Family With Sequence Similarity 83, Member A (FAM83A) As a Promising Prognostic Biomarker in Lung Squamous Cell Cancer

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Research

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Abstract

Background: Increasing studies have found the dysregulated FAM83A as a potential biomarker in various cancers. Its function in cancer cells is largely unknown, and especially their role in LUSC remains unclear. We detected the expression level and prognosis role of FAM83A in LUSC.

Methods: The bioinformatics methods were performed initially to predict the expression level and prognostic value of FAM83A mRNA in LUSC. We used IHC to examine its protein expression level and identify its prognostic value using 132 pairs of tissues.

Results: Results from TCGA and Oncomine databases revealed that FAM83A mRNA expression level was significantly higher in LUSC than that in normal lung tissue. TCGA and GEO databases revealed FAM83A mRNA overexpression was significantly associated with poorer OS of LUSC patients (all P<0.05). Furtherly, our IHC results revealed that FAM83A was overexpressed in 78 (59.1%) patients and 19(14.4%) pancancerous tissues (P<0.001). Kaplan-Meier analyses revealed that high FAM83A protein expression was significantly associated with decreased 5-years' OS (P = 0.007) and PFS (P = 0.007). Via multivariate analysis, FAM83A expression level was independent prognostic factor for both OS (P = 0.006) and PFS (P = 0.002).

Conclusion: FAM83A was overexpressed in LUSC and it could serve as a prognosis prediction biomarker for LUSC. FAM83A could act as one new potential therapeutic target for LUSC treatment.

Background

Lung cancer continues as the leading cause of cancer-related mortality with a higher global incidence than any other cancer type. It accounted for more than 10% of the total cancer incidence worldwide[1]. Lung squamous cell carcinoma (LUSC) is a distinct histologic subtype of non-small cell lung cancer, accounting for about 30% of cases[2]. LUSC is challenging to treat as a result of specific patient and disease characteristics including older age and advanced disease at diagnosis and a higher incidence of comorbidities such as chronic obstructive pulmonary disease and heart disease. LUSC is usually centrally located, typically arising in the proximal bronchi, and as a consequence, it is more likely to invade larger blood vessels[3]. Recently, therapeutic options for the treatment of lung cancer have emerged through better understanding of the molecular mechanisms of tumor formation and progression. However, few inroads in targeted therapy and immune checkpoint inhibitor therapy have been made for LUSC[4]. Chemotherapy is the primary treatment for patients with advanced LUSC. Current 5-year survival estimates in LUSC range from 73% in stage IA disease to 13% in stage IV disease[5]. Future prognostication of outcomes in LUSC will likely be based on a combination of TNM stage and molecular tumor profiling and yield more precise, individualized survival estimates and treatment algorithms.

Family with sequence similarity 83, member A (FAM83A), also known as BJ-TSA-9[6], is located on chromosome 8, locus q24.13, and spans 27 566 base pairs[7]. Recently, increasing studies have found that dysregulated FAM83A is a potential biomarker in various cancers, including breast, hepatocellular and lung adenocarcinoma cancers[7; 8; 9; 10; 11; 12]. It was reported that FAM83A promotes lung adenocarcinoma cancer progression by regulating the Wnt and Hippo [8] and ERK and PI3K/Akt/mTOR pathways [13], making it a promising therapeutic target. Besides, circ-ZKSCAN1/miR-330-5p/FAM83A feedback loop plays important role in promoting the progress of NSCLC[14]. However, the exact expression levels of FAM83A in LUSC and its clinical prognostic value have been unknown. Therefore, in the present study, we used bioinformatics methods initially to predict the differential expression levels

of FAM83A mRNA in LUSC vs normal lung tissues. Then, immunohistochemical staining was used to examine the FAM83A protein expression level and its prognostic value in LUSC. The promising results could provide new target for LUSC treatment.

Methods And Materials

Bioinformatics analysis

The TCGA (the comprehensive catalog of genomic abnormalities) data was analyzed and downloaded via UALCAN web, a comprehensive and interactive web resource for analyzing cancer OMICS data (http://ualcan.path.uab.edu). The Oncomine database (https://www. oncomine.org)[15] was also screened to explore the differential expression levels of FAM83A between LUSC and normal groups. Additionally, Kaplan-Meier Plotter (http://kmplot.com) was used to draw the OS and PFS curves based on the GEO data.

Ihc Staining

We collected 132 pairs of FFPE cancerous and matched pancancerous LUSC tissues in 2012 from the Department of Pathology of Qilu Hospital. We used xylene and rehydration for deparaffinization. Incubation in 3% H_2O_2 was used to block the endogenous peroxidase enzyme activity. The slides were then incubated with primary rabbit anti-FAM83A polyclonal antibody (Abcam, Cambridge, MA, USA) overnight at 4 °C. Afterwards, slides were incubated with biotinylated secondary antibodies and streptavidin-peroxidase complex. Finally, a 3,3'-diaminobenzidine solution was added, and the slides were counterstained with haematoxylin and mounted with neutral balsam. Sections were incubated with PBS instead of the primary antibodies for negative controls. The sections were observed under a light microscope and independently scored by three investigators. For conflicting scores, we selected the value that was consistent between two observers or used the average of scores. The final score was calculated by multiplying the staining intensity (scored as: 0, no staining; 1, weak staining; 2, moderate staining and 3, strong staining) by the percentage of positive cells (scored as: 0, 0–10% positive cells; 1, 10–25% positive cells; 2, 26–50% positive cells; 3, 51–75% positive cells; and 4, 76–100% positive cells). The final staining score was the sum of the staining intensity and percentage of positive cells. It was further graded as follows: 0–1, (−); 2–3, (+); 4–5, (+ +); and 6–7, (+ + +). The expression of FAM83A was divided into a non-overexpressed group (− or +) and an overexpressed group (+ + or + + +).

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University. The research was performed in accordance with relevant guidelines. Informed consent was obtained from all participants.

Statistical analysis

The independent-samples t test was used to compare the differential expression levels of FAM83A mRNA between LUSC and normal lung tissue. The putative associations between clinical parameters and FAM83A were assessed by Chi-square tests. Kaplan-Meier analysis was performed to estimate the survival curves between different subgroups and the log-rank test (Mantel–Cox) was used to compare the curve. We then used cox proportional-hazards model to identify association of FAM83A expression level with survival and to estimate mortality hazard ratios (HRs). Statistical analyses were performed using SPSS statistical software (version 22.0). All P-value were two sided. P-value < 0.05 was considered statistically significant.

Results

FAM83A mRNA was upregulated in LUSC tissues. 555 samples (503 cancerous tissues and 52 normal tissues) from TCGA database were included. We found that FAM83A was significantly upregulated in LUSC tissues compared to normal tissues (median value: 13.464 transcript per million vs 0.411 transcript per million, $P < 0.001$, Fig. 1A). In subgroup analysis, FAM83A mRNA was upregulated in LUSC-not otherwise specified (NOS) type, but not in basaloid, papillary and small cell types based on histology subtype. Besides, FAM83A was upregulated in LUSC tissue of stage 1, 2 and 3 compared with normal tissues, as well as in LUSC tissues of N0, N1 and N2. Compared to normal controls, FAM83A mRNA was overexpressed in all patient subgroups based on age, race, gender and smoking habit (all P values < 0.001, Fig. 1B-H) except the subgroup of patients aged 21–40 years old group. By searching the Oncomine database, a total of 2 GEO-sourced datasets were found. The meta-analysis revealed that FAM83A mRNA levels were dramatically higher in LUSC than in normal lung tissues ($P = 0.032$, Fig. 2A). Moreover, as shown in Fig. 2B-C, results from the dataset was consistent with finding of the above meta-analysis. To verify the expression level of FAM83A protein in LUSC tissues. We performed IHC in 132 pairs of LUSC and paracancerous tissues (Fig. 3). No significant relationship was identified between FAM83A expression and clinicopathological features such as age, gender, smoking, drinking, T stage, N stage and differentiation (Table 1). FAM83A was overexpressed in 78 (59.1%) cancerous tissues and 19(14.4%) pancancerous tissues ($P < 0.001$).

