Breast Cancer Research and Treatment (2019) 173:93–102
https://doi.org/10.1007/s10549-018-4978-5

PRECLINICAL STUDY

Kinesin family member-18A (KIF18A) is a predictive biomarker of poor benefit from endocrine therapy in early ER+ breast cancer

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Received: 17 September 2018 / Accepted: 20 September 2018 / Published online: 10 October 2018

Abstract

Purpose Identification of effective and reliable biomarkers that could be used to predict the efficacy of endocrine therapy is of crucial importance to the management of oestrogen receptor positive (ER+) breast cancer (BC). KIF18A, a key regulator of cell cycle, is overexpressed in many human cancers, including BC. In this study, we investigated the role of KIF18A as a biomarker to predict the benefit from endocrine treatment in early ER + BC patients.

Methods KIF18A expression was assessed at the genomic level using the METABRIC dataset to explore its prognostic and predictive value in ER + BC patients ($n = 1506$). Predictive significance of KIF18A mRNA was validated using KM-Plot datasets ($n = 2061$). KIF18A protein expression was assessed using immunohistochemistry in a large annotated series of early-stage ER + BC ($n = 1592$) with long-term follow-up.

Results High mRNA and protein expression of KIF18A were associated with short recurrence-free survival (RFS), distant-metastasis free survival (DMFS) and BC specific survival (all $P < 0.05$) in ER + BC in patients who received no adjuvant treatment or adjuvant endocrine therapy. In multivariate analysis, high KIF18A expression was an independent prognostic biomarker for poor RFS ($P = 0.027$) and DMFS ($P = 0.028$) in patients treated with adjuvant endocrine therapy.

Conclusion KIF18A appears to be a candidate biomarker of a subgroup of ER + BC characterised by poor clinical outcome. High KIF18A expression has prognostic significance to predict poor benefit from endocrine treatment for patients with ER + BC. Therefore, measurement of KIF18A on ER + BC patients prior to treatment could guide clinician decision on benefit from endocrine therapy.

Keywords Breast cancer · Oestrogen receptor · Endocrine treatment · Predictive biomarker · KIF18A

Introduction

Oestrogen receptor (ER) is the driving transcription factor in up to three-quarters of all BC and its protein expression by immunohistochemistry classifies patients as either having ER+ or ER-negative (ER−) disease. Endocrine therapy is one of the most effective and well-established targeted anti-cancer treatments for ER + BC. However, despite its undisputed efficacy, up to one-third of patients will relapse after treatment for early-stage disease, while in the advanced setting, all will eventually progress [1]. It is therefore desirable to be able to predict, at an early stage of treatment, which ER+ patients will benefit from endocrine therapy [2]. The identification of biomarkers to predict endocrine therapy benefit in addition to ER status is therefore of crucial importance in stratifying ER+ patients for targeted therapy.

KIF18A, a member of kinesin-8 family, plays pivotal roles in regulating microtubule dynamics, chromosome congression and cell division [3]. KIF18A is involved in several cancers: breast, colorectal and hepatocellular cancers and cholangiocarcinoma [4–7] particularly driving proliferation, migration and anoikis in BC [4]. KIF18A protein expression

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-4978-5) contains supplementary material, which is available to authorized users.

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is over expressed in BC compared with normal breast and it has been proposed as a useful predictive marker for lymph node metastasis [8]. In addition, ER is a putative cargo for KIF18A, and presents a novel interaction between them that may have important physiological and pharmacological implications for oestrogen action in various cells [9, 10].

Both oestrogen and ER can up-regulate the expression of KIF18A mRNA and protein in vivo and in vitro suggesting that KIF18A may be associated with ER-related cancers [10]. Nevertheless, the prognostic power of KIF18A in ER + BC and its relation with endocrine therapy efficacy has not been reported. In this study, we explore the possibility of KIF18A as a biomarker for the prognosis of ER + BC patients and as a predictor of endocrine response.

Method

KIF18A mRNA expression

Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) [11], comprising 1506 ER + BC, was used to analyse and explore the prognostic value of KIF18A in ER + BC patients and its role as predictive biomarker of benefit from endocrine treatment. In the METABRIC study, DNA and RNA extracted from primary tumour samples were hybridised using Affymetrix SNP 6.0 arrays (Affymetrix, Inc., Santa Clara, USA) and Illumina Human HT-12 v3 platforms (Illumina, Inc., San Diego, USA). Kaplan Meier Plotter-Breast Cancer (KM-Plotter) software [12] was used to validate the prognostic and predictive value of KIF18A mRNA expression, this dataset contains mRNA expression for 2061 patients with ER + BC.

KIF18A protein expression

KIF18A protein expression was assessed in a large well-characterised cohort of ER+, early-stage primary operable invasive BC patients, aged ≤ 70 years ($n = 1592$). Patients presented at Nottingham City Hospital between 1989 and 2006. Clinical history, tumour characteristics, information on therapy and outcomes are prospectively maintained. The clinic-pathological parameters for the cohort series are summarised in Table 1.

