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The transcription factor Sox11 is a prognostic factor for improved recurrence-free survival in epithelial ovarian cancer

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ABSTRACT

Background: Current prognostic molecular markers for epithelial ovarian cancer (EOC) are insufficient. The aim of the current study was to investigate the role of Sox11 in EOC.
Methods: Using an *in silico* transcriptomic screen, Sox11 was identified as a potential EOC biomarker. Sox11 protein expression was evaluated using immunohistochemistry (IHC) in 76 EOC cases, which were analysed using automated algorithms to develop a quantitative scoring model.
Results: Sox11 mRNA expression was upregulated in EOC compared to normal tissues. Automated analysis of Sox11 in the EOC cohort revealed high expression of Sox11, in 40% of tumours, who had an improved recurrence-free survival (RFS) ($p = 0.002$). Multivariate analysis confirmed that Sox11 was an independent predictor of improved RFS after controlling for stage and grade.
Conclusions: These data suggest that Sox11 is a new prognostic marker in EOC. Loss of Sox11 is associated with a decreased RFS and a more aggressive phenotype.

1. Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gyneacological malignancy and the fifth most common cause of cancer-related death in women. In 2008, it is estimated that 21,650 new ovarian cancer cases will be diagnosed in the United States and that 15,520 will succumb to the disease.[1] The poor ratio of survival to incidence in EOC is related to the high percentage of cases that are diagnosed at an advance stage and the lack of effective therapies for advanced refractory disease. Despite improvements in surgical techniques and the advent of more targeted therapeutics such as bevacizimab, survival of patients with EOC stands at 45% at 5 years.[1] Such poor prognostic statistics indicate that there is an urgent need to improve our understanding of the molecular mechanisms underlying EOC, so as to develop better

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prognostic and predictive assays and identify new therapeutic targets.

EOC, like most other cancers, is a complex heterogenous disease, influenced and controlled by multiple genetic and epigenetic alterations leading to an increasingly aggressive phenotype.[2,3] It is now well recognised that the characteristics of an individual tumour and its life course result from multiple somatic mutations acquired over time (e.g. TP53, PTEN and RAS) and from continual evolution of the host responses to environmental factors (e.g. oestrogen or tobacco exposure).[4] In certain cases, these somatic mutations overlie inherent germline variations (e.g. BRCA1/2).[4,5] From a therapeutic standpoint, EOC is best considered a collection of complex interrelated diseases represented by an immense natural heterogeneity in tumour phenotypes, disease outcomes and response to treatment. A major challenge is consequently to identify and thoroughly validate diagnostic and prognostic biomarkers that can accurately describe the heterogeneity ascribed to EOC. In addition, accurate predictive biomarkers are required to guide current treatment protocols, as well as to guide the development and application of new targeted therapies.

Technologies, such as DNA microarrays, mass spectrometry-based proteomics and metabolomics, have facilitated translational research over the last decade helping us to improve our understanding of the molecular and genetic basis of oncogenesis and affording an opportunity to add new approaches to the practice of clinical oncology. The fundamental premise of 'omic technologies' is that comprehensive examination of changes in the genome (DNA), transcriptome (mRNA), proteome (proteins) or metabolome (metabolites) can provide insight into the physiology and mechanism of disease, by the provision of superior diagnostic tests and therapeutic efficacy to that currently available.[6] The application of DNA microarray technology to cancer biology, in particular, has led to an ever-growing comprehension of the complexity of the underlying pathophysiological pathways and interactions within a tumour.[7,8] Transcriptomic screens have accelerated research into genotypic–phenotypic correlations, with a common aim of elucidating the functional taxonomy of genes in both normal tissues and disease states, such as cancer.[8]

In this study, we initially used the results of a large transcriptomic meta-analysis study [9] to identify a gene, *Sox* (Sry HMG-box) *11*, that was upregulated in a number of different tumour types, and secondly used tissue microarrays (TMAs) and automated image analysis and to assess Sox11 as a new prognostic biomarker for EOC.