Table 1
The correlation of clinicopathologic variables with FAM83A expression in LUSC samples

Clinicopathological features	FAM83A overexpression		P^a value
	No (n = 54)	Yes (n = 78)	
Age			0.369
< 65	25	30	
≥ 65	29	48	
Gender			0.279
Female	23	26	
Male	31	52	
Smoking			0.734
Never or light	38	57	
Heavy	16	21	
Drinking			0.135
Never or light	46	58	
Heavy	8	20	
Differentiation			0.497
Well	19	22	
Moderate	15	29	
Poor	20	27	
T stage			0.404
T1	20	22	
T2	23	33	
T3	11	23	
N stage			0.441
N0	18	19	
N1	13	23	
N2	18	23	
N3	5	13	

P[a]: **Chi-square test.**

The prognostic value of FAM83A in LUSC. Based on TCGA database, high level of FAM83A mRNA was significantly associated with poorer overall survival (OS) of LUSC patients (P = 0.00048, Fig. 4A). We further browsed Kaplan-

Meier database, higher FAM83A mRNA expression level also predicted poorer 5- and 10- years' OS (both $P < 0.001$) (Fig. 4B-C). Furtherly, we analyzed the prognosis value of FAM83A protein level using our own data. Of the 132 patients who provided formalin-fixed paraffin-embedded (FFPE) cancer tissues, 64 (48.5%) survived more than 5 years after pneumonectomy and 68 (51.5%) died during the follow-up period. The mean OS time for all patients was 50.5 ± 17.7 months (range 15–82 months) and mean progression-free survival (PFS) time was 45.5 ± 20.6 months (range 9–82 months). Kaplan-Meier analyses using the log-rank test were performed to calculate the effect of these clinicopathologic factors on OS and PFS rates. High FAM83A protein expression was significantly associated with decreased 5-years' OS ($P = 0.007$) and PFS ($P = 0.007$) (Fig. 5, Table 2). Furthermore, via multivariate analysis, FAM83A expression level was an independent prognostic factor for OS (hazard ratio (HR) (95%CI): 2.160 (1.374–3.396), $P = 0.006$), as well as PFS (HR (95%CI): 2.266 (1.367–3.756), $P = 0.002$, Table 2). Besides, T and N stages were significant prognostic indicators for PFS ($P = 0.008$ and $P = 0.033$, respectively).

Table 2
Univariate and multivariate analyses of prognostic variables for LUSC patients

	OS		OS		PFS		PFS	
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR(95% CI)	*P* value
Gender								
Female	Ref	-			Ref	-		
Male	0.935(0.569–1.539)	0.793			0.958(0.599–1.533)	0.858		
Age								
<65 years-old	Ref	-			Ref	-		
≥65 years-old	1.024(0.632–1.660)	0.923			1.027(0.650–1.624)	0.908		
Smoking								
Never or light	Ref	-			Ref	-		
Heavy	1.589(0.961–2.627)	0.071			0.648(0.401–1.047)	0.076		
Drinking						0.437		
Never or light	Ref	-			Ref	-		
Heavy	1.319(0.753–2.311)	0.333			0.809(0.472–1.388)	0.442		
Differentiation		0.240				0.490		
Poor	Ref	-			Ref	-		
Median	1.606(0.891–2.894)	0.115			1.319(.766-2.274)	0.318		
Well	1.143(0.609–2.146)	0.677			0.993(0.557–1.772)	0.982		
T stage		0.049*		0.080		0.011*		0.008*
T1	Ref	-	Ref	-	Ref	-	Ref	-
T2	1.557(0.848–2.858)	0.153	1.277 (0.688–2.373)	0.438	1.522(0.853–2.713)	0.155	1.243 (0.689–2.245)	0.470
T3	2.202(1.154–4.204)	0.017*	2.057 (1.065–3.971)	0.032*	2.494(1.363–4.565)	0.003*	2.446 (1.323–4.523)	0.004*
N stage		0.024*		0.053		0.024*		0.033*

	OS Univariate analysis		OS Multivariate analysis		PFS Univariate analysis		PFS Multivariate analysis	
N0	Ref	-	Ref	-	Ref	-	Ref	-
N1	1.723(0.836–3.551)	0.140	1.741 (0.832–3.644)	0.141	1.553(0.800-3.015)	0.193	1.605 (0.817–3.154)	0.170
N2	1.981(0.985–3.986)	0.055	1.903 (0.936–3.869)	0.076	1.762(0.928–3.347)	0.083	1.717 (0.895–3.294)	0.104
N3	3.334(1.535–7.242)	0.002*	3.076 (1.380–6.856)	0.006*	3.058(1.487–6.287)	0.002*	3.079 (1.452–6.532)	0.003*
FAM83A								
Low	Ref	-	Ref	-	Ref	-	Ref	-
High	2.058(1.220–3.471)	0.007*	2.160 (1.374–3.396)	0.006*	1.940(1.194–3.151)	0.007*	2.266 (1.367–3.756)	0.002*

Discussion

For the fact of high flexibility of cancer cells and multiple regulatory feedback loops resulting in therapy resistance, LUSC remains largely incurable. Consequently, promising molecular targets have to be found. FAM83A was recently described to be highly upregulated in several cancer specimens. Its function in cancer cells is largely unknown, and especially their role in LUSC remains unclear. In order to acquire a better understanding of FAM83A, we detected its expression and prognosis role using online databases and 132 pairs of FFPE samples in this study. We found that FAM83A mRNA was significantly upregulated in LUSC tissues compared to normal tissues via TCGA and GEO databases. It corresponds to those of previous studies that could identify elevated amounts of FAM83A in various tumor tissues[11; 12; 16; 17]. Moreover, elevated expression of FAM83A mRNA affected survival negatively based on TCGA and Kaplan-Meier databases. Then, to confirm the predictive results, IHC was used to investigate the expression levels of FAM83A protein. Identical with the previous predictive findings[7; 9; 18], our multivariable analysis revealed FAM83A protein level to be an independent prognostic factor for 5-years' OS as well as PFS of LUSC patients. In summary, these findings suggest that FAM83A protein expression could serve as a prognosis biomarker of LUSC patients, and FAM83A might be an important target gene involved in the growth and metastasis of LUSC.

Calculating studies revealed the mechanisms of FAM83A in various cancers. Zheng YW et al.[8] found that FAM83A promotes lung cancer progression by regulating the Wnt and Hippo signaling pathways. Hu HY et al. found that FAM83A promotes tumorigenesis of NSCLC at least partly via ERK and PI3K/Akt/mTOR pathways, making it a promising therapeutic target[13]. Zhou FR et al. [19] found that co-expression of FAM83A and PD-L1 in tumor cells was a credible biomarker predictor for worse survival in resected LAC patients. FAM83A may promote the expression of PD-L1 through ERK signaling pathway, thus causing immune escape of tumor. However, converse to the overexpression level and oncogene roles of FAM83A in cancers, Xu JF et al.[16] found that FAM83A may exert a tumor-suppressive role in cervical cancer by suppressing the expression of integrins, which may offer new insight

into FAM83A regulating mechanisms in cancers. However, the regulating mechanisms of FAM83A in LUSC is largely unknown and we will focus on its regulatory role in the future.

