ARID1A/BAF250a is significantly overexpressed in primary invasive breast cancer

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Background: ARID1A (also known as BAF250a, p270 or SMARCF1) is a major component of the mammalian SWI/SNF family that is involved in the regulation of the chromatin structure. ARID1A gene mutations have been associated with many types of malignancies, including breast cancer. This study aimed to explore the expression of BAF250a protein in breast cancer and its association with the clinical and pathological characteristics and prognosis of breast cancer.

Methods: We assessed the BAF250a expression in 119 invasive breast carcinomas samples and 92 healthy control and correlated this expression pattern with various clinical and pathologic parameters including histologic type and grade, tumor size, lymph node status, estrogen receptor (ER) status, progesterone receptor (PR) status. Immunohistochemical analysis of BAF250a, ER, PR, was carried out, and evaluation of stainings was performed.

Results: The mean value of BAF250a expression in the experimental group was higher than in healthy control (P=0.001). The expression is unrelated to age, menopausal status, lymph node status, tumor size and location, grade and histologic type of tumor, and hormonal status (ER, PR).

Conclusions: These data suggest that BAF250a is overexpressed in breast cancers. BAF250a may play context-dependent tumor-promoting and tumor-suppressive roles in cancer.

Keywords: ARIDI1A/BAF250a; biomarker; prognosis; breast carcinoma; immunohistochemistry

Introduction

Cancer development and progression may result from genomic as well as epigenetic alterations (1-3). In a variety of human cancers, epigenome is affected by mutations in some genes, which are involved in the regulation of the chromatin structure (4,5). The chromatin structure is established by two major groups of functional units, which interact dynamically with each other. The first group of complexes modifies the association of DNA and histone octamers involving chemical energy derived from ATP hydrolysis. The latter one modulates histone N-terminal tails in a covalent manner (5,6).

ATP-dependent remodelers were first discovered in 1984 in studies of yeast (*Saccharomyces cerevisiae*) as SWI/SNF (SWItch/Sucrose Non Fermentable) complexes. A few years later that discovery was followed by a detection of corresponding complexes in *Drosophila* (7).

BAF250a (also known as ARID1A, p270 or SMARCF1) is a key component of the mammalian SWI/SNF family, it cooperates with transcriptional activators and repressors, and in this manner triggers the recruitment of the remodeling complex and its activity (8-10). Dysregulated activation of ATP-dependent chromatin remodelers can be detected in a variety of tumors. The BAF250a subunit is the most frequently affected among all SWI/SNF subunits (9). ARID1A gene mutations have been found in many types of malignancies, including breast cancer (4,10).

Our study was designed to evaluate the expression of BAF250a in 119 females diagnosed with primary breast cancer by immunohistochemical staining (11). The results were correlated with clinicopathological features such as age, breast cancer type, menopause, tumor size and location, and lymph nodes metastasis.

Methods

Patients

Ethics approval (number: KB 132/2018) was obtained by the Bioethics Committee of the Wroclaw Medical University. The study was performed using formalin-fixed and paraffin-embedded (FFPE) blocks of 119 primary breast cancer tissues and 92 healthy controls surgically removed at the 2nd Department of General and Oncological Surgery, Wroclaw Medical University between January 2008 and April 2014. The subsequent information, such as grade and histological type, location and size of tumor, lymph node status, hormonal (ER, PR) and menopausal status and patient's age was gained from medical records.