Western blotting

Primary antibody specificity of KIF18A 1:500 (HPA039484, Sigma–Aldrich, UK) was validated by Western blotting using MDA-MB-436 human BC cell line (American Type

Table 1 Clinicopathological characteristics of ER + BC cohort

Clinic-pathological characteristics	METABRIC cohort No. (%)	Nottingham cohort No. (%)
Tumour size (cm)		
<2	475 (31.5)	806 (55.7)
≥2	1031 (68.5)	640 (44.3)
Grade		
1	166 (11.5)	388 (24.7)
2	707 (49.1)	661 (42.1)
3	565 (38.4)	522 (33.2)
Nottingham prognostic index		
GPG	623 (41.3)	598 (41.4)
MPG	772 (51.2)	668 (46.1)
PPG	111 (7.5)	180 (12.5)
Endocrine therapy		
No	234 (15.5)	884 (55.7)
Yes	384 (25.5)	558 (35)
Other	888 (59)	149 (9.3)
Nodal stage		
1	404 (36.2)	1025 (65.1)
2	634 (56.8)	439 (27.9)
3	78 (7)	111 (7)
PR		
Negative	486 (23.2)	300 (21.3)
Positive	1020 (76.8)	1103 (78.7)

GPG Good prognostic group, *MPG* moderate prognostic group, *PPG* poor prognostic group

Culture Collection; Rockville, MD, USA). Proteins were detected using IRDye 800CW and 600RD fluorescent secondary antibodies (1:15 000 dilution. 926-32213 and 926-68072, LI-COR Biosciences) and visualised using the Odyssey Fc with Image Studio 4.0 (LI-COR Biosciences). Anti-β-actin primary antibody (Sigma–Aldrich) was used as a loading control (1:5000). A specific band for KIF18A was visualised at the correct predicted size (102 kDa; Fig. 1a).

Tissue arrays and immunohistochemistry

Tumour samples were arrayed as previously described [13]. Immunohistochemical staining was performed on 4 µm TMA sections using Novolink polymer detection system (Leica Biosystems, RE7150-K). Briefly, tissue slides were deparaffinised with xylene and rehydrated through three changes of alcohol. Heat-induced antigen epitope retrieval was performed in citrate buffer (pH 6.0) for 20 min using a microwave oven (Whirpool JT359 Jet Chef 1000W). Endogenous peroxidase activity was blocked by Peroxidase Block for 5 min. Slides were washed with Tris-Buffered Saline (TBS, pH 7.6), followed by application of Protein Block for 5 min. Following another TBS wash, sections were incubated, for overnight at 4 °C, with the primary KIF18A antibody diluted at 1:300 in Leica antibody diluent (RE AR9352, Lieca, Biosysytems, UK). Slides were washed with TBS followed by incubation with Post Primary Block for 30 min followed by a TBS wash. Novolink polymer was applied for 30 min. 3,3′-diaminobenzidine (DAB) chromogen was applied for 5 min. Slides were counterstained with Novolink haematoxylin for 6 min, dehydrated and cover-slipped.

Stained TMA sections were assessed using high-resolution digital images (Nanozoomer, Hamamatsu Photonics) and viewing software (Xplore; Philips, UK). Evaluation of staining for KIF18A was based on a semiquantitative assessment of immunoreactivity using a modified histochemical score (H-score), which includes an assessment of both the intensity and the percentage of stained cells [14]. Staining intensity was assessed as follows 0 = negative; 1 = weak; 2 = moderate; 3 = strong and the percentage of the positively stained tumour cells was estimated subjectively. The final H-score was calculated multiplying the percentage of positive cells (0–100) by the intensity (0–3), producing a total range of 0–300. For KIF18A protein expression, the cut-off