There are limitations in this study. Firstly, the number of FFPE samples was small, which may influence the statistical analysis to some extent. Second, further in vitro and in vivo experiments were not performed to investigate its regulatory mechanisms in LUSC. We will address its mechanisms in the future studies.

Conclusion

In conclusion, FAM83A was overexpressed in LUSC and it could serve as a promising prognostic biomarker for LUSC patients. FAM83A may serve as a new potential therapeutic target for the treatment of LUSC.

Abbreviations

FAM83A, Family With Sequence Similarity 83, Member A; LUSC, Lung Squamous Cell Cancer; IHC, Immunohistochemistry; TCGA, the comprehensive catalog of genomic abnormalities; LUSC-not otherwise specified (NOS); FFPE. formalin fixed paraffin-embedded; OS, overall survival; PFS, progression-free survival; HR, hazard ratio.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Qilu Hospital of Shandong University. The research was performed in accordance with relevant guidelines. Informed consent was obtained from all participants.

Consent for publication: All authors have read the manuscript and have agreed to submit the paper in its present form.

Availability of data and material: All online data were available from UALCAN (http://ualcan.path.uab.edu), Oncomine database (https://www. oncomine.org) and Kaplan-Meier Plotter (http://kmplot.com). Other data was available from the corresponding author.

Competing interests: The authors declare no conflict of interest

Funding: None.

Authors' contributions: LM designed research; LM, WC and TH conducted research; LRF, FZT and LYM analyzed data; LM and WC wrote the paper; LM had primary responsibility for final content. All authors have read and approved the manuscript.

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Figures

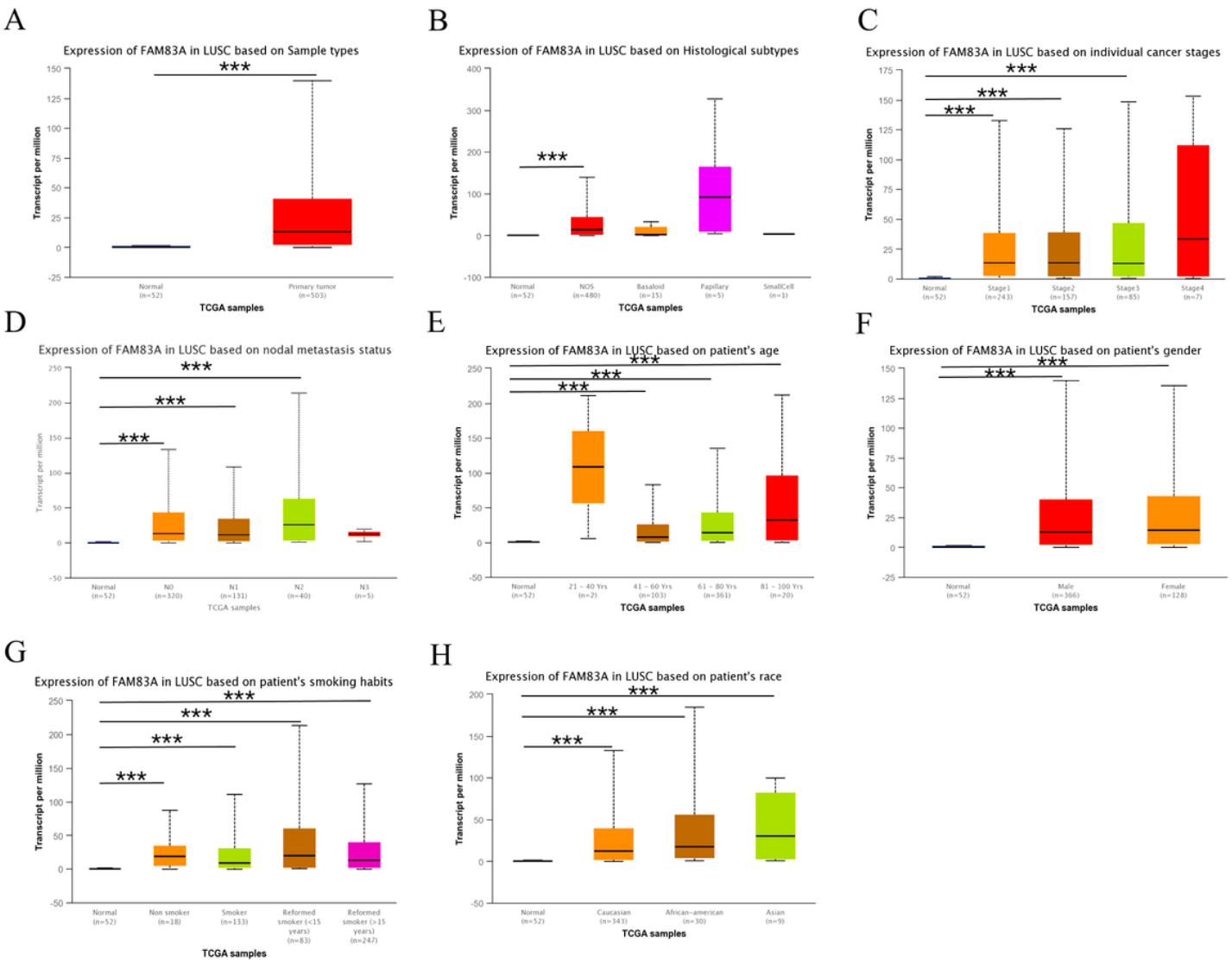
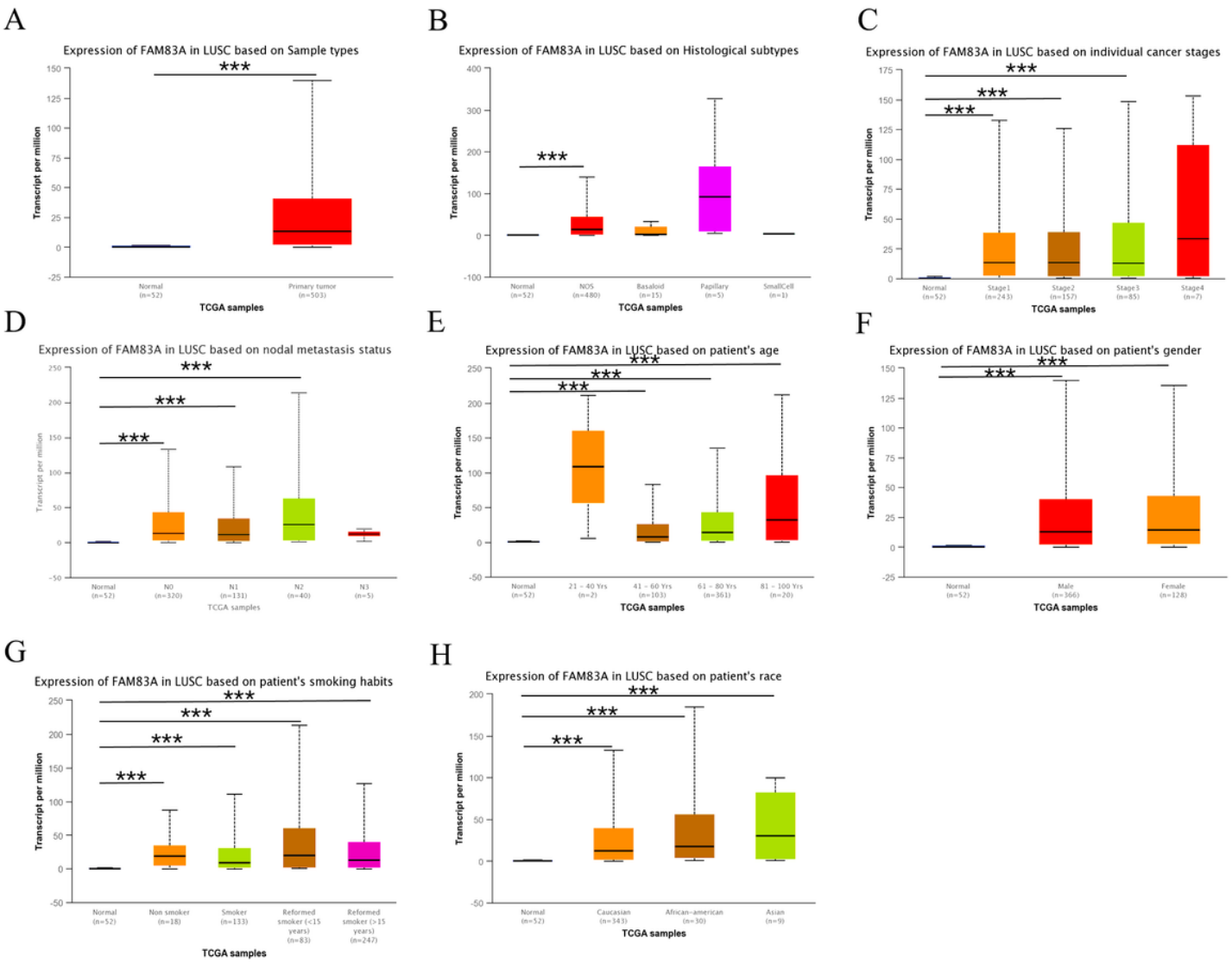