Immunohistochemical analysis

All women had Patey's conservative radical mastectomy. In regard to the recommendations of the Polish Union of Oncology, postoperative adjuvant therapy was performed. Immunohistochemical analysis was conducted according to the methods of Agrawal et al. 2016 (12). First, FFPE samples were sliced at 4 mm sections. Afterward, specimens underwent deparaffinization in two fresh xylene soaks, rehydration by using alcohol washes of decreasing concentrations (96%, 80%, 70%), and staining with hematoxylin-eosin. Then, slides were washed in distilled water, dehydrated through alcohols (70%, 80%, 96%), cleared in xylene and mounted in mounting medium. The H&E stained sections were prepared for the histopathologic examination. Following the histopathological analysis, further immunohistochemical staining of ARID1A antibody expression was evaluated. Prior to antibody staining, the epitope retrieval step was performed by boiling slides in a citric buffer [0.1M citric acid, 0.05% Tween 20 (pH 6.0); Sigma-Aldrich] for 8 minutes. To remove non-specific bindings and the staining from the background, specimens were incubated for 10 minutes with a peroxidase blocking reagent and, after washing, with protein block reagent for another 10 minutes. The tissues were incubated with primary antibodies and stored overnight at 4 ℃ [ARID1A Antibody (PSG3); sc-32761 dilution 1/100, Santa Cruz]. The next day, after PBS washing, slides were incubated for 15 minutes with secondary biotin and streptavidin-HRP-conjugated antibody. The immunoreactivity was visualized using 3,3-diaminobenzidine (DAB) method. Finally, the samples were counterstained with hematoxylin, dehydrated and cleared in xylene.

The BAF250a protein expression was presented as a percentage of tumor cells exhibiting a positive reaction. Two independent pathologists evaluated immunohistochemical reaction using light microscopes (Olympus BX51) and the results were agreed thereafter.

Statistics

The statistical analysis was performed by the use of Statistica v. 12 software (StatSoft, Inc., Tulsa, OK, USA). Expression values between normal (control) and cancer specimens were compared by the non-parametric Mann-Whitney U test and for the comparison between three or more groups, the Kruskal-Wallis test followed by Dunn's multiple comparison test was conducted. P values lower than 0.05 (P<0.05) were considered as statistically significant.

Results

The clinicopathological features of a total of 119 female patients with primary invasive breast carcinoma are listed in *Table 1*. Patients' age ranged between 29 and 84 years (mean: 59.0 years; SD: 12.9). The majority of the group consisted of women at postmenopausal age (89/119; 73.1%). The most common histological type of tumor was ductal carcinoma (99/119; 83.2%). The sizes of the tumors varied from 2 to 45 mm with an average of 18.5 mm (SD: 8.3). More than often (63/119; 52.9%) the right breast was affected by the tumor and almost half of the tumors (54/119; 45.4%) were localized in the upper outer quadrant of the

Table 1 Clinical characteristics of female patients

Variable	Statistics
Age (at the time of diagnosis)	
M ± SD	59.0±12.9
Me (Q$_1$; Q$_3$)	59 (48; 67)
Min to max	29–84
Age group	
Between 31 and 40 years old	8 (6.7%)
Between 41 and 50 years old	27 (22.7%)
Over 50 years old	84 (70.6%)
Menopausal status	
Premenopause	32 (26.9%)
Postmenopause	87 (73.1%)
Diagnosis	
Ductal carcinoma	99 (83.2%)
Lobular carcinoma in situ	8 (6.7%)
Intraductal carcinoma	4 (3.4%)
Other carcinoma	8 (6.7%)
Tumor size (mm)	
M ± SD	18.5 ± 8.3
Me (Q1; Q3)	18 (13; 23)
Min to max	2–45
Number of patients with primary tumor size:	
pT1	81 (68.1%)
pT2	37 (31.1%)
pT4	1 (0.8%)
Side	
Right breast	63 (52.9%)
Left Breast	56 (47.1%)
Primary tumor location	
Upper outer quadrant	54 (45.4%)
Upper inner quadrant	28 (23.5%)
Lower outer quadrant	16 (13.4%)
Lower inner quadrant	3 (2.5%)
Superior breast	5 (4.2%)
Inferior breast	2 (1.7%)
Outer breast	1 (0.8%)
Inner breast	1 (0.8%)
Central breast	9 (7.6%)

Table 1 (*continued*)

