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*Original Article*

# FAT1 expression in different breast lesions and its down-regulation in breast cancer development

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**Abstract:** Background: Breast cancer is one of the most common cancers in women and the mechanisms under the progression from ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC) remain incompletely understood. FAT1 is an important tumor regulatory factor. The aim of the study is to detect the possible discrepancy in their expression about FAT1 in different breast lesions and to explore the role of FAT1 in the development of breast cancer. Patients and methods: We used immunohistochemistry to detect protein expression of FAT1 in 10 patients diagnosed with breast benign disease, 5 patients diagnosed with DCIS, 5 patients diagnosed with IDC and 25 patients diagnosed with invasive ductal carcinoma and accompanying ductal carcinoma in situ (IDC-DCIS). Results: FAT1 cadherin was expressed by both neoplastic and non-neoplastic mammary epithelia. FAT1 cadherin expression was not significantly changed in DCIS group in comparison with the benign group (P=0.392). Comparing with the DCIS group, expression in the IDC group appeared to be down-regulated. There was a significant difference for the positive rate between the DCIS and IDC group (P=0.048). In the IDC-DCIS group, the total staining score of the IDC component was significantly lower than the score of DCIS component (P=0.002). Conclusions: FAT1 cadherin expression was found to be significantly decreased in IDC group compared with the DCIS group, which indicated it might have tumor suppressive function in late stage of breast cancer development. FAT1 cadherin can be identified as a new biomarker in clinical practice.

**Keywords:** Ductal carcinoma in situ, invasive ductal carcinoma, FAT1, breast cancer, tumor progression

## Introduction

Breast cancer is one of the most common cancers in women in the world [1, 2]. The traditional model of human breast cancer progression proposes a linear multi-step process, normal epithelium develops into carcinoma in situ, which is the precursor of invasive cancer [3-5]. Carcinoma in situ is relatively common but only a small proportion appears to progress to invasive cancer. In tumors containing both ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC), DCIS is frequently an immediate precursor lesion for co-existing IDC and however in tumors containing only IDC component, it is assumed that IDC arises de novo [6-9]. The mechanisms under the progression from DCIS to IDC remain incompletely understood. Many cancers develop because of genetic dysregulation which leads to gene mutations [10, 11] and inherited mutations in BRCA1 or BRCA2 predispose to breast cancer [12]. Many scientists had studied the gene expression change between DCIS and IDC and had found a lot of important genes [13-15]. Identification of the altered gene and the related specific protein expression in DCIS and IDC can help us learn more about breast cancer development.

FAT1 gene is the human homolog of Drosophila FAT, which functions as a tumor suppressor gene and is required for correct morphogenesis [16-18]. The human FAT gene family is composed of the FAT1, FAT2, FAT3 and FAT4 genes. FAT1 gene is localized at human chromosome 4q35.2 and its complete sequence was first reported by Dunne et al. in 1995 [19]. The FAT1 gene product, which has 34 tandem cadherin-type repeats, 5 epidermal growth factor-like repeats and a laminin A-G domain, is one of the members of the cadherin superfamily [19].

**Table 1.** Patient's characteristics in DCIS, IDC and IDC-DCIS

| Characteristic | DCIS | | IDC | | IDC-DCIS | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Age (year) | | | | | | |
| ≤50 | 4 | 80 | 2 | 40 | 18 | 72 |
| >50 | 1 | 20 | 3 | 60 | 7 | 28 |
| Tumor size (cm) | | | | | | |
| ≤2 | 3 | 60 | 2 | 40 | 8 | 32 |
| 2-5 | 1 | 20 | 3 | 60 | 13 | 52 |
| >5 | 1 | 20 | 0 | 0 | 4 | 16 |
| IDC grade | | | | | | |
| 1 | | | 0 | 0 | 0 | 0 |
| 2 | | | 3 | 60 | 14 | 56 |
| 3 | | | 2 | 40 | 11 | 44 |
| DCIS grade | | | | | | |
| Low | 0 | 0 | | | 0 | 0 |
| Middle | 5 | 100 | | | 18 | 72 |
| High | 0 | 0 | | | 7 | 28 |
| Lymph nodes status | | | | | | |
| 0 | 5 | 100 | 2 | 40 | 13 | 52 |
| 1-3 | 0 | 0 | 2 | 40 | 5 | 20 |
| 4-9 | 0 | 0 | 1 | 20 | 5 | 20 |
| ≥10 | 0 | 0 | 0 | 0 | 2 | 8 |
| ER | | | | | | |
| Positive | 5 | 100 | 3 | 60 | 20 | 80 |
| Negative | 0 | 0 | 2 | 40 | 5 | 20 |
| PR | | | | | | |
| Positive | 5 | 100 | 4 | 80 | 18 | 72 |
| Negative | 0 | 0 | 1 | 20 | 7 | 28 |
| HER-2 | | | | | | |
| Positive | 4 | 80 | 1 | 20 | 17 | 68 |
| Negative | 1 | 20 | 4 | 80 | 8 | 32 |
| Ki67 index | | | | | | |
| ≤14% | 2 | 40 | 0 | 0 | 3 | 12 |
| >14% | 3 | 60 | 5 | 100 | 22 | 88 |

