane 4 beta.
[b] Data were calculated by unconditional logistic regression adjusted by age and gender status.
[c] OR, odds ratio.
[d] CI, confidence interval.

The association between *LAPTM4B* genotypes and various clinicopathological features in cases were analyzed by χ^2 test (Table 2). There was no association between *LAPTM4B* genotypes and gender, age, subtype, Clark level of invasion, Breslow thickness, ulceration, clinical stage, and C-KIT, BRAF gene mutation status. In this study, AM and MM were the most common subtypes accounted for 40% and 26.8% of all cases. Clark level of invasion and Breslow thickness are melanoma measurement system that related the degree of penetration of melanoma into the skin to the 5-year survival rate after surgical removal of the melanoma, but they are only suitable for skin original melanoma. Therefore, 26.8% mucosal melanoma origin from gastrointestinal tract, vagina, or choroid and 13.2% primary site unknown cases in this study could not be measured by Clark or Breslow system. Because the site of the primary lesion was obscured, detection of melanoma in China was usually late and 79.5% patients were first diagnosed with lymph node or distant metastasis. Four common genes mutation were also observed in this study. The frequencies of *C-KIT* gene and *BRAF* gene mutation were 6.4% (11/171) and 20.5% (35/171) respectively, but *NRAS* and *PDGFR* genes mutation were not observed (Table 3).

Table 3. Distribution of Various Genotypes of *LAPTM4B*[a] in Relation to Clinicopathological and other Variables in Cases Group

Variable	*LAPTM4B* genotype		*P* value	*LAPTM4B* genotype		*P* value
	*1/1	*1/2		*1/1	*2/2	
Gender			0.729			0.627
Male	48	46		48	7	
Female	53	56		53	10	
Age			0.84			0.914
≤50	43	42		43	7	
>50	58	60		58	10	
Subtypes			0.943			0.594
AM[b]	39	41		39	8	
MM[c]	26	28		26	5	
CSD[d]	14	15		14	0	
Non-CSD[e]	7	7		7	1	
UP[f]	15	11		15	3	
Clark level of invasion			0.714			0.527
I-II	6	4		6	2	
III-V	13	15		13	1	
Unknown	82	83		82	14	
Breslow thickness			0.144			0.354
≤1.5 mm	1	4		1	1	
>1.5 mm	20	12		20	4	
Unknown	80	86		80	12	
Ulceration			0.317			0.615
Positive	46	38		46	5	
Negative	40	45		40	6	
Unknown	15	19		15	6	
Stage			0.971			0.766
0-II	21	21		21	3	
III-IV	80	81		80	14	
C-KIT gene aberration			0.146			0.451
Positive	3	7		3	1	
Negative	79	69		79	12	
Unknown	19	26		19	4	
BRAF gene mutation			0.715			0.418
Positive	17	14		17	4	
Negative	65	62		65	9	
Unknown	19	26		19	4	

Analyzed by χ^2 test

[a] *LAPTM4B*, lysosome-associated protein transmembrane 4 beta.
[b] AM, acral lentiginous melanoma.
[c] MM, mucosal melanoma.
[d] CSD, chronic sun damage.
[e] Non-CSD, non chronic sun damage.
[f] UP, unknown primary.

Discussion

In this study, we demonstrated that *LAPTM4B* gene polymorphism is one of the susceptible factors of melanoma occurrence in Chinese population. Compared with the Western countries, the subtypes of melanoma diagnosed in Chinese patients are different. Previous studies showed that the two most commonly histology subtypes were AM and MM, which accounted for 49.4% and 22.6% [6]. For primary lesions were located in the ultraviolet less contact sites, both the subtypes were not associated with sunlight exposed. The rapid increasing melanoma incidence in China may be associated with the lifestyle changes, although the specific causative factor was still unclear [6]. In this case-control study, notable higher distribution of *LAPTM4B* *2 allele and *LAPTM4B* *2/2 in the cases group suggests that *LAPTM4B* *2 be one of risk factors of melanoma in Chinese patients.

Previous studies showed that *LAPTM4B**2 allele was associated with increased susceptibility of lung cancer [20], gastric cancer [21], colorectal cancers [22], lymphoma [26], cervical cancer [23] and breast cancer [24]. The risk of developing these cancers were increased to 1.720, 1.710, 1.512, 1.610, 1.490, and 1.301 fold in individuals carrying allele *2 in comparison with *1, respectively. In this study, the *LAPTM4B* *2 carrier had a 1.457-fold risk of suffering melanoma than *LAPTM4B* *1 carrier. Our result was consistent with previous findings.