Figure 1

FAM83A mRNA expression level in LUSC by TCGA database. (A) FAM83A mRNA levels in LUSC vs. normal lung tissue. (B-H) FAM83A mRNA expression levels stratified by histological subtype, individual cancer stage, nodal metastasis stage, patient's age, gender, smoking habit and race.



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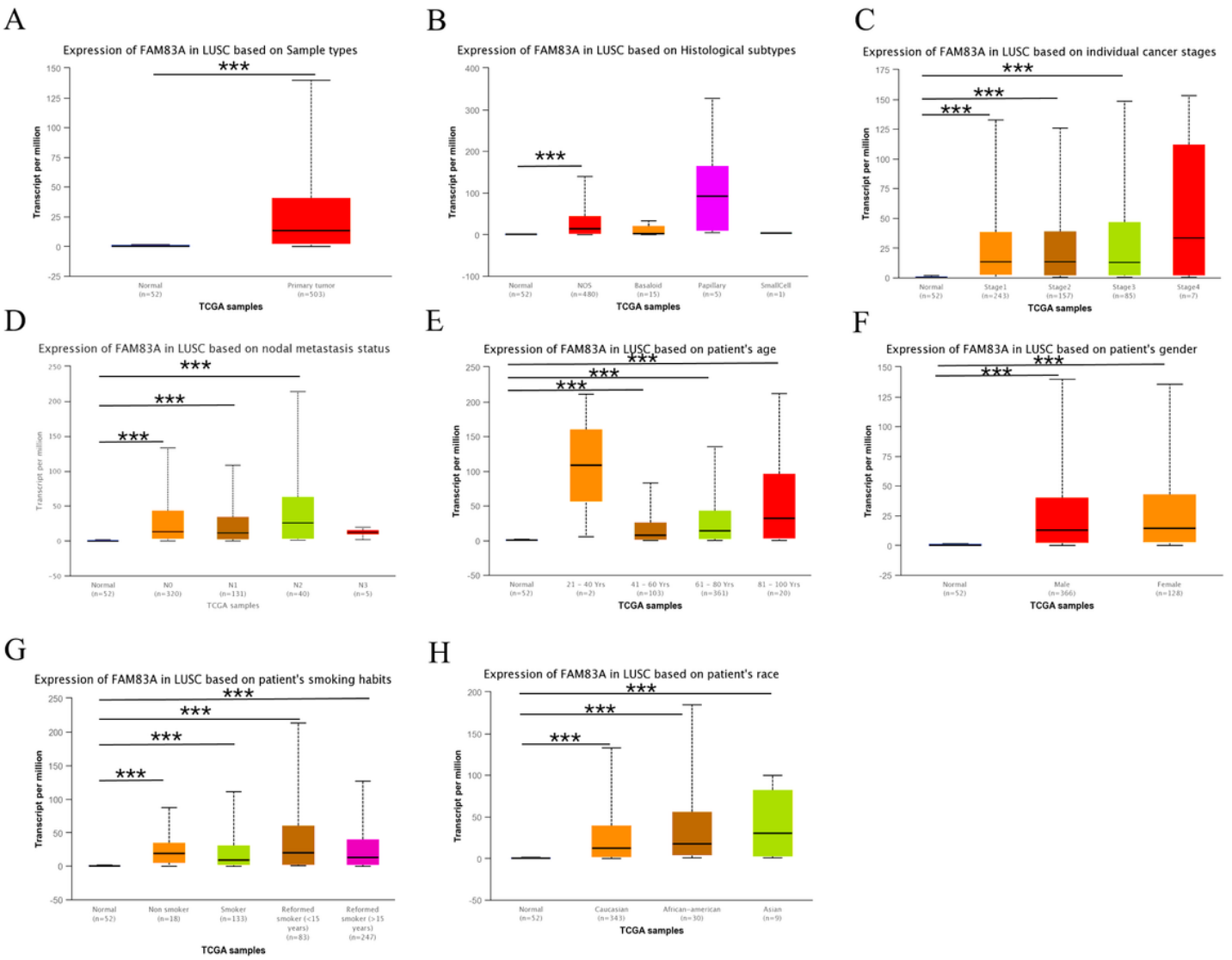