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Variable	Statistics
Number of patients with metastatic lymph nodes	
pN0	71 (59.7%)
pN1	38 (31.9%)
pN2	7 (5.9%)
pN3	3 (2.5%)
Metastatic lymph nodes (metastasis)	
M ± SD	1.8±4.7
Me (Q1; Q3)	0 (0; 2)
Min to max	0–38
Number of lymph nodes dissected during operation	
M ± SD	13.2±5.8
Me (Q1; Q3)	13 (10; 17)
Min to max	1–38
Number of patients with distant metastases:	
pM0	119 (100.0%)

M, average; SD, standard deviation; Me, median; Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

breast. Among all of the 119 patients' tumors were classified as pT1: 81 (68.1%), pT2: 37 (31.1%), and pT3: 1 (0.8%). Over half of the experimental group (59.7%) had no lymph node positivity at the time of surgery. None of the patients showed distant metastases.

The mean value of BAF250a expression in the experimental group was higher (79.4%; SD: 21.1) than in healthy control (67.6%; SD: 18.1) and the difference was statistically significant (P=0.001; Mann-Whitney test; *Figure 1*). The characteristics of the tested marker expression are shown in *Table 2*.

Analysis of the relationship between clinicopathological factors such as age, menopausal status, histological subtype of the tumor, size of the tumor, affected side of the body, location and lymph node metastases) and BAF250a expression shows no statistically significant correlation (P>0.05; Kruskal-Wallis/Mann-Whitney tests; *Tables 3–9*, *Figure 2*). *Figure 3* presents the positive immunohistochemical staining for BAF250a in cells of invasive ductal breast carcinoma.

Discussion

Mammalian SWI/SNF is highly conservative and consists

3940

Szpon et al. ARIDI1A/BAF250a is overexpressed in invasive breast cancer
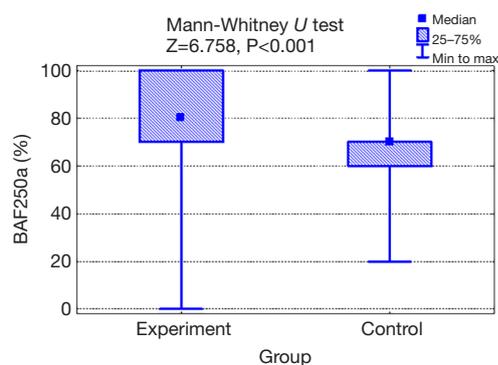
Figure 1 BAF250a expression comparison between the experimental and control group, using Mann-Whitney test.

of 12–28 subunits (1). Within this class of complexes, two categories can be distinguished: (I) BAF (Brg/Brahma-associated factors) complexes consisting of ARID1A/B (AT-rich interactive domain containing protein 1A/B) subunits and (II) PBAF (polybromo-associated BAF) complexes consisting of ARID2 (AT-rich interactive domain containing protein 2) and PBMR1 (Polybromo 1) subunits (1,8). Chromatin regulatory machinery modifies nucleosome structure and modulates DNA accessibility to cellular mechanisms involving transcription, proliferation and DNA damage response (9).

BAF250a/ARID1A belongs to the family of DNA-binding proteins and regulates SWI/SNF chromatin

Table 2 Expression characteristics of BAF250a

Expression BAF250a (%)	Test group (n=119)	Control group (n=92)	Test result
M ± SD	79.4 ± 21.1	64.5 ± 14.9	P=0.001
Me (Q$_1$; Q$_3$)	80 (70; 100)	70 (60; 70)	
Min to max	0–100	20–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 3 Primary expression statistics of BAF250a marker in different age groups, Kruskal-Wallis test result

BAF250a (%)	Age group			Test result
	Below 40 years old (n=8)	Between 41 and 50 years old (n=27)	Over 50 years old (n=84)	
M ± SD	88.8±12.5	80.6±19.3	78.1±22.2	P=0.400
Me (Q$_1$; Q$_3$)	90 (80; 100)	80 (70; 100)	80 (70; 950)	
Min to max	70–100	40–100	0–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 4 Statistical analysis of BAF250a expression in patients with different menopausal status, Mann-Whitney test result