FAT1 cadherin was localized at filopodial tips, lamellipodial edges, and cell-cell boundaries, overlapping with dynamic actin structures and it has been demonstrated to modulate cell contacts and polarity in human cells [20]. The altered expression of FAT1 cadherin has been found in a number of solid tumors. In human disease, FAT1 cadherin was expressed by a range of leukemia cell lines and high FAT1 mRNA expression was predictive of shorter relapse-free and overall survival in precursor B-cell acute lymphoblastic leukemia [21]. The expression of FAT1 was found to be high in grade IV glioma cell lines and hepatocellular carcinoma cell lines but low in grade III glioma cell lines and primary human hepatocytes [22, 23]. However, loss-of-function of FAT1 cadherin contributed to the development of head and neck carcinoma and oral cancer [24, 25]. In a word, FAT1 appears to be an oncogenic or tumor suppressor in different types of tumors, but the function of this cadherin in cancer remains incompletely understood.

In the present study, we developed a clinically practical immunohistochemistry assay using Anti-FAT1 antibody produced in rabbit to examine the FAT1 expression in different breast diseases including breast benign lesions, DCIS, invasive ductal carcinoma and accompanying ductal carcinoma in situ (IDC-DCIS) and IDC. Ductal carcinoma was divided into three groups as outlined above: DCIS, IDC and IDC-DCIS. The last one was defined as the presence of in situ component of invasive ductal carcinoma [26]. The IDC-DCIS group was set to compare the immunohistochemistry staining of the in situ component with the concurrent invasive component. We evaluate the staining intensity and percentage of stained cells and the results may show the true function of FAT1 in human breast cancer.

## Materials and methods

### *Case selection and patient data*

Formalin-fixed and paraffin-embedded tissue specimens from a total of 45 patients including 10 patients diagnosed with breast benign disease, 5 patients diagnosed with DCIS, 5 patients diagnosed with IDC and 25 patients diagnosed with IDC-DCIS were randomly selected between April 2014 and December 2016 from Zhongda Hospital. All patients were women, ranging in age from 25 to 68 (mean 46.2). Every patient received operations immediately and none of the breast cancer patients received neoadjuvant therapy. The other characteristics are shown in **Table 1**. The diagnosis and pathological results of all cases were reviewed independently by two pathologists according to the World Health Organization classification [27] and The Nottingham combined histologic grade [28]. Informed consent was obtained from all patients before their surgery and before examination of the specimens.

**Table 2.** FAT1 protein immunohistochemistry scores

| Groups | Stain score | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| Benign group | 0 | 0 | 0 | 1 | 0 | 3 | 2 | 4 | 10 |
| DCIS | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 4 | 5 |
| IDC | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 0 | 5 |
| IDC-DCIS | | | | | | | | | |
| IDC component | 0 | 0 | 6 | 0 | 3 | 8 | 5 | 3 | 25 |
| DCIS component | 0 | 0 | 0 | 0 | 1 | 9 | 8 | 7 | 25 |