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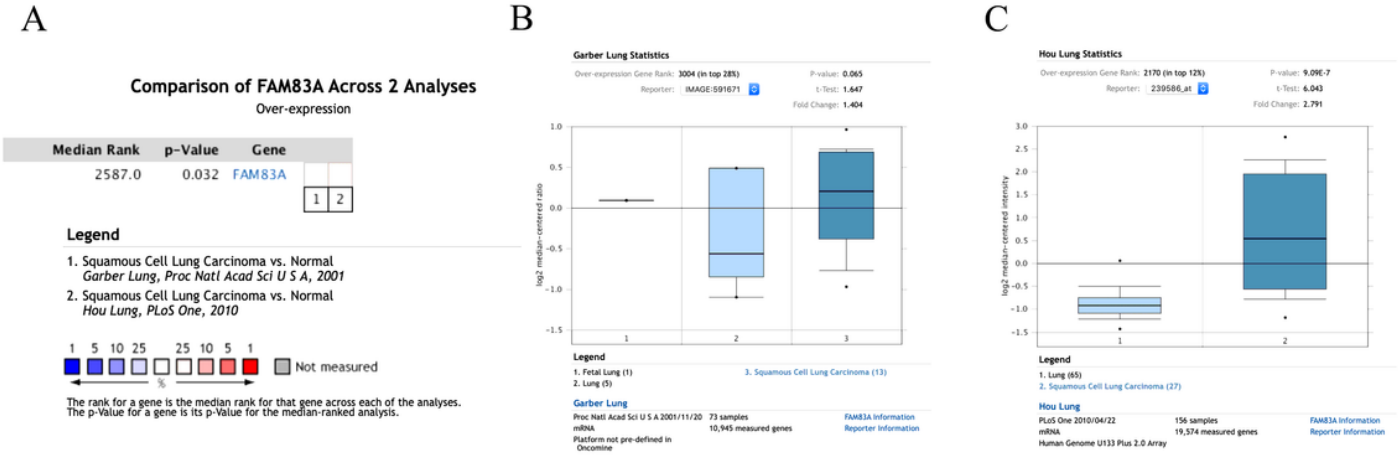
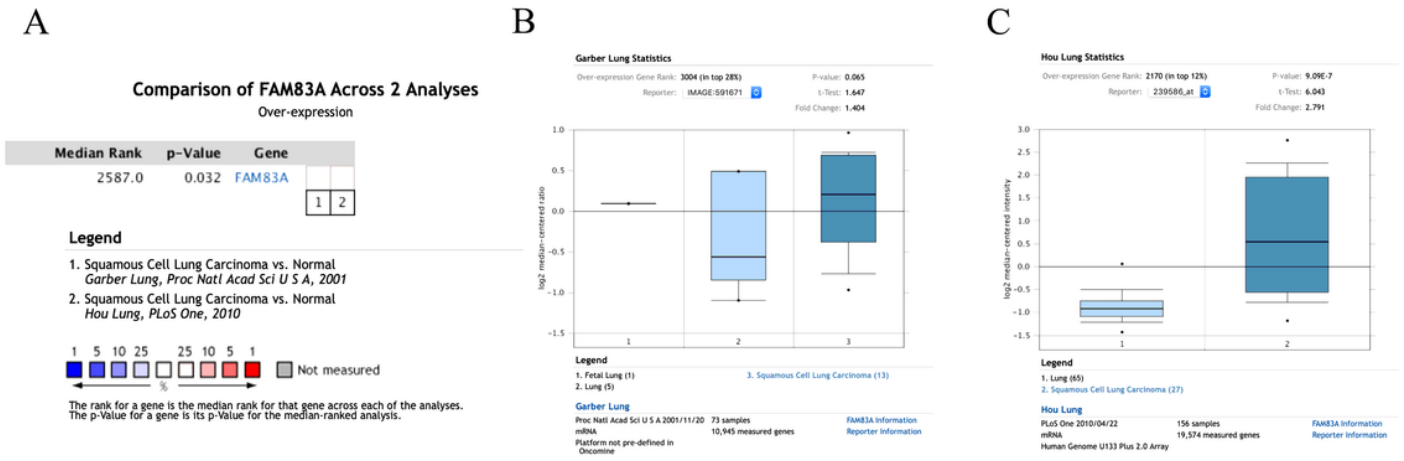


Figure 2

Overexpression of FAM83A mRNA in LUSC predicted by Oncomine database. (A) Meta-analysis of the 2 datasets on FAM83A mRNA levels in LUSC vs. normal lung tissue by Oncomine database. (B-C) FAM83A mRNA expression level in Garber Lung (GSE number: GSE3398) and Hou Lung (GSE number: GSE19188) datasets.



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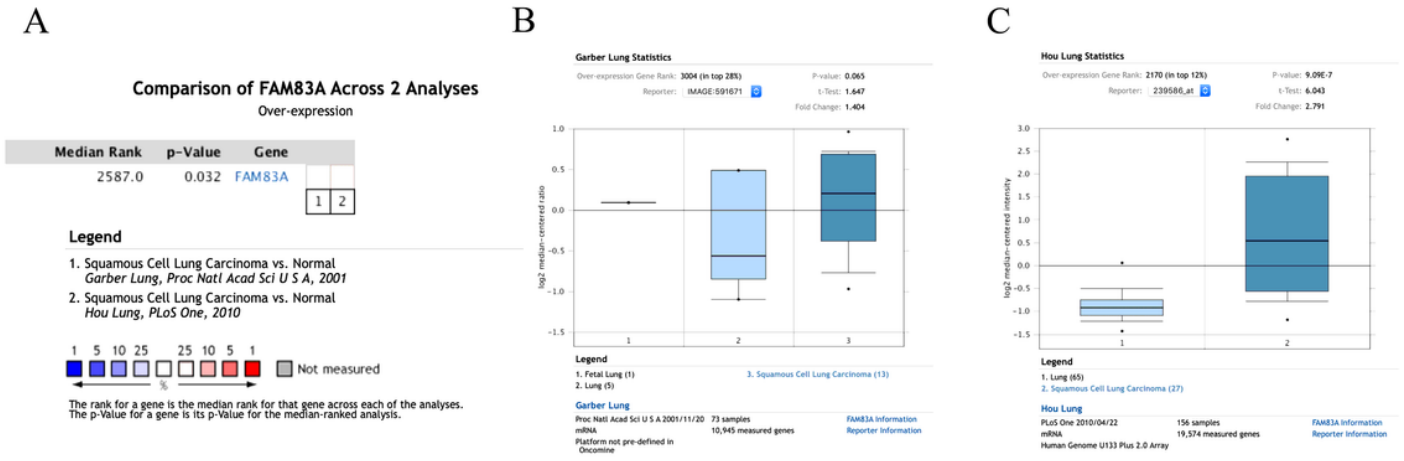