BAF250a (%)	Status		Test result
	Before menopause (n=32)	After menopause (n=87)	
M ± SD	83.3±17.1	77.9±22.3	P=0.286
Me (Q$_1$; Q$_3$)	82.5 (70; 100)	80 (70; 100)	
Min to max	40–100	0–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 5 Statistical analysis of BAF250a expression in patients with different diagnoses, Kruskal-Wallis test result

BAF250a (%)	Diagnosis				Test result
	Ductal carcinoma (n=98)	Lobular carcinoma in situ (n=8)	Intraductal carcinoma (n=4)	Other carcinoma (n=9)	
M ± SD	78.1±22.1	81.3±17.3	97.5±5.0	83.3±12.2	P=0.172
Me (Q$_1$; Q$_3$)	80 (70; 100)	80 (65; 100)	100 (95; 100)	80 (80; 90)	
Min to max	0–100	60–100	90–100	60–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 6 Statistical analysis of BAF250a expression in patients with a different tumor size, Kruskal-Wallis test result

BAF250a (%)	Tumor			Test result
	T1 (n=81)	T2 (n=37)	T4 (n=1)	
M ± SD	79.3±18.6	78.9±26.0	100	P=0.320
Me (Q$_1$; Q$_3$)	80 (70; 90)	90 (70; 100)	–	
Min to max	0–100	0–100	–	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 7 Statistical analysis of BAF250a expression in patients with different side of body affected, Mann-Whitney test result

BAF250a (%)	Side of body		Test result
	Right breast (n=63)	Left breast (n=56)	
M ± SD	79.0±22.0	79.9±20.2	P=0.959
Me (Q$_1$; Q$_3$)	80 (70; 100)	80 (70; 100)	
Min to max	0–100	0–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 8 Statistical analysis of BAF250a expression in patients with a different tumor location, Kruskal-Wallis test result

Tumor location	BAF250a (%)			
	N	M ± SD	Me (Q$_1$; Q$_3$)	Min to max
Upper outer quadrant	54	80.1±20.5	80 (70; 100)	10–100
Upper inner quadrant	28	82.5±16.0	80 (75; 100)	50–100
Lower outer quadrant	16	75.6±27.6	80 (65; 100)	0–100
Lower inner quadrant	3	63.3±20.8	70 (40; 80)	40–80
Superior breast	5	74.0±42.2	90 (80; 100)	0–100
Inferior breast	2	85.0±7.1	85 (80; 90)	80–90
Outer breast	1	80	80	80–80
Inner breast	1	40	40	40–40
Central breast	9	83.3±10.0	80 (80; 90)	70–100
Kruskal-Wallis test		P=0.686		

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

Table 9 Statistical analysis of BAF250a expression in patients with different lymph node metastases, Kruskal-Wallis test result

BAF250a (%)	Lymph node metastases				Test result
	N0 (n=71)	N1 (n=38)	N2 (n=7)	N3 (n=1)	
M ± SD	77.2±21.8	82.9±19.4	79.3±26.2	86.7±11.5	P=0.394
Me (Q$_1$; Q$_3$)	80 (70; 100)	90 (80; 100)	85 (60; 100)	80 (80; 100)	
Min to max	0–100	0–100	30–100	80–100	

M, average; SD, standard deviation; Me, median, Q$_1$, lower quartile (25%); Q$_3$, upper quartile (75%); Min, minimum value; Max, maximum value.

remodeling complex activity in cell nucleus (13). According to Li and co-workers BAF250a affects in direct manner histone H2B using ubiquitination (14). Its expression is correlated with cell cycle and shows the highest level in G$_0$/G$_1$ phase and lowest during S, G$_2$/M phases (15). Promoter-BAF250a cooperation is associated with cell cycle genes repression (16) and normal cell cycle arrest is compromised in cells with BAF250a depletion (17). As BAF250a/ARID1A plays a role in cell cycle repression, it is presumed to be a tumor suppressor based on loss-of-function mutational profiles observed in a broad variety of cancers (18). Furthermore, BAF250a/ARID1A as a potential tumor suppressor gene may contribute to carcinogenesis and cancer progression (19).