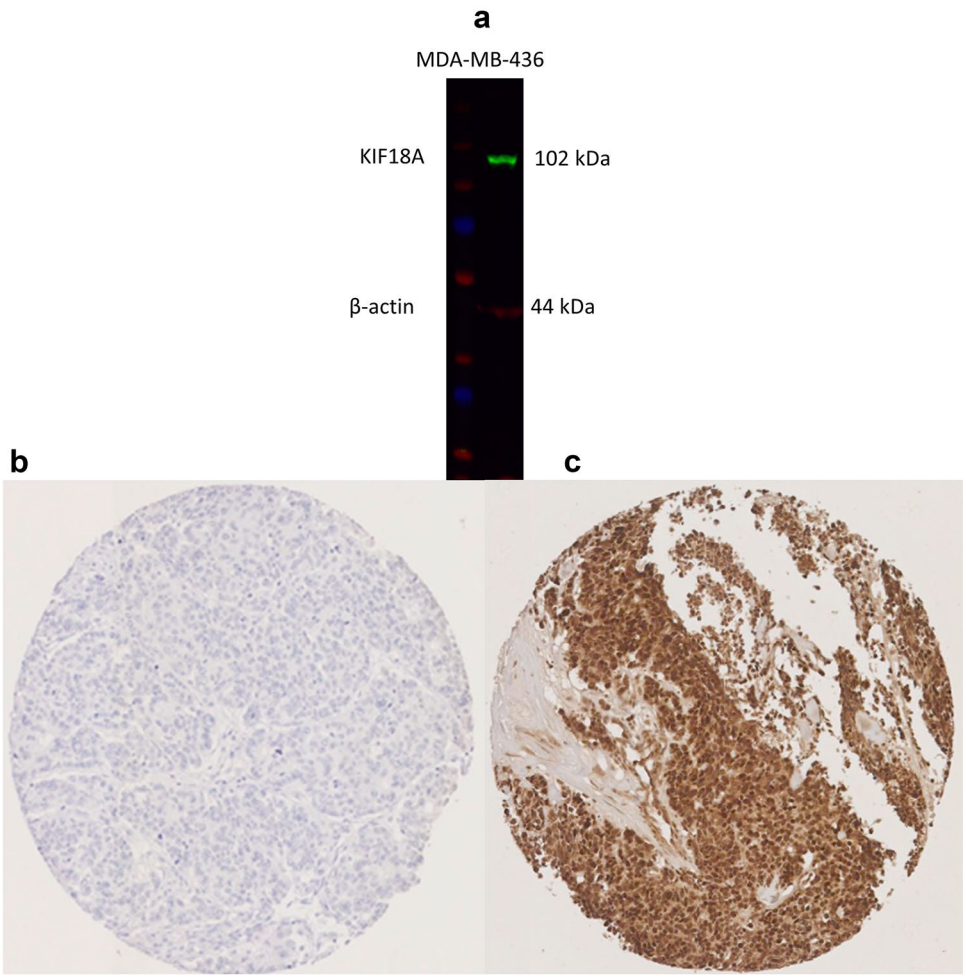

Fig. 1 Western blotting result for **a** KIF18A expression in MDA-MB-436 BC cell lysates. KIF18A protein expression in invasive BC cores. **b** Negative IHC expression and **c** positive IHC expression

was an H-score of 80 determined using X-Tile (X-Tile Bioinformatics Software, Yale University, version 3.6.1), with the samples stratified to high and low expression groups based on patient outcome.

Clinical outcome

The primary outcomes were recurrence-free survival (RFS), defined as the time in months from surgery until developing local or regional recurrence, distant-metastases free survival (DMFS), defined as the time in months from surgery until developing distant-metastasis and BC specific survival (BCSS), defined as the time in months from the date of primary surgery to the date of BC-related death, and their association with tamoxifen efficacy. Secondary outcomes included associations with clinicopathological factors.

Statistical analysis

Statistical analysis was performed using SPSS 24.0 statistical software (SPSS Inc., Chicago, IL, USA). The analysis for this study compared the low and high expression of KIF18A. For the continuous variables, differences between three or more groups were assessed using one-way analysis of variance (ANOVA) with the post-hoc Tukey multiple comparison test. Spearman's correlation coefficient was carried out to examine the association between two continuous variables. The Chi square test was performed for inter-relationships between categorical variables. Kaplan–Meier and log-rank analysis were used to assess RFS, DMFS and BCSS. Hazard ratios and confidence intervals were calculated from univariate Cox regression survival analysis. Multivariate Cox Regression analysis with adjustment of covariates was used to identify independent prognostic biomarkers. Benjamini–Hochberg procedure for multiple test correction was performed. *P* value of ≤ 0.05 was considered significant.

Result

KIF18A expression in ER + BC

KIF18A protein expression was observed, predominantly in the nucleus of invasive BC cells, with expression levels varying from absent to high (Fig. 1b, c). High KIF18A mRNA expression was observed in 987/1506 (65.5%) of the METABRIC cohort and KIF18A protein expression was observed in 213/406 (52%) of cases of Nottingham cohort.

KIF18A expression and clinicopathological parameters

High KIF18A mRNA expression was significantly associated with poor Nottingham Prognostic Index (NPI) ($P < 0.0001$, Fig. 2a), higher tumour grade ($P < 0.0001$, Fig. 2b) and larger tumour size ($P = 0.0002$). However, KIF18A protein expression showed no statistical significance association with grade, tumour size or NPI.