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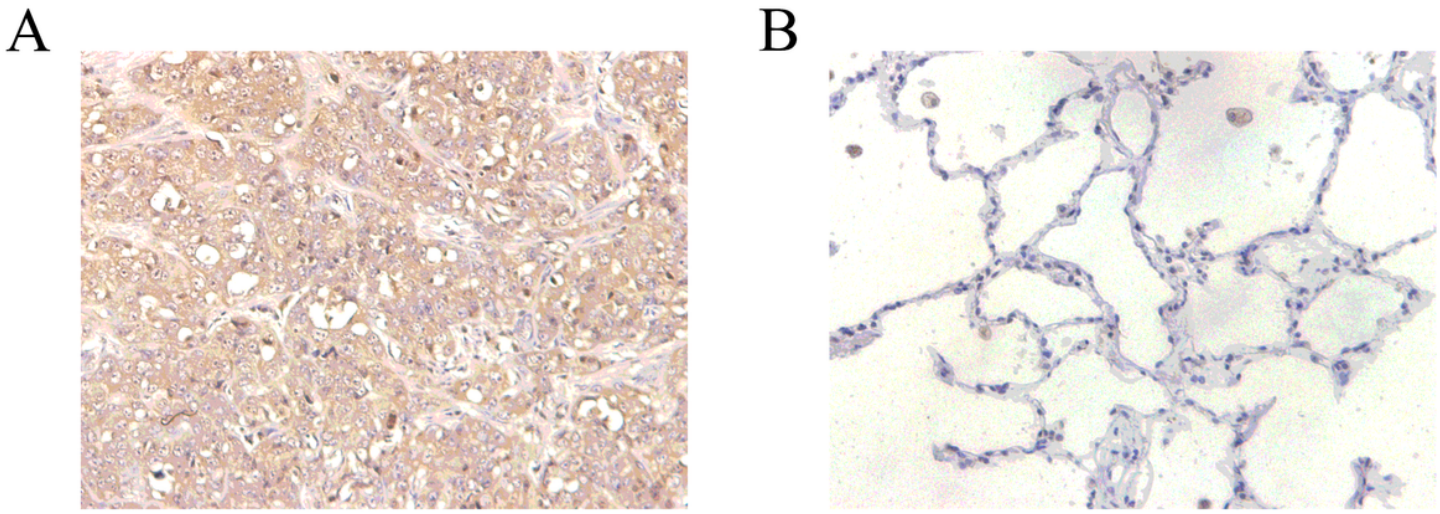
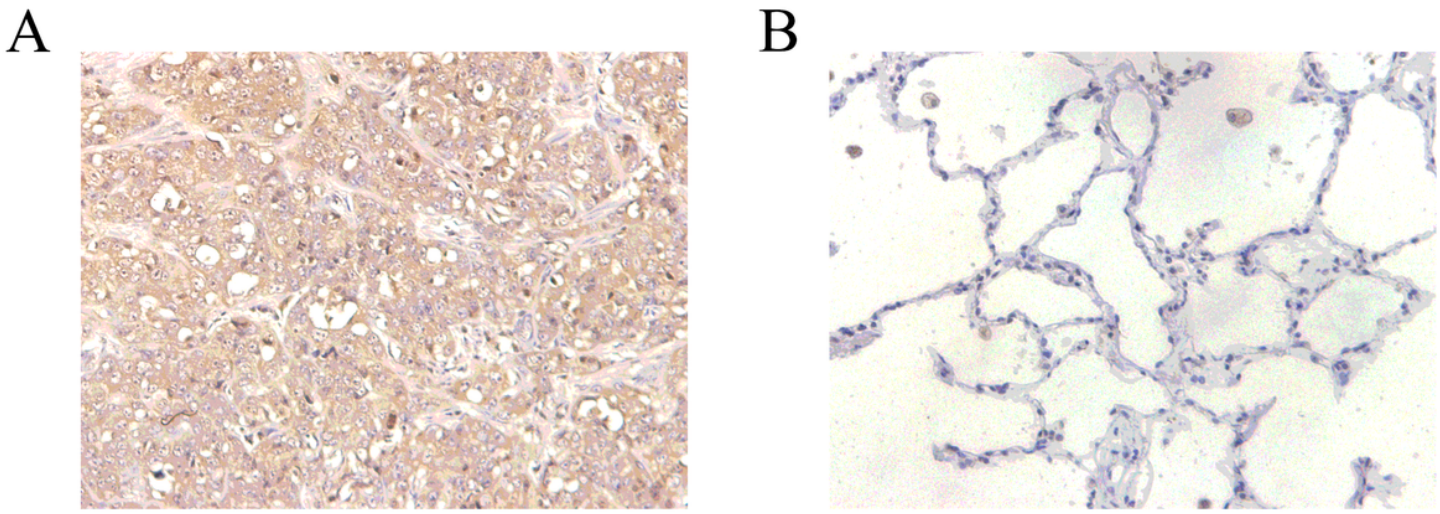


Figure 3

Immunohistochemical staining of FAM83A in LUSC tissues and matched paracancerous lung tissue (200×). (A) High expression level of FAM83A in LUSC. (B) Low expression level of FAM83A in normal lung tissue.



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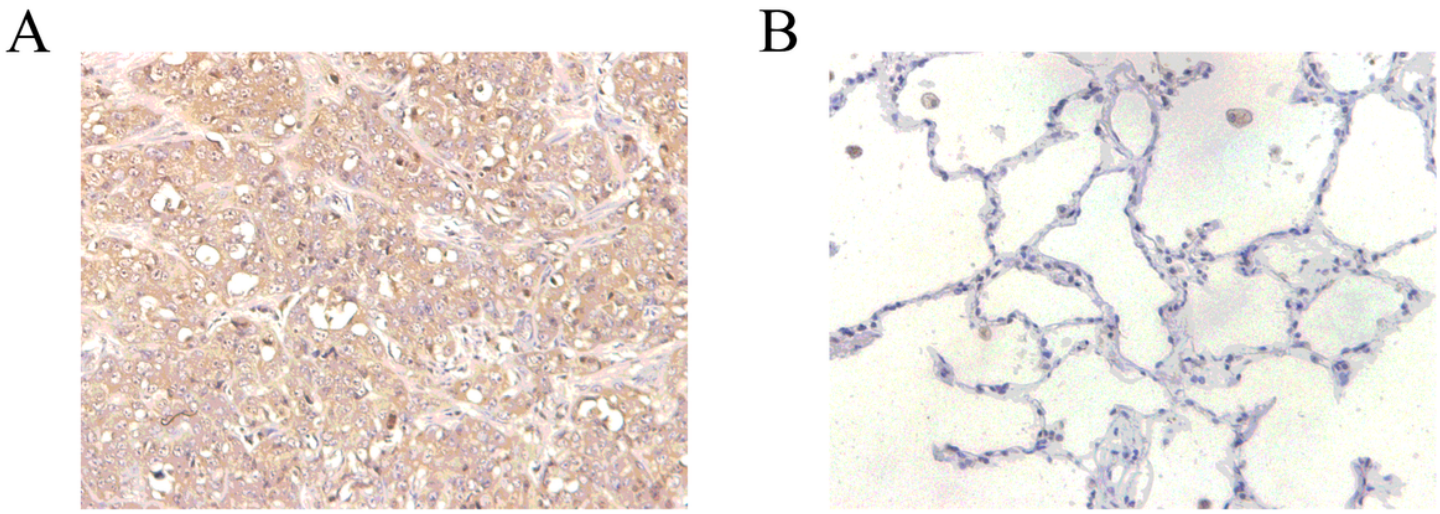

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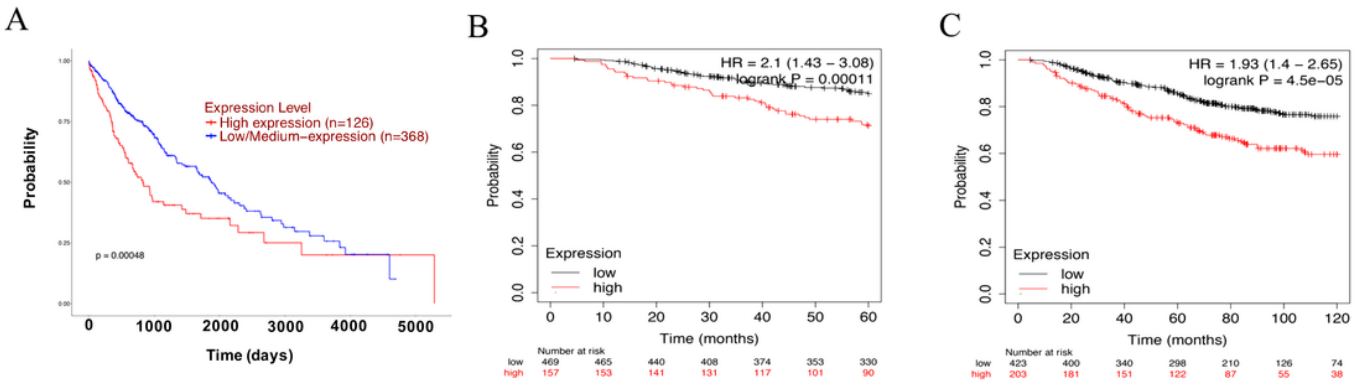
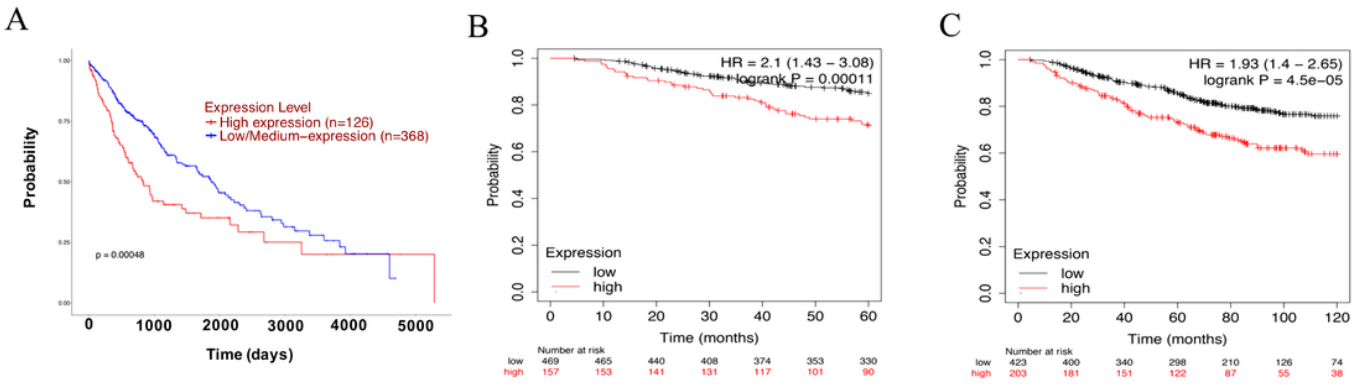