The transcription factor *Sox11* is a member of the Sox gene family and has been mapped to chromosome 2p25.3.[10] Sox proteins are identified as proteins that contain a DNA-binding high mobility group (HMG) domain with strong amino acid homology (usually >50%) to the HMG domain of the male sex determination gene, Sry.[11] More than 20 orthologous Sox genes have been identified in the human and mouse genomes, and family members are divided into eight subgroups according to the degree of homology within and outside the HMG domain.[12] All Sox genes characterised to date have a specific expression pattern and most of them have critical roles in the determination of cell fate and tissue remodelling.[13] Sox proteins act as transcription factors by binding to the minor groove of DNA and by inducing a sharp bend of DNA allowing them to play a key architectural role in the assembly of transcriptional enhancer complexes.[13,14] In addition to protein-DNA interactions, Sox proteins also interact with various other transcription factors to increase their efficiency and specificity of action.[13]

Sox11 belongs to the C subgroup, along with Sox4 and Sox12,[12] and all three proteins demonstrate a high degree of homology within both the C-terminal transactivation domain and the HMG domain.[13,15] Sox11 and Sox4 play major roles in cardiac, neuronal and other major embryonic processes, whilst less is known about Sox12.[13]

We have recently demonstrated that the nuclear Sox11 is specifically upregulated in mantle cell lymphoma (MCL) and distinguishes MCL from other B-cell lymphomas.[16] Sox4 is a prominent transcription factor in the lymphocytes of both the B-and T-cell lineage,[11,17] and is crucial for B lymphopoiesis,[18] whilst Sox11 has no known lymphopoietic function and is not expressed in B-cells,[16] Both Sox4 and Sox11 are expressed in medulloblastoma,[19] and Sox11 is also overexpressed in malignant glioma.[20] Additionally, Sox4 is expressed in bladder cancer with increased levels of expression associated with an improved patient outcome.[21]

This study outlines the expression of Sox11 mRNA across a large number of normal tissues and tumours, and reveals Sox11 mRNA to be overexpressed in a large number of malignant tissues. In addition, we specifically examined Sox11 protein expression in EOC and demonstrated that increased levels of Sox11 protein, as determined by image analysis, were associated with an improved recurrence-free survival (RFS).

2. Materials and methods

2.1. *Transcriptional profiling*

Sox11 mRNA expression levels across a large number of human tissues were retrieved from transcriptomic meta-analysis study (Kilpinen and colleagues, Genome Biology, manuscript in preparation) containing data from 9783 samples analysed using Affymetrix gene expression microarrays. Samples cover 43 normal tissue types, 68 cancer types and 64 other disease types.

2.2. *Patients and tumour samples*

Prior to commencing the study, a power calculation revealed that a cohort of 54 patients would allow for a power of 0.95. The TMA, used in this study, was constructed from a consecutive cohort of 76 patients diagnosed with primary invasive epithelial ovarian cancer at the National Maternity Hospital, Dublin, with a median follow-up of 4.3 years. The patient cohort is summarised in Table 1. The standard surgical approach was a total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy with the cytological evaluation of peritonea fluid or washings. Residual disease was resected to less than 2 cm where possible. Stage and volume of residual disease (no residual disease, residual disease greater or less than 2 cm) were recorded in all cases. All pa-

Table 1 – Patient and tumour characteristics.

Age	
Median (Range)	52 (31–77)
Histology	
Serous	50
Mucinous	4
Endometrioid	17
Clear cell	1
Other	4
Grade	
Well differentiated	12
Moderately differentiated	29
Poorly differentiated	35
Stage	
1	0
2	21
3	54
4	1

tients received adjuvant chemotherapy consisting of cisplatin or carboplatin prior to 1992 and were combined with paclitaxel from 1992 to 2002. No patient received neo-adjuvant chemotherapy. Benign or borderline ovarian cancers, non-epithelial ovarian cancer and cases with histological features typical of secondary ovarian cancer were excluded from the study. Diagnostic specimens were all formalin fixed and paraffin-embedded in the Department of Pathology at the National Maternity Hospital, Dublin, Ireland. All tissue blocks were stored in this department prior to the construction of the TMA. Full ethical approval was obtained from the ethics committee of the National Maternity Hospital, Dublin.

2.3. Tissue microarrays and immunohistochemistry

Seventy-six paraffin-embedded tumour specimens were used for tissue microarray (TMA) construction. Areas representative of invasive cancer were marked on haematoxylin and eosin-stained slides, and the TMA was constructed, using a manual tissue arrayer (MTA-1, Beecher Inc, WI). The array consisted of four cores per patient. Two 1.0 mm cores were extracted from each donor block and assembled in a recipient block. Recipient blocks were limited to approximately 100 cores each. In general, cores were taken from the peripheral part of the tumour in cases where the tumour had well-defined borders. In more diffusely growing tumours, areas with the highest tumour cell density were primarily targeted. Necrotic tissue was avoided.