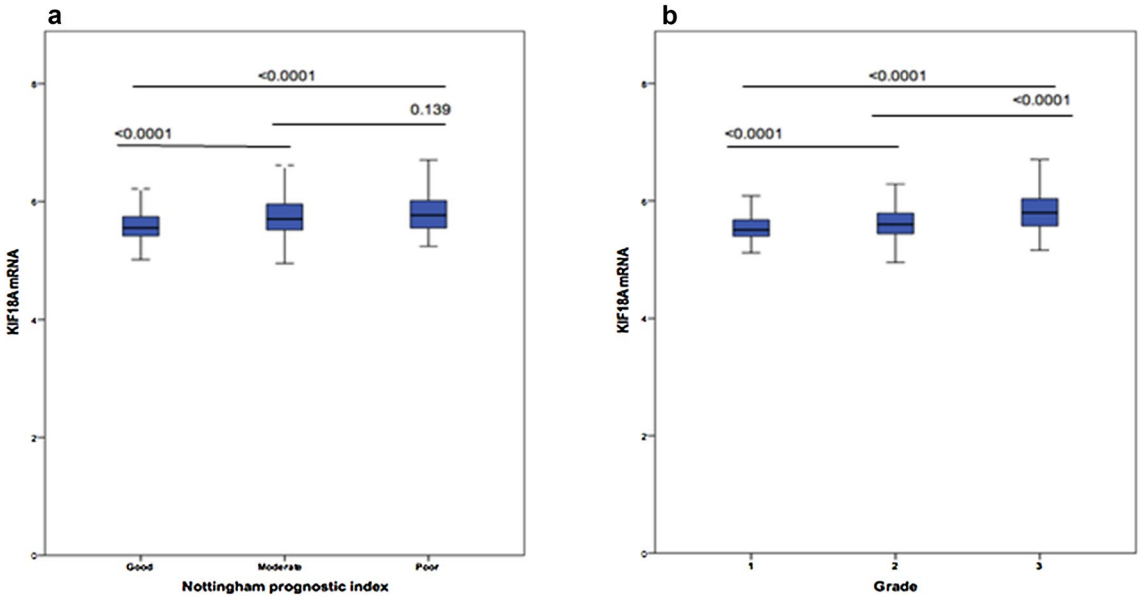

Fig. 2 KIF18A mRNA expression and its association with **a** Nottingham prognostic index (NPI) and **b** tumour grade

KIF18A prognosis in ER + BC

High expression of KIF18A was highly associated with poor clinical outcome in ER + BC patients. Specifically, KIF18A mRNA overexpression was associated with poor RFS ($P = 0.00013$), DMFS ($P = 0.00003$) and BCSS ($P = 0.000008$) in ER + BC using the METABRIC dataset (Fig. 3a, c, e). These observations were confirmed in the KM-Plotter cohort: RFS ($P = 2.1 \times 10^{-10}$), DMFS ($P = 1.1 \times 10^{-6}$) and BCSS ($P = 4.0 \times 10^{-8}$) (Supplementary Fig. 1A–C).