*Immunohistochemistry*

Anti-FAT1 antibody produced in rabbit was purchased from Sigma-Aldrich. Immunohistochemistry for FAT1 was performed with the standard streptavidin-biotin complex method with 3,3'-diaminobenzidine (DAB) as the chromogen. Standard 5-μm sections were mounted on glass slides, deparaffinized and rehydrated with xylene and a series of grades of alcohol. Endogenous peroxidase was inactivated with 3% hydrogen peroxide for 5 minutes, following which the sections were washed in phosphate buffered saline (PBS) for 5 minutes. Antigen retrieval was conducted by heating in an autoclave in citrate buffer (pH 6.0) for 4 minutes, and this was followed by cooling at room temperature and rinsing in PBS. Sections were blocked with 10% normal goat serum for 20 minutes and incubation with anti-FAT1 antibody (1:50 dilution; Sigma) was performed overnight at 4°C. Sections were incubated with biotin-conjugated secondary antibody for 30 minutes at 37°C, streptavidin-horseradish peroxidase for 20 minutes at 37°C, and color was developed by incubation with 3,3'-diaminobenzidine (DAB). The last step was all the sections were counterstained with hematoxylin.

*Staining evaluation*

The FAT1 protein expression was scored by two experienced pathologists independently, who were blinded to the clinicopathologic characteristics and in cases of disagreement, a consensus was reached after reviewing the staining result together. The location of immunoreactivity, intensity and percentage of stained cells were determined in all cases. The staining intensity was categorized into four grades (0-3): 0. no staining; 1. weak staining; 2. moderate staining; and 3. strong staining. The percentage of positive cells was graded on an arbitrary scale of 0 to 4 as follows: 0. 0% of stained cells; 1. <25% of stained cells; 2. 25-49% of stained cells; 3. 50-74% of stained cells; 4. ≥75% of stained cells. The sum of the scores of staining intensity and percentage of positive cells was recorded as the total score. FAT1 was considered as positive if the total score was between 5 and 7, and when the total score was between 0 and 4, we considered it as negative.

*Statistical analysis*

All statistical analyses were carried out using SPSS Statistics software (Version 21.0 for Windows). Chi-square test was performed for group rate comparison. The comparisons of the benign group, DCIS group and IDC group were evaluated by ANOVA. The average score of DCIS and IDC component in the IDC-DCIS group was compared by the two independent t-tests. $P<0.05$ was considered statistically significant.

## Results

Immunoreactivity for FAT1 cadherin was localized on cytoplasm and/or cytomembrane of the neoplastic and non-neoplastic mammary epithelia. **Table 2** summarizes the FAT1 protein expression results in different breast diseases.

*Breast benign lesions*

The staining result of the ten patients was almost all positive (9/10, 90%; **Table 2**; **Figure 1A** and **1B**) except one patient whose pathological diagnosis was fibroadenoma with mucoid degeneration. The benign lesions included intraductal papilloma, fibroadenoma, phyllodes tumor, adenosis and sclerosing adenosis. The immunohistochemistry positive specimens displayed moderate to strong staining with more than 50% stained cells.

*DCIS and IDC*

As FAT1 was expressed in the cytoplasm and/or cytomembrane, staining expression was generally homogenous in the cytoplasm within the same tumor when it was present. The tumors of DCIS displayed moderate to strong immunoreactivity while the tumors of IDC displayed weak to moderate immunoreactivity (**Figure 1C-F**). Positive immunostaining for FAT1 cadherin was observed in 5 (100%) in DCIS and 1 (20%) in