TMA sections (4 μm) were dried, deparaffinised, rehydrated and put through descending concentrations of ethanol. Heat-mediated antigen retrieval was performed in a BORGdecloaker (Biocare, Concord, CA, USA) at pH 9.0, and sections were then stained with the primary rabbit anti-human Sox11 antibody (1:100) at room temperature for 25 min. This specific antibody targeted the following protein sequence: FMVWSKIERRKIMEQSPDMHNAEISKRLGKRWKMLKDSEKIPFIREAERLRLKHMADYPDYKYRPRKKPKMDPSAKPSASQSPEKSAAGGGGSAGGGAGGAKTSKGSSKK and was raised, as previously described.[15] Signal was detected using the Dako REAL Detection system, which contained the secondary biotinylated goat anti-rabbit/mouse antibody, the strepavidin/horseradish peroxidase complex and 3,3′- diaminobenzidine, applied according to the manufacturer's protocol. Slides were counterstained with Mayers haematoxylin (Sigma–Aldrich, St. Louis, MO).

2.4. Image acquisition, management and automated analysis

The Aperio ScanScope XT Slide Scanner (Aperio Technologies, Vista, CA) system was used to capture whole slide digital images with a 20X objective. Slides were de-arrayed to visualise individual cores, using TMA Lab (Aperio). A colour deconvolution algorithm (Aperio) was used to develop a quantitative scoring model for Sox11 expression.

2.5. Statistical analysis

Spearman's Rho correlation was used to estimate the relationship between cores from individual tumours. Differences in the distribution of clinical data and tumour characteristics between samples with a high and low Sox11 expression (described below) were evaluated using the χ^2-test. Kaplan Meier analysis and the log rank test were used to illustrate differences between RFS and overall survival (OS). Cox regression proportional hazards models were used to estimate the relationship between survival and Sox11, stage and grade. All calculations were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL). p-Value < 0.05 was considered statistically significant.

3. Results

3.1. Sox11 mRNA expression in normal and tumour tissues

A meta-analysis of Sox11 mRNA expression levels was performed in 9783 samples analysed using the Affymetrix gene expression microarrays, which include data from 43 normal tissue types, 68 different tumour types and 64 other disease types. Each dot in Fig. 1 represents the expression of *Sox11* in a particular tissue sample. Samples from tissues having higher than average expression or having an outlier expression profile were additionally coloured in Fig. 1 with the corresponding legend visible on the top left corner.

As demonstrated in Fig. 1, high levels of Sox11 mRNA expression were only evident in normal prostate tissue. In contrast, increased levels of Sox11 mRNA expression were evident in a number of cancer types, including ALL, leukaemia, glioma, neuroblastoma, primary peritoneal, sarcoma, testicular, renal, breast and ovarian carcinoma (Fig. 1).

3.2. Sox11 protein expression in ovarian cancer

Having identified Sox11 as a gene that was overexpressed in a variety of different tumours, Sox11 protein expression was examined using IHC in EOC as illustrated in Fig. 2. Sox11 expression was seen exclusively in tumour epithelium and IHC signal was evident in both the nucleus and the cytoplasm.