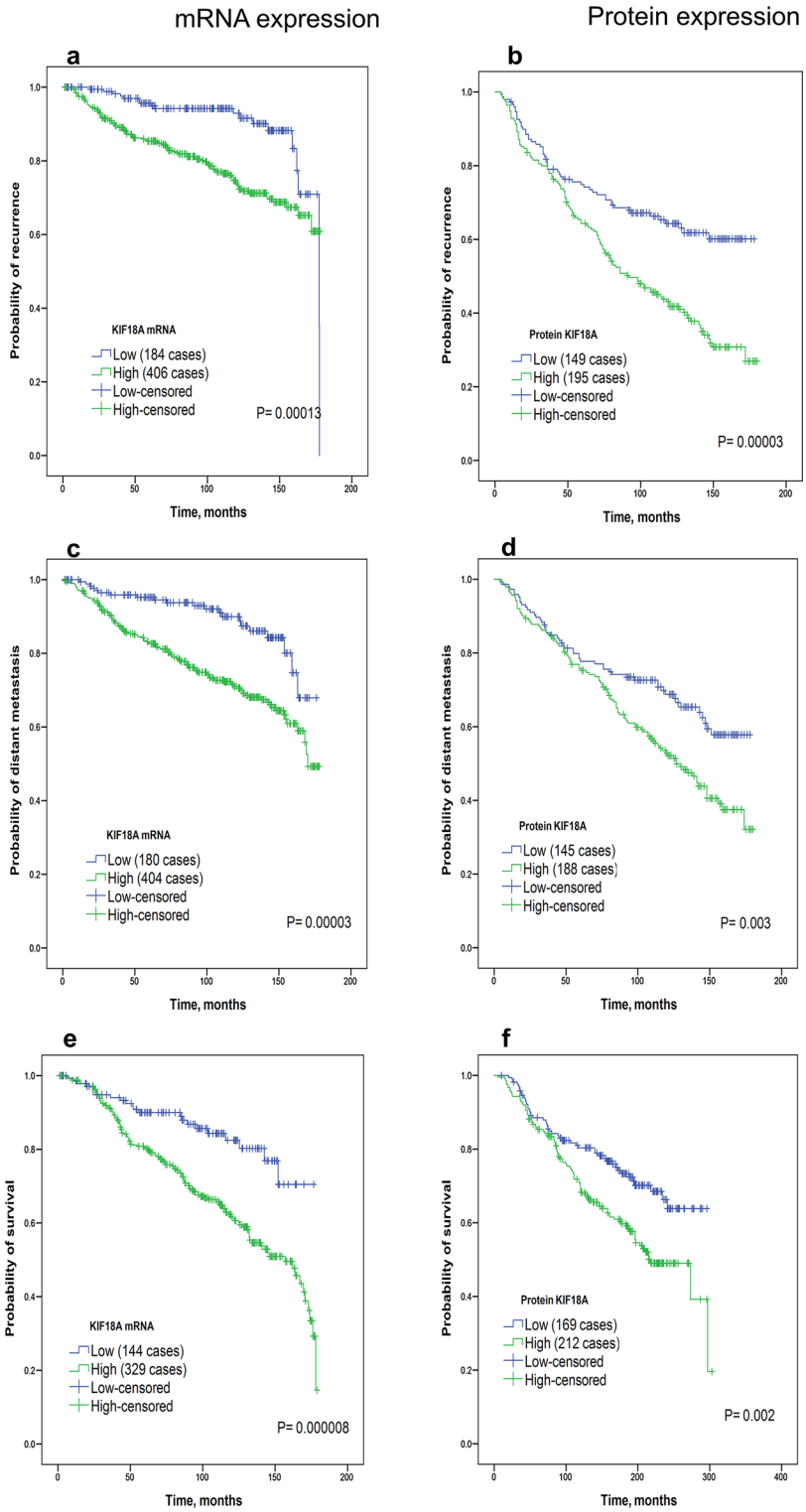

Fig. 3 High KIF18A expression as a prognostic biomarker of poor clinical outcome in patients with ER + BC. Kaplan–Meier survival plots for **a** recurrence, **c** distant-metastasis and **e** breast cancer specific survival, comparing high and low groups of KIF18A mRNA expression. Kaplan–Meier survival plots for **b** recurrence, **d** distant-metastasis and **f** breast cancer specific survival for expression of KIF18A protein levels

The above findings at the gene expression level were confirmed at the protein level where high KIF18A protein in tumours was significantly associated with a shorter RFS ($P=0.00003$), and DMFS ($P=0.003$) together with poor BCSS ($P=0.002$) compared with the low expression group, which showed better clinical outcome (Fig. 3b, d, f).

KIF18A is a predictive biomarker of resistance to endocrine therapy

Since high expression of KIF18A confers poor clinical outcome in patients with ER + BC, we hypothesised that KIF18A may play a potential role in hormone therapy resistance. To validate this hypothesis, we compared the association of KIF18A expression with RFS, DMFS and BCSS in two sub-populations of ER + BC (untreated vs endocrine-treated).

In patients who received endocrine therapy, tumours with high KIF18A mRNA expression had a poor RFS ($P=0.007$) and DMFS ($P=0.004$) (Fig. 4b, d) in comparison to patients with low mRNA expression of KIF18A. A similar observation was seen in patients who did not receive any adjuvant treatment: RFS ($P=0.001$) and DMFS ($P=0.014$) (Fig. 4a, c), In addition, high KIF18A mRNA was a predictive of long-term short BCSS in those treated with endocrine therapy ($P=0.016$, Fig. 4f) but not in those patients not receiving any adjuvant therapy ($P=0.075$, Fig. 4e).

These observations were confirmed in the KM-Plotter dataset where patients who had high KIF18A mRNA and received endocrine therapy had a poor RFS ($P=1.4\times10^{-5}$), DMFS ($P=8.3\times10^{-6}$) and BCSS ($P=0.018$) (Supplementary Fig. 2B, D and F). This was similar to those patients who did not receive any adjuvant therapy where high KIF18A mRNA expression was associated with poor RFS ($P=0.0012$), DMFS ($P=0.0026$) and short BCSS ($P=0.0053$) (Supplementary Fig. 2A, C and E).

These results were validated at the protein level where high KIF18A protein was significantly associated with poor RFS ($P=0.00001$), DMFS ($P=0.004$) and BCSS ($P=0.001$) in patients who had endocrine therapy (Fig. 5b, d, f). In untreated patients, high KIF18A was predictive of a poor RFS ($P=0.001$), DMFS ($P=0.036$) and short BCSS ($P=0.042$) (Fig. 5a, c, e).

KIF18A expression in ER + BC is an independent prognostic factor

Multivariate analysis of KIF18A mRNA expression in ER + BC demonstrated that KIF18A expression was an independent prognostic factor for RFS ($P=0.01$), DMFS ($P=0.04$) and BCSS ($P=0.03$) Table 2. The same observations were demonstrated with KIF18A protein levels: RFS ($P=0.00001$), DMFS ($P=0.005$) and BCSS ($P=0.02$), Table 3.

In patients who received endocrine therapy, KIF18A mRNA expression was not independent of tumour grade, tumour size and nodal stage, Table 4. However, KIF18A protein expression remained an independent predictive factor of poor RFS ($P=0.027$) and DMFS ($P=0.028$) and short BCSS ($P=0.050$), in those patients who were treated with endocrine therapy Table 5.

Discussion

Over the last two decades anti-oestrogenic strategies have resulted in a paradigm shift in the treatment of BC. Endocrine therapies now represent the cornerstone of systemic treatment for women with ER + tumours at every stage of management. For adjuvant therapy of ER + BC, tamoxifen improves overall survival and reduces risk for development of BC [15]. However, an unpredictable subset of patients who received adjuvant endocrine therapy will relapse and die as a result of the disease [2]. Therefore, prediction of those patents that may or may not benefit from adjuvant endocrine therapy would be beneficial for ER + BC patients.

KIF18A, is a member of the kinesin 8 family and a key regulator of cell cycle, has been demonstrated to play important roles in chromosome alignment during mitosis [3, 16, 17]. Several studies have revealed that KIF18A upregulation may affect the biological characteristics of cancer cells [5–7]. Nevertheless, the prognostic power of KIF18A in ER + BC and its relation with endocrine therapy have not been reported before. This study shows that high KIF18A mRNA expression is associated with poor prognostic factors in ER + BC which in consistent with a previous study that suggested KIF18A may play an important role in human BC carcinogenesis and KIF18A overexpression is associated with tumour grade, metastasis and poor survival [4].