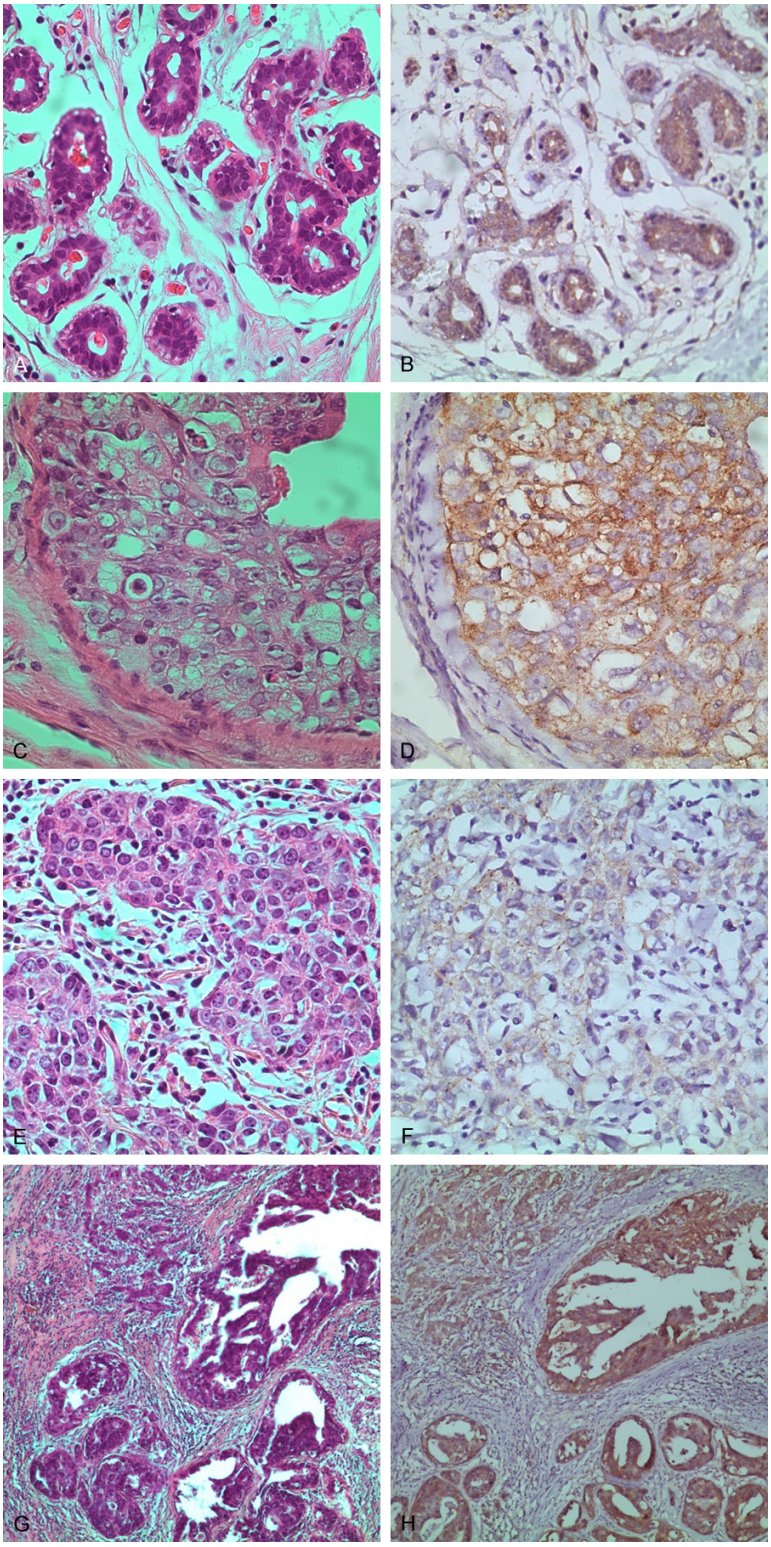


**Figure 1.** (A) Shows the HE staining in breast benign lesions and (B) shows the Immunohistochemical staining of FAT1 in breast benign lesions. Magnification: 400×. (C) Shows the HE staining in DCIS and (D) shows the Immunohistochemical staining of FAT1 in DCIS. Magnification: 400×. (E) Shows the HE staining in IDC and (F) shows the Immunohistochemical staining of FAT1 in IDC. Magnification: 400×. (G) Shows the HE staining in IDC-DCIS and (H) shows the Immunohistochemical staining of FAT1 in IDC-DCIS. Magnification: 100×.

IDC, respectively. Fisher's exact test revealed that the positive proportion rate was significantly higher in DCIS group than in IDC group (P=0.048; **Table 3**).

*Comparison between benign breast lesions and DCIS or IDC*

The scoring system incorporating the percentage of positive-staining tumor cells and the intensity of staining was applied to calculate the total score. Using ANOVA, we found that there was no significantly difference between the benign group and the DCIS group (P=0.392; **Table 4**) and the FAT1 staining score was significantly lower in IDC group comparing with the benign group (P=0.013; **Table 4**).