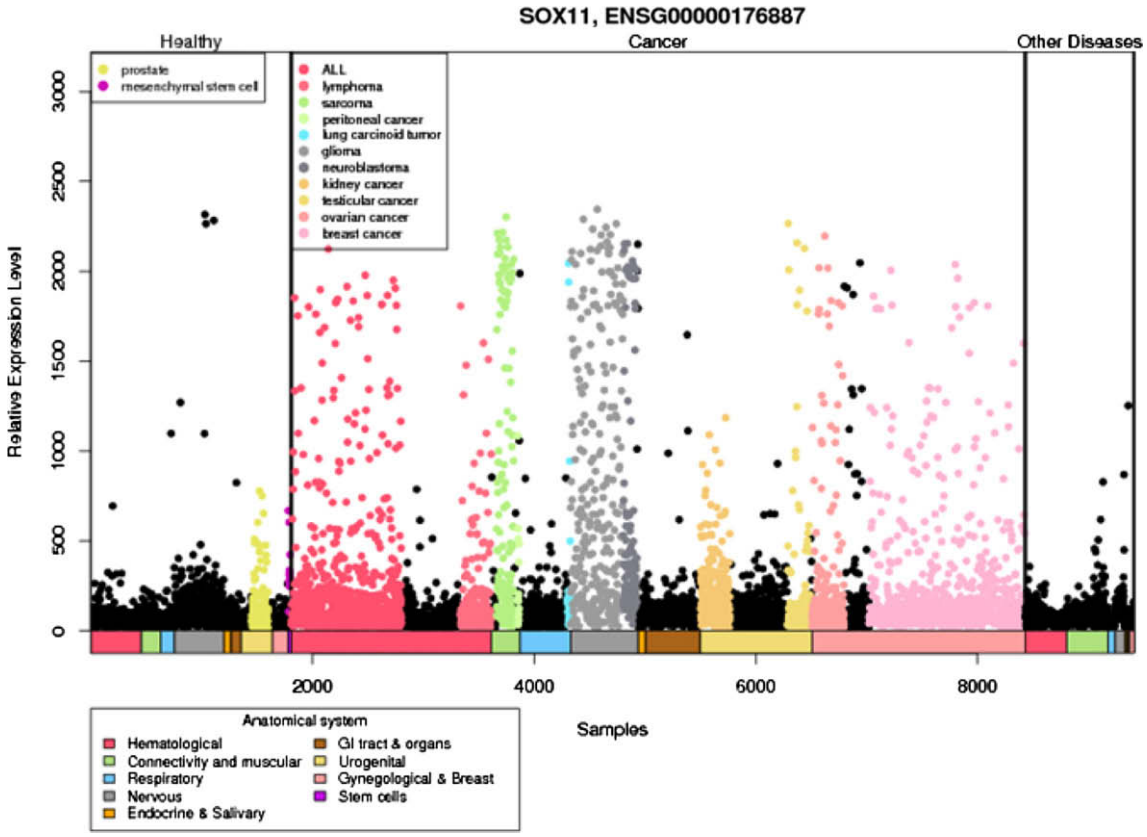

Fig. 1 – Sox11 mRNA is overexpressed in a number of different tumour types. Expression profile of Sox11 across 9783 samples. Y-axis shows Sox11 expression levels and the X-axis represents samples, ordered according to tissue and pathological types. Anatomical origins of each sample can be seen in the colour bar below the image.

Nuclear expression of Sox11 was present only when accompanied by cytoplasmic signal, whereas a proportion (49%) of tumours did demonstrate cytoplasmic expression in the absence of nuclear signal (Fig. 2).

3.3. *Quantitative determination of Sox11 expression as determined by image analysis*

Quantitative determination of Sox11 expression was ascertained, using an image analysis approach, in particular via the use of a commercial colour deconvolution algorithm (Aperio). A pseudo-colour 'mark-up' image was generated as an algorithm result, thus allowing confirmation that the algorithm was accurately identifying epithelial and stromal pixels (Fig. 2). A full description of the algorithm was recently published.[22]

The algorithm was used to calculate a total intensity (TI) for Sox11 for each core. There was a strong correlation between quadruplicate cores from individual tumours for TI (Spearman's Rho = 0.858, $p < 0.001$), indicating that Sox11 has a homogenous pattern of expression in ovarian cancer and is suitable for TMA-based analysis. As tumours were arrayed in quadruplicate, the median value for each tumour was used for further analysis. The algorithm accurately distinguished between nuclear and cytoplasmic staining in all cores, as confirmed by a histopathologist.

A histogram of Sox11 image analysis data for the entire cohort is shown in Fig. 3A. Using this histogram, the tumours were placed into three categories – high, medium and low levels of Sox11 expression, as determined by image analysis. Based on the image analysis categorisation, 20% ($n = 17$) of tumours were classified as having high levels, 43% ($n = 35$) medium levels and 29% ($n = 24$) low/negative levels of Sox11 expression, as determined by image analysis. Tumours in the high expression group showed expression of nuclear and cytoplasmic Sox11, whilst those in the medium group generally exhibited only cytoplasmic Sox11. No association was found between Sox11 expression and age, grade or stage of disease.