Zusev and Benayahu reported that both oestrogen and ER could up-regulate the expression of KIF18A mRNA and protein, suggesting that KIF18A may be associated with ER-related cancers [10]. Our study is the first to show that high expression of KIF18A at both the mRNA and protein levels is highly associated with poor outcome in ER + BC. Thus its high levels was associated with poor RFS, DMFS and BCSS, and these results indicate its role as a poor prognostic biomarker of ER + BC.

Previous studies report a novel interaction between KIF18A and ER where MBA-15 cells treated by oestrogen express higher levels of KIF18A mRNA, which demonstrates involvement of KIF18A in ER signalling [9, 10]. Further, inhibition of KIF18A expression significantly inhibits the proliferative capability of BC cells in vitro and in vivo, and decreases cancer cell migration by stabilising

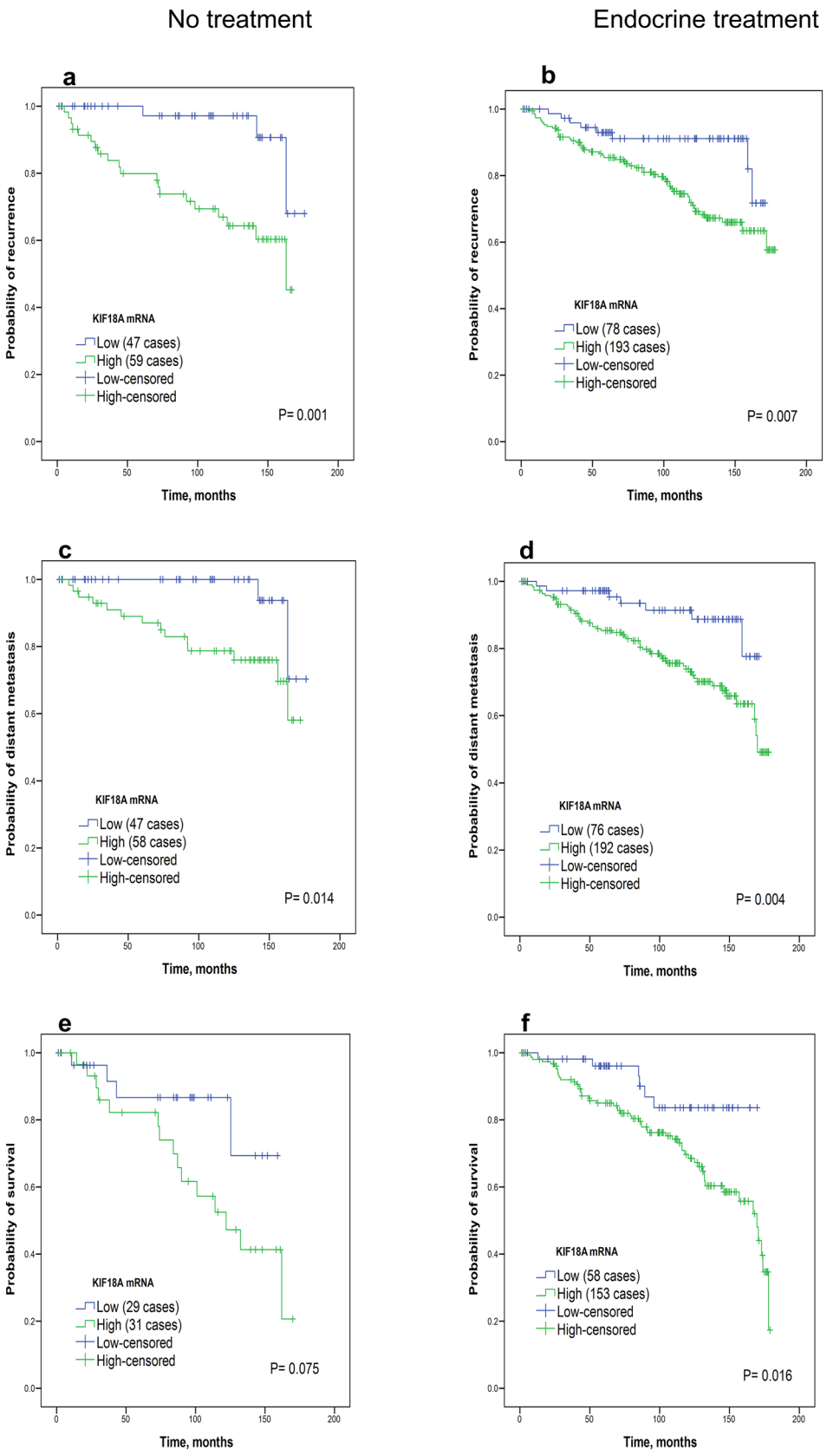

Fig. 4 KIF18A mRNA expression as a prognostic biomarker for poor clinical outcome in untreated patients with ER + BC **a** recurrence, **c** distant-metastasis, **e** breast cancer specific survival. KIF18A mRNA expression as a predictive biomarker for poor benefit from endocrine therapy in patients with ER + BC **b** recurrence, **d** distant-metastasis, **f** breast cancer specific survival