ARID1A mutations are not frequently reported in breast cancers. Mutated ARID1A is detected in approximately 4% of BCs. Copy number loss is more frequent and involves 13–35% of BC cases (4,20,21).

According to Zhang *et al.* in a variety of primary invasive BCs limited BAF250a, expression results from hypermethylation of ARID1A gene promotor (22). BAF250a limited expression shows a significant correlation with ARID1A gene hypermethylation in 86.4% of invasive ductal breast cancers (19). Yamamoto and co-workers reported that BAF250a subunit dysregulation may alter PI3K/Akt, the signaling pathway and this correlation potentially links low BAF250a expression with ovarian clear cell carcinoma (23).

According to Mamo *et al.* decreased ARID1A expression is potentially associated with higher aggressiveness of BCs (21). However, prognostic values of ARID1A gene mutation remain unclear. Kandoth and co-workers found that ARID1A mutations are not significant in BC (24). Contrarily, Zhao and co-workers in their study indicated ARID1A deletion as an independent prognostic marker in BC (25). Moreover, Lin *et al.* reported that ARID1A down-regulation was related to a poorer response to paclitaxel-based chemotherapy (26).

As it has been reported the SWI/SNF subunits expression differs significantly in various human cancer cell lines (27). Data concerning aberrant ARID1A mRNA/protein expression in breast cancer tissue as well as breast cancer cell lines is highly diversified. According to Wang *et al.* BAF250a activity is deficient in 10% BCs (28) and in contrast to other studies shown, even up to 64% (21).