3.4. *Associations between Sox11 expression as determined by automated image analysis and survival*

Kaplan Meier analysis of RFS based on the expression of Sox11 revealed a stepwise decrease in RFS between the high, medium and low groups ($p = 0.033$) (Fig. 3B). Further analysis revealed a significantly reduced RFS in patients with low levels of Sox11 expression, compared to tumours expressing high and medium levels of Sox11 ($p = 0.02$) (Fig. 3C). Multivariate Cox regression analysis of RFS revealed that Sox11 expression was an independent predictor of RFS, when compared to stage and grade (Table 2). Kaplan Meier analysis of OS

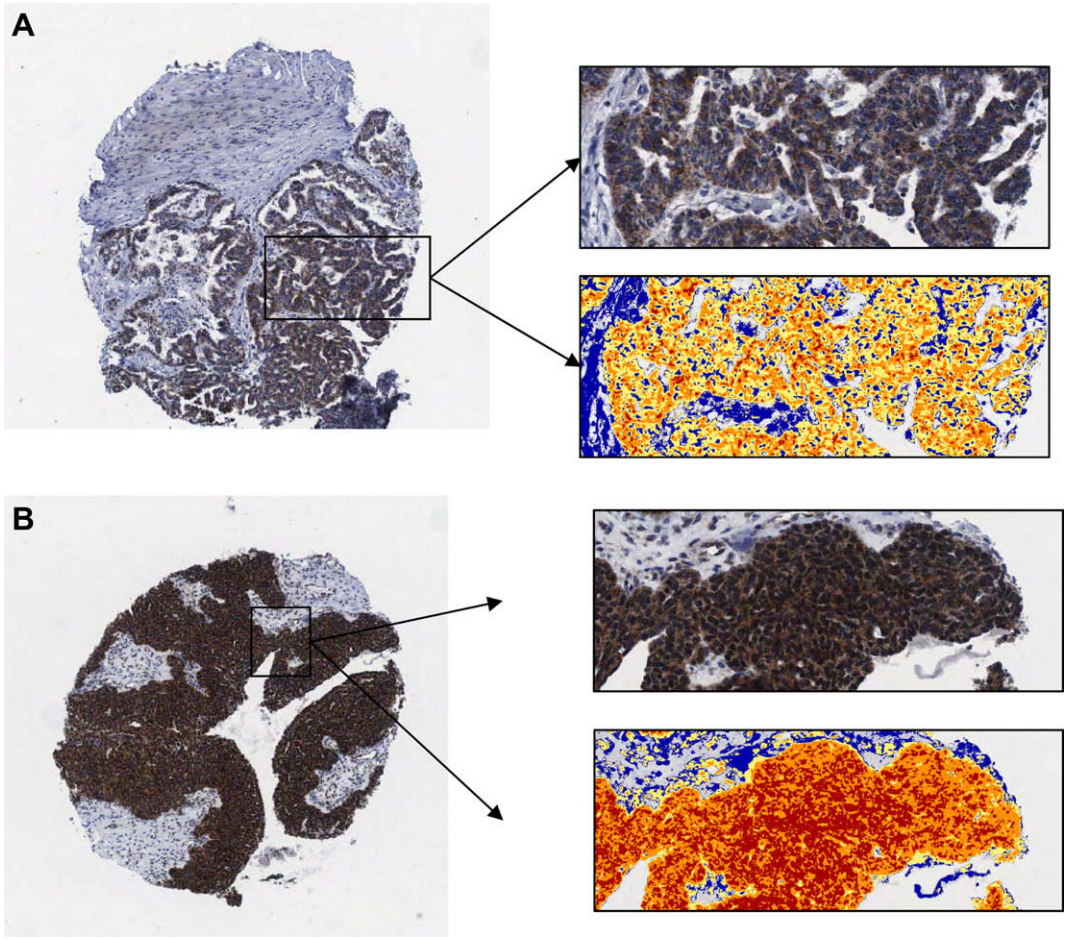

Fig. 2 – Sox11 protein expression in ovarian cancer. Immunohistochemical staining of Sox11 showing cytoplasmic expression (A) and cytoplasmic and nuclear expression (B). Corresponding markup image of the colour deconvolution algorithm showing stroma in blue, cytoplasmic staining in yellow and orange and nuclear expression in red.

confirmed that high levels of Sox11 were associated with an improved OS (data not shown); however, multivariate Cox regression analysis of OS did not confirm Sox11 as an independent predictor of OS (Table 2).