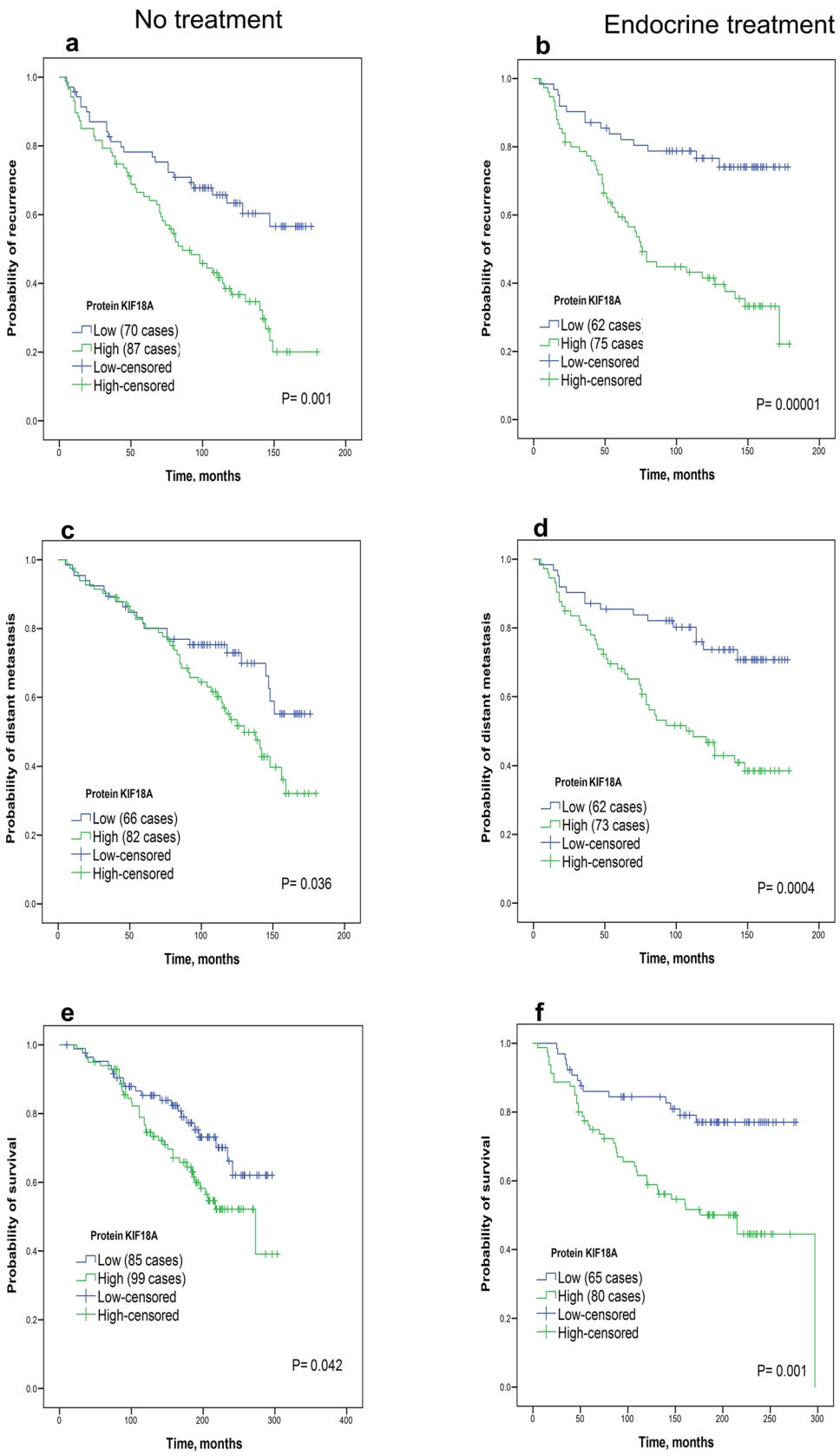

Fig. 5 KIF18A protein expression as a prognostic biomarker for poor clinical outcome in untreated patients with ER + BC **a** recurrence, **c** distant-metastasis, **e** breast cancer specific survival. KIF18A protein expression as a predictive biomarker for poor benefit from endocrine therapy in patients with ER + BC **b** recurrence, **d** distant-metastasis **f** breast cancer specific survival

Table 2 Multivariate analysis of associations between KIF18A mRNA expression and clinicopathological parameters in ER + BC patients

Parameters	HR (95% CI)	*P*	*P**
Recurrence-free survival			
KIF18A	3.308 (1.568–6.979)	**0.002**	**0.01**
Grade	1.223 (0.868–1.723)	0.250	0.41
Nodal stage	1.106 (0.769–1.590)	0.587	0.73
Tumour size	1.359 (0.856–2.159)	0.194	0.48
Distant-metastasis free survival			
KIF18A	2.887 (1.301–6.410)	**0.009**	**0.04**
Grade	1.406 (0.952–2.075)	0.087	0.1
Nodal stage	1.397 (0.959–2.035)	0.081	0.1
Tumour size	1.878 (1.109–3.179)	0.019	0.04
Breast cancer specific survival			
KIF18A	3.729 (1.332–10.439)	**0.012**	**0.03**
Grade	1.897 (1.193–3.016)	0.007	0.03
Nodal stage	1.375 (0.917–2.062)	0.123	0.15
Tumour size	1.842 (1.028–3.302)	0.040	0.06