Figure 4

Overall survival (OS) curves of LUSC patients based on the differential expression levels FAM83A mRNA (low vs. high) by TCGA and GEO databases. (A) OS curve based on TCGA database; (B) 5 years' OS curve based on GEO database; (C) 10 years' OS curve based on GEO database.



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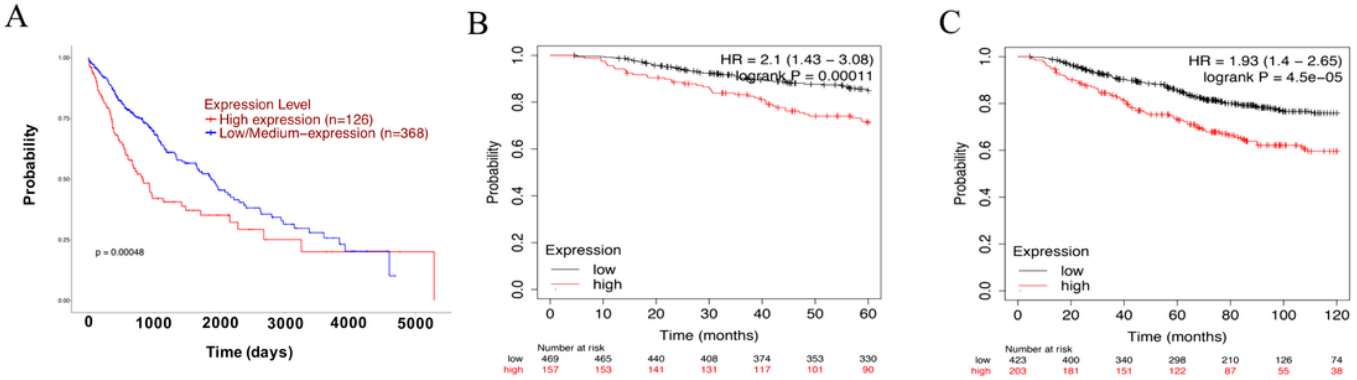

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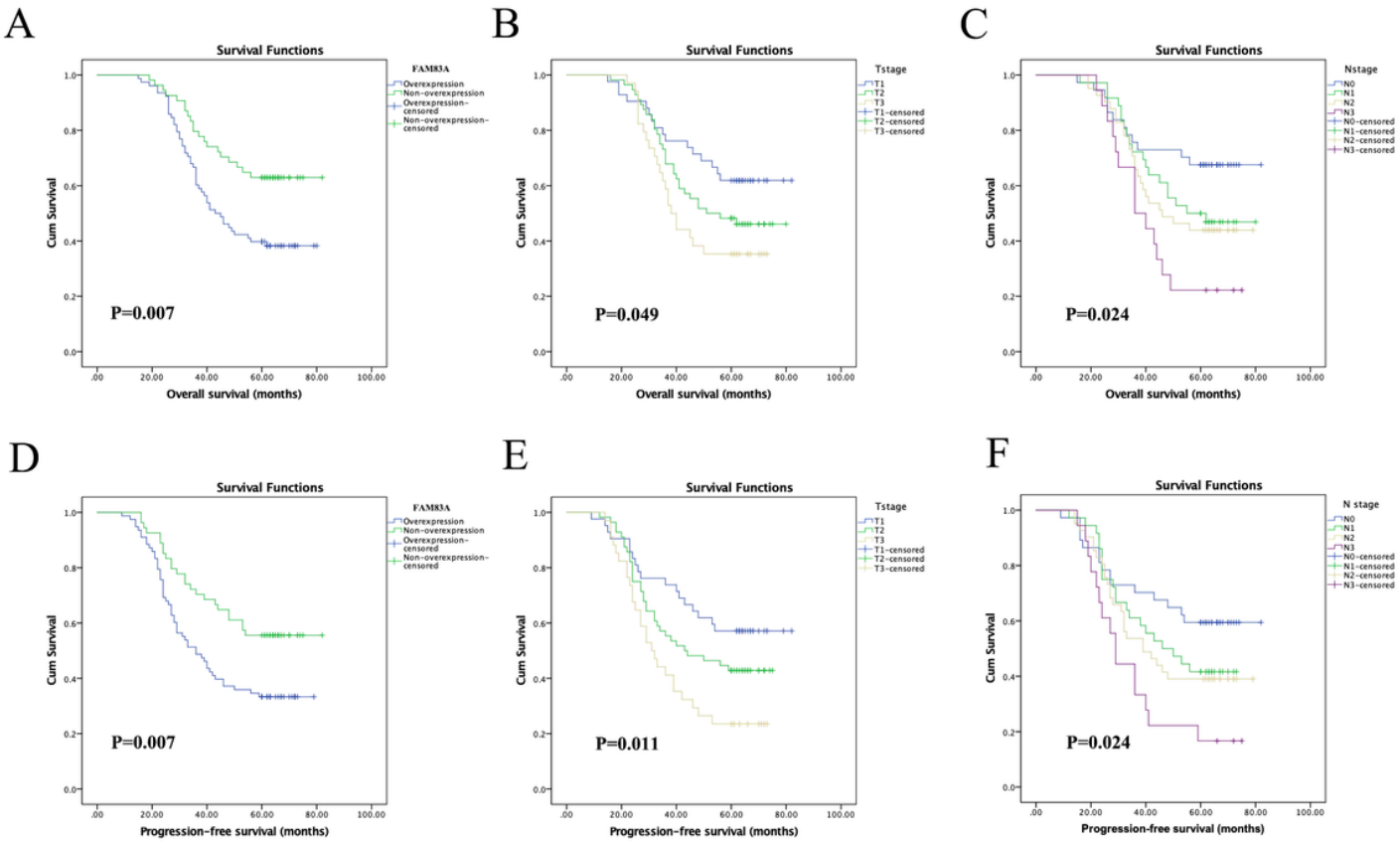
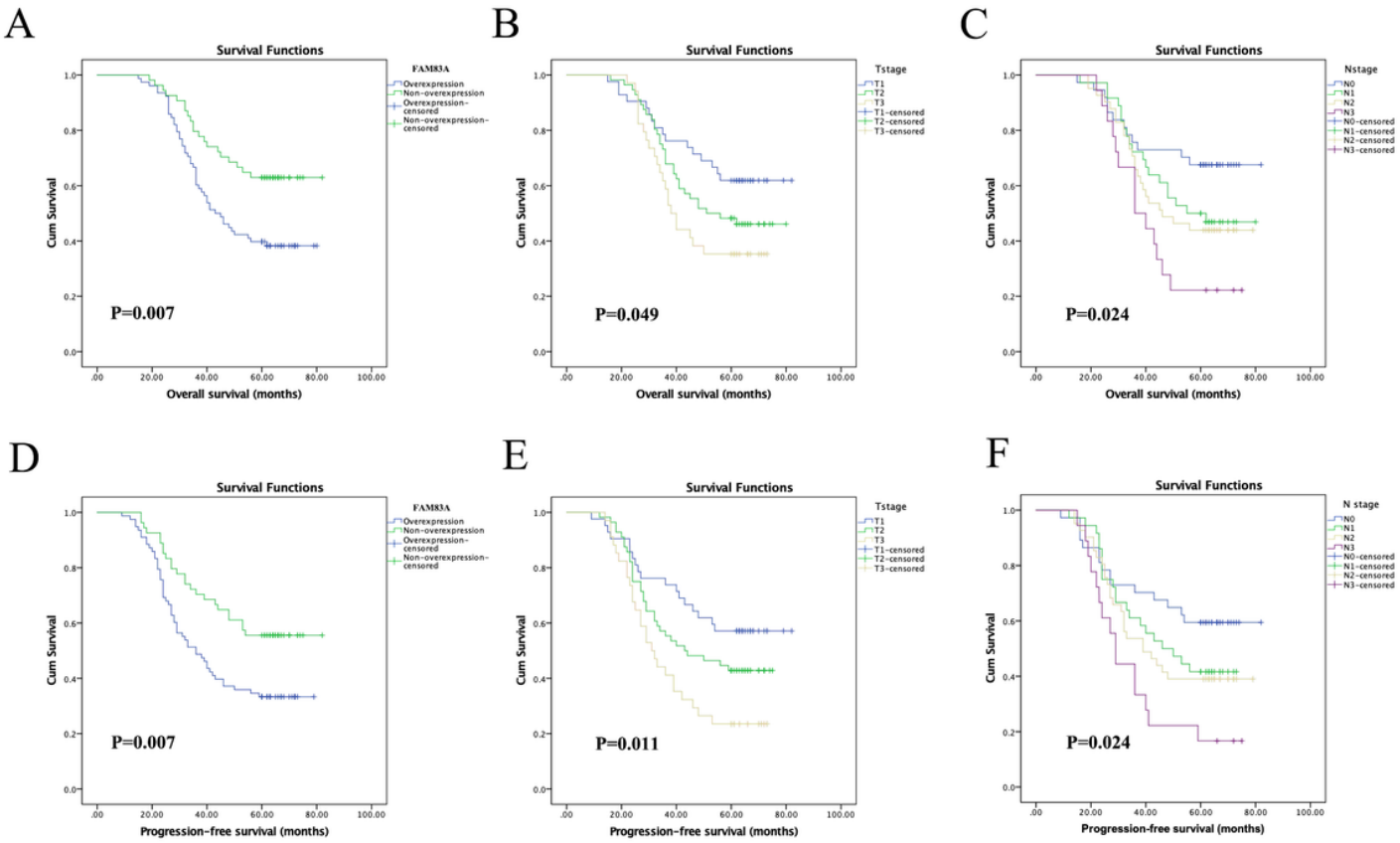