4. Discussion

An improved understanding of the underlying molecular mechanisms of EOC should lead to better patient outcomes. In this study, we combined a meta-analysis of transcriptomic data, TMAs and automated image analysis to identify and validate Sox11 as a prognostic biomarker in EOC. This study is the first to describe the relationship between Sox11 expression and prognosis in EOC. Having previously identified Sox11 as a new diagnostic marker in MCL,[16] data from a meta-analysis of 9783 samples analysed with the Affymetrix gene expression microarrays were used to profile the expression of Sox11 mRNA over 43 normal tissue types, 68 different tumour types and 64 other disease types. Increased levels of Sox1 mRNA were not seen in normal tissues, except the prostate. In contrast, increased levels of Sox11 mRNA expression were evident in a number of cancer types.

TMAs and a quantitative automated analysis of IHC were then used to evaluate Sox11 protein expression in EOC in relation to survival. This revealed epithelial-specific Sox11 expression in both the nuclear and cytoplasmic compartments. Increased levels of Sox11, particularly nuclear Sox11, were associated with an increased RFS, and Cox regression multivariate analysis revealed that Sox11 was an independent predictor of RFS when controlling for grade and stage (Table 2). However, Sox11 was not an independent predictor of OS and this could be explained by the fact that all patients would have received similar adjuvant chemotherapy (platinum + taxol) only up until their first recurrence, but different regimens would have been used after this.

Sox11 plays an important role in embryogenesis and tissue remodeling, and consequently is present during gastrulation and early post-gastrulation development throughout the embryo.[23,24] Later during development, Sox11 is prominently expressed in the developing nervous system and at many sites throughout the embryo where epithelial-mesenchymal interactions occur.[23] At the sites of such epithelial-mesenchymal interactions, Sox11 can be found in the mesenchymal or epithelial compartment, and it has been postulated to be involved in inductive remodeling.[23] Sox11 expression in most tissues is transient and as a consequence, little Sox11