*DCIS-IDC*

The DCIS components of the IDC-DCIS tumors displayed moderate to strong immunoreactivity while the IDC components displayed weak to moderate immunoreactivity (**Figure 1G** and **1H**). Positive result was observed in 25 (100%) in DCIS components and in 19 (76%) in IDC components. However, the total staining score between the two components was significantly different (P=0.002).

## Discussion

The FAT1 protein is one of the members of the $Ca^{2+}$-dependent adhesion superfamily and it appears to have a dual role as both an oncogene as well as a tumor suppressor in different types of tumors [21-25]. In the present study, we used a specific anti-FAT1 antibody to analyze the FAT1 expression in benign and malignant breast diseases. Here,

**Table 3.** FAT1 protein immunohistochemistry results in DCIS and IDC

| FAT1 immunohistochemistry | DCIS | | IDC | | *P* Value |
|---|---|---|---|---|---|
| | NO | % | NO | % | |
| Positive | 5 | 100 | 1 | 20 | 0.048 |
| Negative | 0 | 0 | 4 | 80 | |

**Table 4.** Comparison between Benign breast lesions and DCIS or IDC

| Comparison group | *P* value |
|---|---|
| DCIS group VS benign group | 0.392 |
| IDC group VS benign group | 0.013 |

we found that FAT1 cadherin was expressed by both neoplastic and non-neoplastic mammary epithelia. The breast benign lesions group and DCIS group all showed moderate to strong expression intensity and high staining score. FAT1 cadherin expression was found to be not significantly changed in DCIS group in comparison with the benign group (P=0.392). Comparing with the DCIS group, expression in the IDC group appeared to be down-regulated. The staining intensity and the percentage of positive cells in the IDC group was both apparently inferior to the DCIS group with a significant difference for the positive rate between the two groups (P=0.048). In the IDC-DCIS group, the positive rate of IDC component (16/25) was much higher than the pure IDC group (1/5). Nevertheless, the total staining score of the IDC component was significantly lower than the score of the DCIS component (P=0.002).

FAT1 expression was found to be not significantly changed in DCIS group compared with the benign group, which represented the protein didn't change in early stage of breast cancer development. But the high levels of protein expression in samples of DCIS versus low levels of expression in IDC indicated that the FAT1 protein changed in late stage of breast cancer development. In the previous study of FAT1 cadherin immunoexpression in human breast tissues [29], the authors compared the different expressions only between the pure IDC and pure DCIS group. However, our study also included non-malignant breast lesions and the tumors which had the DCIS and IDC component simultaneously. Comparing the FAT1 cadherin expression between DCIS and IDC in the same tumor can help us learn more about the role of FAT1 gene in cancer development and progression directly. Our findings demonstrated FAT1 protein was down-regulated from DCIS to IDC in concordance with another previous study [13]. As FAT1 gene is a protein coding gene, the protein level change represents the genetic change. All the results may be explained by the tumor suppressive function of FAT1. Morris et al. predicted that the inactivation of FAT1 may converge to uncheck Wnt/b-catenin signaling which can drive cancer development [30]. Nevertheless, what makes the FAT1 protein down-regulated and by which the Wnt/β-catenin pathway is activated are still unknown. We acknowledge that our current study has several limitations and the most prominent problem is the small data set. Because of the small data, we also didn't find any relationship between FAT1 expression level and clinicopathologic characteristics such as ER, PR, HER2, Ki67, lymph node involvement and so on. The next steps what we should take include collecting more patients and creating an animal model to figure out the function of FAT1.

Breast cancer is acknowledged as a heterogeneous disease [31] and DCIS is the most common non-invasive type of breast cancer. Until now, it is unclear when and how the DCIS will develop into IDC at the molecular level. The purpose of treating DCIS is to prevent it evolving into IDC. Wong et al. thought IDC co-existing with DCIS was characterized by lower proliferation and metastatic potential than size-matched pure IDC [27]. Similarly, Dieterich et al. made a conclusion that IDC accompanied by DCIS was associated with lower local recurrence than IDC alone [26]. From the above studies, we can say IDC-DCIS tends to have lower disease aggressiveness than pure IDC. Notwithstanding, the current systemic treatment of IDC-DCIS depends entirely on the pathological and molecular characteristics of IDC. As IDC-DCIS doesn't behave identically to pure IDC, the disparity between the two groups may have significant influence on the systematic adjuvant treatment. DCIS is also a heterogeneous disease like invasive breast cancer, the same type of DCIS must possess potential biological differences which make some to remain stable and the others to progress. Our study showed a general decrease tendency from benign lesions and DCIS to IDC about FAT1 expression and FAT1 cadherin can be identified as a new bio-

marker in clinical practice. It is possible that through further study of FAT1 genetic mutations and the related altered pathways we can identify some specific defects which can be used as a potential therapeutic target spot for breast cancer.