Figure 5

Kaplan-Meier analysis and log-rank test for 5 years' OS and PFS of LUSC patients. (A, D) High FAM83A protein expression significantly predicted decreased OS and PFS. (B-C, E-F) T stage and N stage were also associated with OS and PFS of LUSC.



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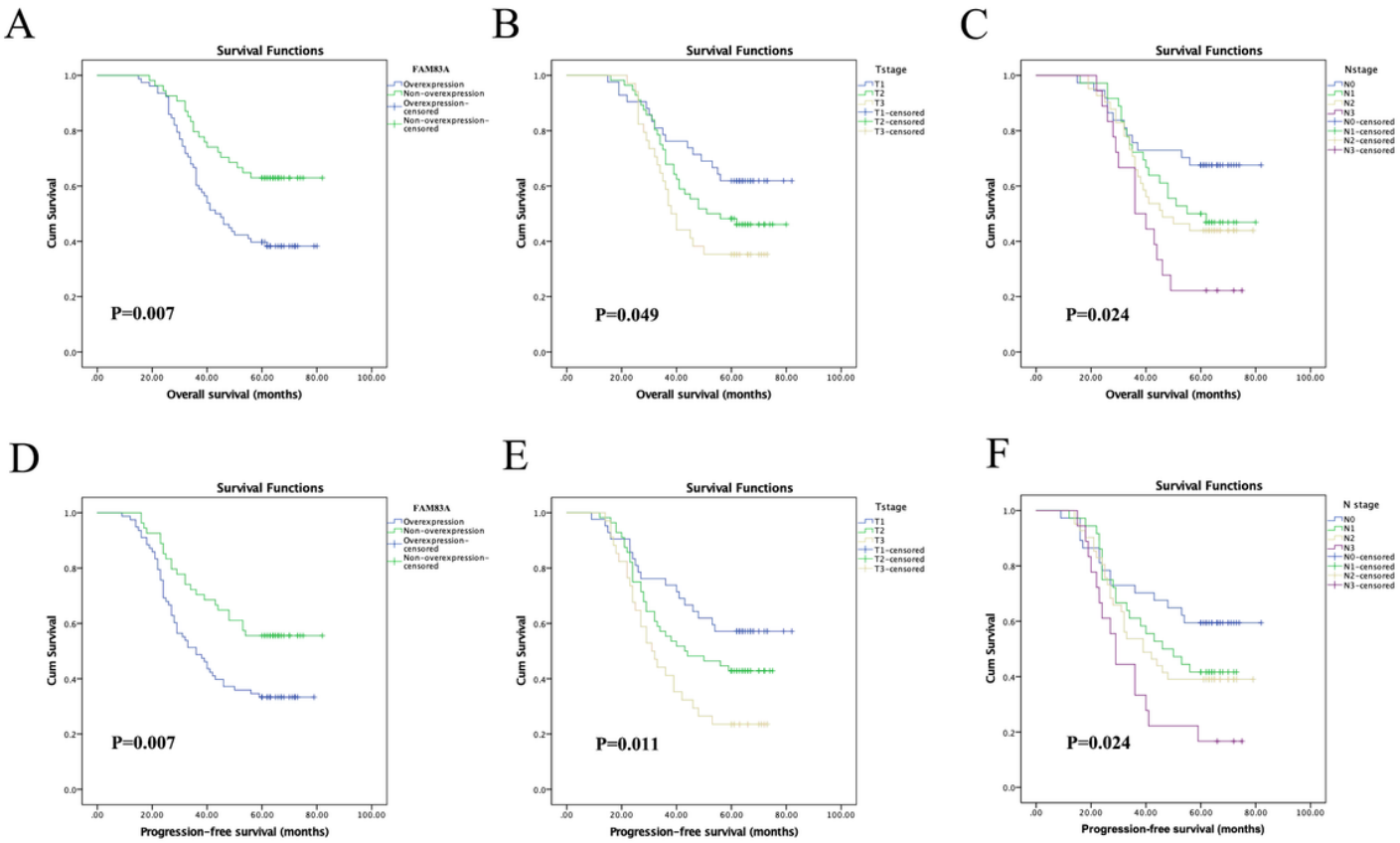

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