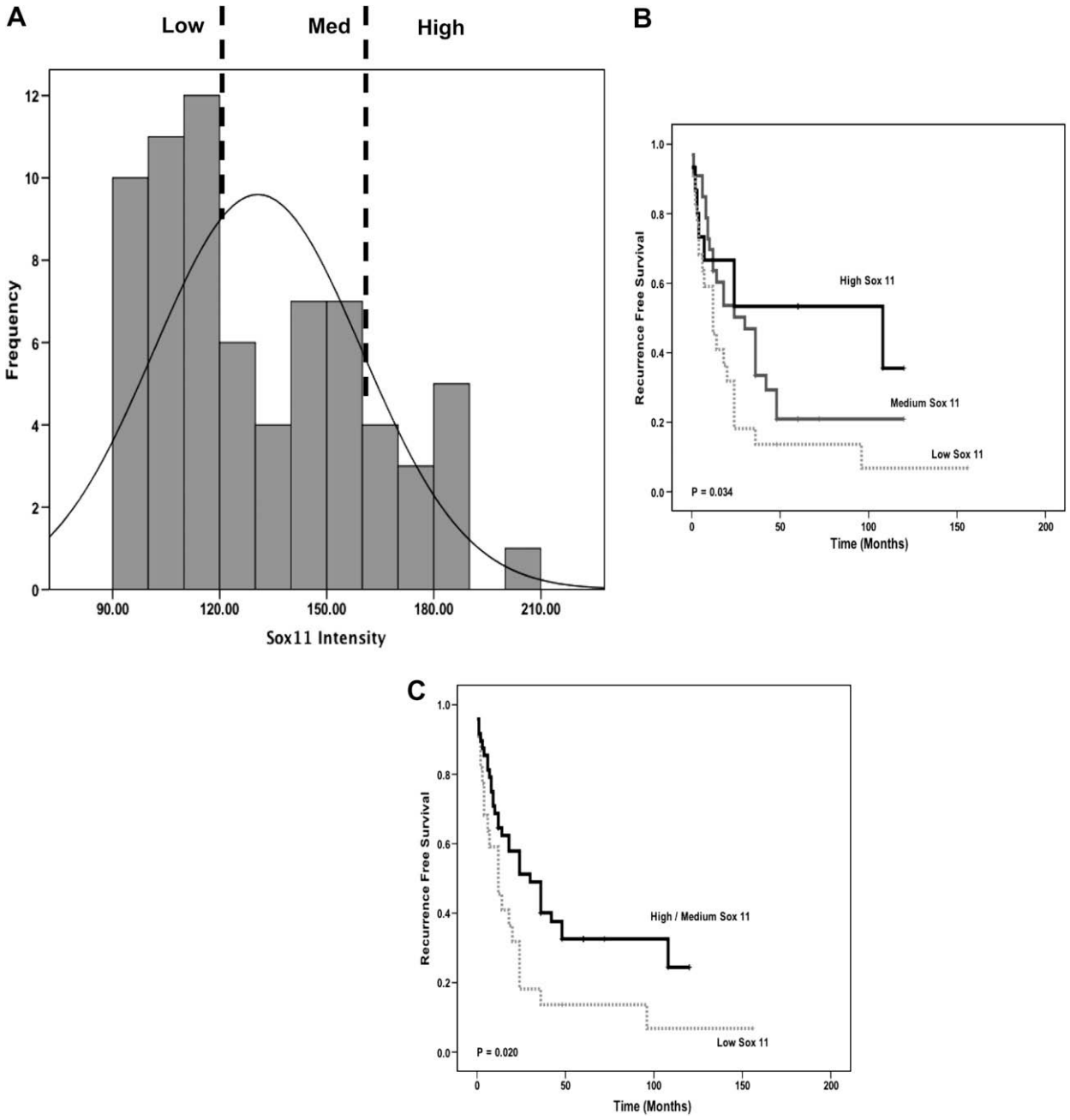

Fig. 3 – Sox11 protein expression and survival in ovarian cancer. Sox11 expression classified into low, medium and high levels based on the histogram (A). Kaplan Meier estimate of RFS based on the three Sox11 groups (B). Kaplan Meier estimate of RFS based on the comparison of high and medium levels of Sox11 to low levels (C).

Table 2 – Multivariate[a] Cox regression analysis of RFS and OS.

	Recurrence-free Survival			Overall survival		
	HR	95.0% CI	P value	HR	95.0% CI	P value
Sox11 (high/medium versus low)	0.56	0.319–0.997	0.049	0.65	0.339–1.24	0.19
Stage (continuous)	1.92	0.971–3.800	0.061	2.84	1.171–6.913	0.021
Grade (well and moderately differentiated versus poorly differentiated)	1.08	0.740–1.562	0.702	1.57	0.553–4.473	0.396

Abbreviations: HR = Hazard ratio, 95% CI = 95% Confidence intervals.
a Adjusted for all other variables in the table.

expression has been found in terminally differentiated adult tissues, in contrast to its widespread expression during embryogenesis.[24] Our findings complement these data, whereby Sox11 expression was absent in normal tissue.

The role played by Sox11 in tumourogenesis remains poorly understood. As mentioned previously, a marked upregulation of Sox11 mRNA was evident in a variety of different tumour types. The exact functional role of Sox11 in adult tissues is not fully understood, although the Sox proteins appear to play a dual role: (i) DNA-binding and (ii) transcriptional partner selection, which may permit selective recruitment of individual Sox proteins to specific genes.[16] Whilst a number of studies have described Sox11 expression in gliomas,[20] neuroblastomas,[19] and MCL,[16] its functional role in these tumours is poorly understood. In fact, although functional studies have shown that Sox11 can influence the expression of pro-and anti-apoptotic genes,[25] this is the first study to show that Sox11 is a prognostic antigen in any cancer entity.

Our finding that the loss of expression of Sox11 protein is associated with a more aggressive phenotype is consistent with the previous findings regarding Sox4, which is highly homologous to Sox11, and its expression in bladder cancer.[21] IHC-based analysis of Sox4 in bladder cancer revealed that increased levels of Sox4 protein were associated with an increased disease-specific survival.[21] It is possible to hypothesise that Sox11 expression in EOC may lead to aberrant regulation of genes associated with cell survival/death, promoting a pro-apoptotic, less aggressive phenotype.

In summary, we believe that this is the first description of the differential expression of Sox11 in EOC and the first identification of Sox11 as prognostic antigen. Our findings suggest that Sox11 is an independent predictor of improved RFS in EOC, and present studies focus on its exact functional role in EOC. In particular, the identification of Sox11 regulated genes in EOC may allow for the discovery of new therapeutic targets.

5. Conflict of interest statement

None declared.

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