In conclusion, this study tries to make it clear the role of FAT1 gene in breast cancer development. As the tumor occurrence is mainly caused by the dysregulation of some important genes, it is popular to study the gene mutations in cancer development. FAT1 gene is one of the key genes which had been found. Considering the small data set of our study, we can add the FAT1 cadherin into the conventional biomarkers like ER, PR, Ki67 and HER2 to get more information about the expression in different breast lesions. Future work is needed to identify the critical genes and biological processes specifically or commonly changed in DCIS and IDC.

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## Disclosure of conflict of interest

None.

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## References

[1] Cheng WQ, Zheng RS, Baade PD, Zhang SW, Zeng HM, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66: 115-132.

[2] DeSantis CE, Fedewa SA, Sauer AG, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. CA Cancer J Clin 2016; 66: 31-42.

[3] Allred DC and Mohsin SK. Biological features of premalignant disease in the human breast disease. J Mammary Gland Biol 2000; 5: 351-364.

[4] Allred DC, Wu Y, Mao S, Nagtegaal ID, Lee S, Perou CM, Mohsin SK, O'Connell P, Tsimelzon A and Medina D. Ductal carcinoma in situ and the emergence of diversity during breast cancer evolution. Clin Cancer Res 2008; 14: 370-378.

[5] Allred DC, Mohsin SK and Fuqua SA. Histological and biological evolution of human premalignant breast disease. Endocr Relat Cancer 2001; 8: 47-61.

[6] Steinman S, Wang JM, Bourne P, Yang Q and Tang P. Expression of cytokeratin markers, ER-alpha, PR, HER-2/neu, and EGFR in pure ductal carcinoma in situ (DCIS) and DCIS with coexisting invasive ductal carcinoma (IDC) of the breast. Ann Clin Lab Sci 2007; 37: 127-134.

[7] Alexe G, Dalgin GS, Ganesan S, Delisi C and Bhanot G. Analysis of breast cancer progression using principal component analysis and clustering. J Biosciences 2007; 32: 1027-1039.

[8] Iakovlev VV, Arneson NC, Wong V, Wang CJ, Leung S, Iakovleva G, Warren K, Pintilie M and Done SJ. Genomic differences between pure ductal carcinoma in situ of the breast and that associated with invasive disease: a calibrated aCGH study. Clin Cancer Res 2008; 14: 4446-4454.

[9] Wong H, Lau S, Yau T, Cheung P and Epstein RJ. Presence of an in situ component is associated with reduced biological aggressiveness of size-matched invasive breast cancer. Brit J Cancer 2010; 102: 1391-1396.

[10] Hollstein M, Sidransky D, Vogelstein B and Harris CC. p53 mutations in human cancers. Science 1991; 253: 49-53.

[11] Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, Fulton LL, Dooling DJ, Ding L, Mardis ER, Wilson RK, Ally A, Balasundaram M, Butterfield YS, Carlsen R, Carter C, Chu A, Chuah E, Chun HJ and Coope RJ; Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012; 490: 61-70.

[12] Venkitaraman AR. Cancer review: cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002; 108: 171-182.

[13] Lee S, Stewart S, Nagtegaal I, Luo JQ, Wu Y, Colditz G, Medina D and Allred DC. Differentially expressed genes regulating the progression of ductal carcinoma in situ to invasive breast cancer. Cancer Res 2012; 72: 4574-4586.

[14] Hou L, Chen M, Wang M, Cui X, Gao Y, Xing T, Li J, Deng S, Hu J, Yang H and Jiang J. Systematic analyses of key genes and pathways in the development of invasive breast cancer. Gene 2016; 593: 1-12.

[15] Gao YX, Niu Y, Wang XW, Wei L and Lu S. Genetic changes at specific stages of breast cancer progression detected by comparative genomic hybridization. J Mol Med 2009; 87: 145-152.