The two sequence alleles of the *LAPTM4B* are in homology, with the exception of a 19-bp difference in the first exon. Shao [8] showed that *LAPTM4B* *1 was predicted to encode a 35 kD protein. In allele *2, the extra 19-bp sequence changed open reading frame of *LAPTM4B* gene and made *LAPTM4B**2 encode one more protein isoform, a 40-kD protein, than *LAPTM4B**1 (Figure 3). The N-terminal sequence of LAPTM4B is crucial for its functions, such as enhancing cell proliferation and signal transduction [19,27]. The two different protein isoforms may influence physiological activities and functions of the cancer cell [22]. Moreover, the 19-bp sequence may act as a cis-acting element to participate in genetic transcriptional regulation.

The gene mutation status of melanoma patients were also observed in this study. *C-KIT* and *BRAF* are the most common mutated genes in Asian melanomas [28,29]. It has been reported that the incidence of somatic mutations within the *C-KIT, BRAF, NRAS* and *PDGFRA* genes was 10.1% (58/573), 25.9% (121/468), 7.2% (33/459) and 4.8% (17/352), respectively in Chinese melanoma cases[28,29]. The frequencies of *C-KIT* and *BRAF* mutation were 6.4% (11/171) and 20.5% (35/171) in this study, closing to previous studies. There was no difference between *2 allele carrier and *1 allele carrier in *C-KIT* and *BRAF* gene mutation, nor in other clinicopathological features. Therefore, we believed that *LAPTM4B* was an independent risk factor in melanoma developing.

To our knowledge, this is the first case-control study focusing on the possible role of *LAPTM4B**2 in melanoma. We concluded that *LAPTM4B**2 is likely contributing to a higher risk of melanoma. Carrying *LAPTM4B* *2 is a susceptible factor to melanoma in Chinese patients.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (No. 81071422). We would like to thank all people and patients who participated in this study.

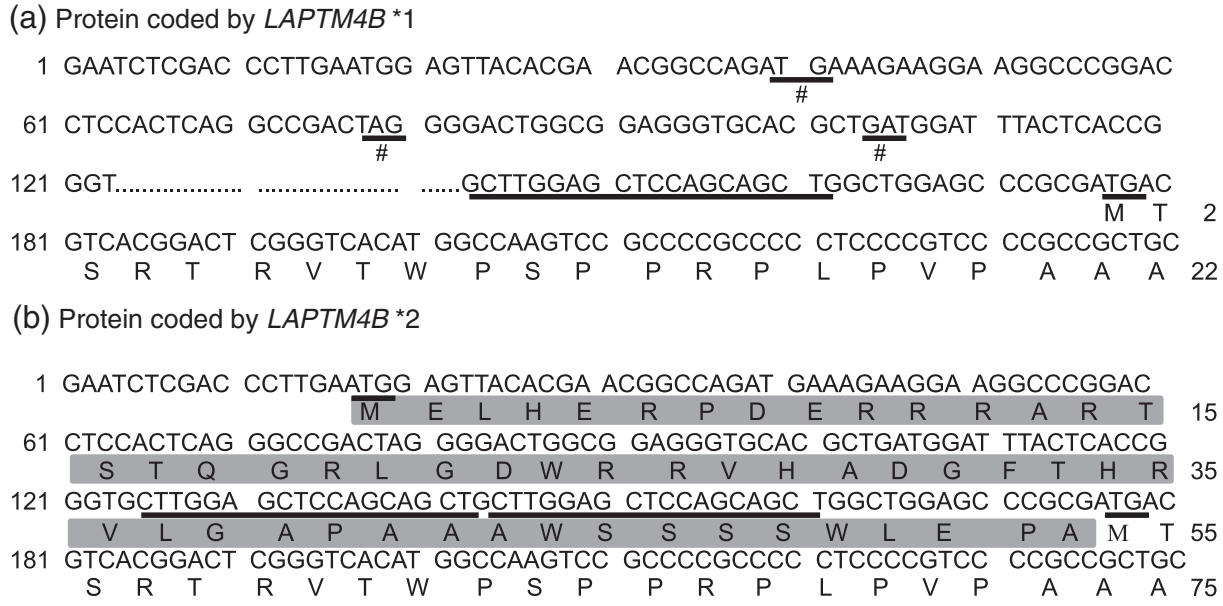

Figure 3. Comparison of the predicted proteins encoded by LAPTM4B*1 and *2. This schematic diagram shows the initial segments of first exon in LAPTM4B *1 (a) and LAPTM4B (b). The sequence numbers of the first nucleotide (left) and the final amino acid (right) in each row are shown, respectively. The nucleotide sequences are numbered with the putative transcription start site as +1. Termination codons are underlined and marked by symbols #. The 19-bp sequences in both of the alleles are underlined. The mRNA of allele *1 can only starts translation at nt 157, because of the termination codons at nt 40 and nt 103. However, allele *2 start translation at nt 17, producing an extra stretch of amino acids (53 aa, gray-shaded letters) at N terminus of LAPTM4B.

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