An inconsistent body of evidence encouraged our research to investigate BAF250a expression in BC patients diagnosed with different types of primary invasive carcinomas. In contrast to our initial hypothesis and previous papers on a limited number of patients, our data based on a cohort of female patients show that ARID1A is significantly overexpressed in primary invasive breast cancer comparing to healthy control samples. Moreover, the expression is unrelated to age, menopausal status, lymph node status, tumor size and location, grade and histologic type of tumor, and hormonal status (ER, PR). The results do not confirm the expression pattern described by Zhao *et al.* and Lin *et al.* (25,26). These contrasting results may be explained by the recent findings of Sun *et al.* that gain of ARID1A function promoted initiation via enhanced oxidative stress, while loss of ARID1A during the later phases of tumor growth decreased DNA accessibility and inhibited transcription of genes associated with migration, invasion, and metastasis (18). We presume that ARID1A may play context-dependent tumor-promoting and tumor-suppressive roles in cancer. Further studies are warranted to explain the observed differences in the expression of this biomarker.
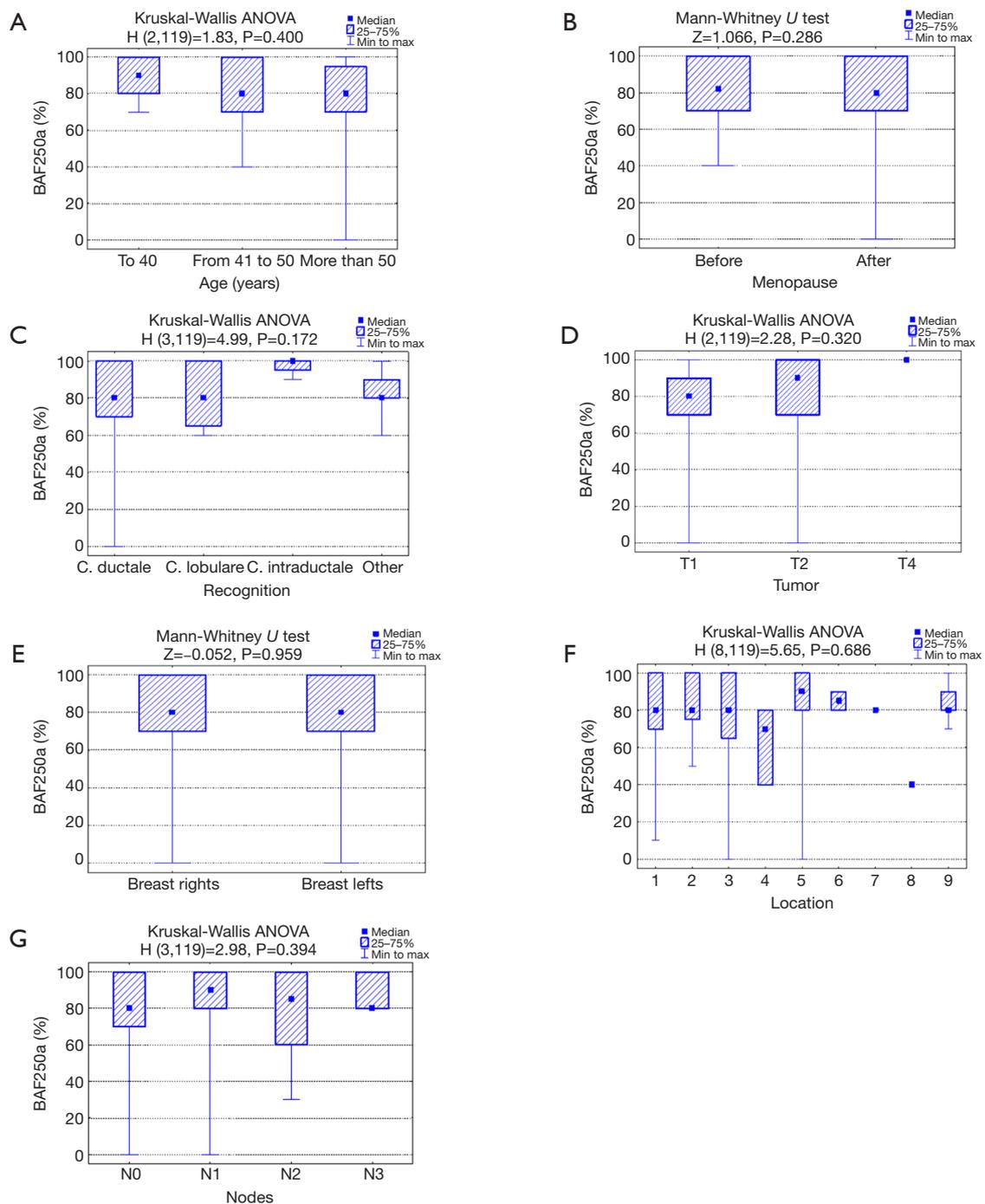
Figure 2 Expression comparison of BAF250a in different groups. (A) The BAF250a level decreases with age but the difference in the BAF250a expression was statistically insignificant (P>0.05). (B) Comparison of BAF250a expression in groups of patients with different menopausal status, (P>0.05). (C) Comparison of BAF250a expression in groups of patients with different diagnoses (P>0.05). (D) Comparison of BAF250a expression in groups of patients with different tumor sizes (P>0.05). (E) Comparison of BAF250a expression in groups of patients with different side of body affected (P>0.05). (F) Comparison of BAF250a expression in groups of patients with a different tumor location (P>0.05). (G) Comparison of BAF250a expression in groups of patients with different lymph node metastases (P>0.05).
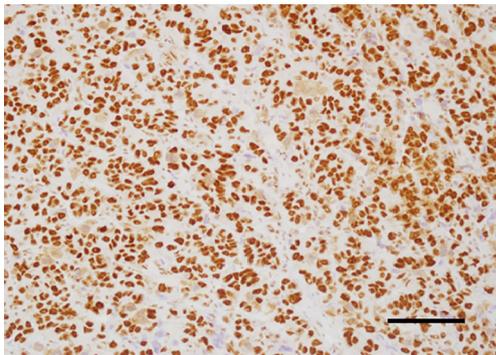
Figure 3 Immunohistochemical staining for BAF250a in invasive ductal breast carcinoma showing positive nuclear and cytoplasmic signal, detected by DAB, and counterstained with hematoxylin, as described in Methods section. Scale bar =500 µm.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-19-2422). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics approval (number: KB 132/2018) was obtained by the Bioethics Committee of the Wroclaw Medical University.

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