Bold values indicate statistically significant

*P** Adjusted *P* value

Table 3 Multivariate analysis of associations between KIF18A protein expression and clinicopathological parameters in ER + BC patients

Parameters	HR (95% CI)	*P*	*P**
Recurrence-free survival			
KIF18A	1.897 (1.375–2.617)	**0.000009**	**0.00001**
Grade	0.892 (1.088–1.387)	0.346	0.43
Nodal stage	1.529 (1.211–1.932)	0.0003	0.0008
Tumour size	1.176 (0.868–1.594)	0.294	0.49
Distant-metastasis free survival			
KIF18A	1.701 (1.216–2.379)	**0.002**	**0.005**
Grade	1.374 (1.081–1.748)	0.010	0.016
Nodal stage	1.825 (1.428–2.331)	0.000001	0.00001
Tumour size	1.498 (1.079–2.080)	0.016	0.02
Breast cancer specific survival			
KIF18A	1.616 (1.137–2.299)	**0.008**	**0.02**
Grade	1.408 (1.088–1.1822)	0.009	0.015
Nodal stage	1.735 (1.337–2.250)	0.00003	0.0002
Tumour size	1.357 (0.959–1.929)	0.85	1.06

Bold values indicate statistically significant

*P** Adjusted *P* value

MTs at leading edges and ultimately induces anoikis of cells with inactivation of the PI3K signalling pathway [4]. To our knowledge, dysregulation of cell cycle checkpoints is common in cancer and promote antiestrogen resistance in ER + BC [18]. However, the association between KIF18A

Table 4 Multivariate analysis of associations between KIF18A mRNA expression and clinicopathological parameters in endocrine-treated patients

Parameters	HR (95% CI)	*P*	*P**
Recurrence-free survival			
KIF18A	2.624 (1.033–6.664)	**0.042**	0.21
Grade	1.144 (0.728–1.798)	0.559	1.39
Nodal stage	1.087 (0.685–1.725)	0.723	1.20
Tumour size	0.999 (0.658–1.519)	0.922	1.15
Distant-metastasis free survival			
KIF18A	2.449 (0.957–6.267)	0.062	0.31
Grade	1.255 (0.769–2.049)	0.363	0.45
Nodal stage	1.413 (0.884–2.258)	0.149	0.37
Tumour size	1.354 (0.718–2.552)	0.349	0.58

*P** Adjusted *P* value

Table 5 Multivariate analysis of associations between KIF18A protein expression and clinicopathological parameters in endocrine-treated patients

Parameters	HR (95% CI)	*P*	*P**
Recurrence-free survival			
KIF18A	1.790 (1.143–2.804)	**0.011**	**0.027**
Grade	1.463 (0.998–2.145)	0.051	0.085
Nodal stage	1.805 (1.253–2.602)	0.002	0.01
Tumour size	0.999 (0.658–1.519)	0.998	1.24
Distant-metastasis free survival			
KIF18A	1.729 (1.104–2.709)	**0.017**	**0.028**
Grade	2.325 (1.622–3.333)	0.000004	0.00001
Nodal stage	2.814 (2.050–3.862)	1.52e-10	< 0.00001
Tumour size	1.223 (0.789–1.897)	0.368	0.46
Breast cancer specific survival			
KIF18A	1.702 (1.054–2.748)	**0.030**	**0.050**
Grade	1.780 (1.166–2.716)	0.007	0.017
Nodal stage	1.933 (1.307–2.859)	0.001	0.005
Tumour size	1.050 (0.664–1.660)	0.836	1.04

*P** Adjusted *P* value

overexpression and relapse with endocrine therapy in patients with ER + BC has previously not been investigated. Our results show the significant predictive power of KIF18A in ER + BC particularly where high levels of KIF18A are correlated with poor RFS and DMFS after endocrine therapy. KIF18A expression appears to be a candidate marker of a subgroup of ER + BC characterised by poor outcome in those patients treated with endocrine therapy.

The American Society of Clinical Oncology (ASCO) guidelines for ER measurement attempts to make the benefit of endocrine therapy available to the widest range of patients, by recommending 1% as universal cut point to

distinguish between ER positivity and negativity to help determine likelihood of patients responding to endocrine therapy [19]. However, this might lead to overtreatment and unnecessary endocrine therapies with the potential of causing more harm than good for patients with ER + BC, who will resist and fail to respond to endocrine therapy and eventually will relapse. Therefore, we conclude that KIF18A expression has the potential to predict those who might fail to benefit from endocrine therapy.

Acknowledgements We thank the Nottingham Health Science Biobank and Breast Cancer Now Tissue Bank for the provision of tissue samples. We thank the University of Nottingham (Nottingham Life Cycle 6 and Cancer Research Priority Area) and Saudi Arabia Cultural Embassy for funding.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval This study was approved by the Nottingham Research Ethics Committee 2 under the title "Development of a molecular genetic classification of breast cancer".

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