[16] Mahoney PA, Weber U, Onofrechuk P, Biessmann H, Bryant PJ and Goodman CS. The fat tumor suppressor gene in drosophila encodes a novel member of the cadherin gene superfamily. Cell 1991; 67: 853-868.
[17] Katoh M. Function and cancer genomics of FAT family genes (review). Int J Oncol 2012; 41: 1913-1918.
[18] Katoh Y and Katoh M. Comparative integromics on FAT1, FAT2, FAT3 and FAT4. Int J Mol Med 2006; 18: 523-528.
[19] Dunne J, Hanby AM, Poulsom R, Jones TA, Sheer D, Chin WG, Ming Da S, Zhao Q, Beverley PCL and Owen MJ. Molecular cloning and tissue expression offat, the human homologue of thedrosophila fatgene that is located on chromosome 4q34-q35 and encodes a putative adhesion molecule. Genomics 1995; 30: 207-223.
[20] Tanoue T and Takeichi M. Mammalian Fat1 cadherin regulates actin dynamics and cell-cell contact. J Cell Biol 2004; 165: 517-528.
[21] de Bock CE, Ardjmand A, Molloy TJ, Bone SM, Johnstone D, Campbell DM, Shipman KL, Yeadon TM, Holst J, Spanevello MD, Nelmes G, Catchpoole DR, Lincz LF, Boyd AW, Burns GF and Thorne RF. The Fat1 cadherin is overexpressed and an independent prognostic factor for survival in paired diagnosis-relapse samples of precursor B-cell acute lymphoblastic leukemia. Leukemia 2012; 26: 918-926.
[22] Dikshit B, Irshad K, Madan E, Aggarwal N, Sarkar C, Chandra PS, Gupta DK, Chattopadhyay P, Sinha S and Chosdol K. FAT1 acts as an upstream regulator of oncogenic and inflammatory pathways, via PDCD4, in glioma cells. Oncogene 2013; 32: 3798-3808.
[23] Valletta D, Czech B, Spruss T, Ikenberg K, Wild P, Hartmann A, Weiss TS, Oefner PJ, Muller M, Bosserhoff AK and Hellerbrand C. Regulation and function of the atypical cadherin FAT1 in hepatocellular carcinoma. Carcinogenesis 2014; 35: 1407-1415.
[24] Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015; 517: 576-582.
[25] Nakaya K, Yamagata HD, Arita N, Nakashiro Ki, Nose M, Miki T and Hamakawa H. Identification of homozygous deletions of tumor suppressor gene FAT in oral cancer using CGH-array. Oncogene 2007; 26: 5300-5308.
[26] Dieterich M, Hartwig F, Stubert J, Klocking S, Kundt G, Stengel B, Reimer T and Gerber B. Accompanying DCIS in breast cancer patients with invasive ductal carcinoma is predictive of improved local recurrence-free survival. Breast 2014; 23: 346-351.
[27] WHO classification of tumours of the breast. 4th edition. In: Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ, editors. IARC Press; 2012.
[28] Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark CG, Edge SB, Hayes DF, Hughes LL, Hutter RV, Morrow M, Page DL, Recht A, Theriault RL, Thor A, Weaver DL, Wieand HS and Greene FL. Revision of the American joint committee on cancer staging system for breast cancer. J Clin Oncol 2002; 20: 3628-3636.
[29] Wang L, Lyu S, Wang S, Shen H, Niu F, Liu X, Liu J and Niu Y. Loss of FAT1 during the progression from DCIS to IDC and predict poor clinical outcome in breast cancer. Exp Mol Pathol 2016; 100: 177-183.
[30] Morris LG, Kaufman AM, Gong YX, Ramaswami D, Walsh LA, Turcan S, Eng S, Kannan K, Zou YL, Peng LK, Banuchi VE, Paty P, Zeng ZS, Vakiani E, Solit D, Singh B, Ganly I, Liau L, Cloughesy TC, Mischel PS, Mellinghoff IK and Chan TA. Recurrent somatic mutation of FAT1 in multiple human cancers leads to aberrant Wnt activation. Nat Genet 2013; 45: 253-261.
[31] Polyak K. Heterogeneity in breast cancer. J Clin Invest 2011; 121: 3786-3788.