Research Article

Ceren Sucularli*

Computational assessment of SKA1 as a potential cancer biomarker

SKA1'in potansiyel bir kanser biyobelirteci olarak bilgisayımsal değerlendirilmesi

https://doi.org/10.1515/tjb-2019-0148
Received April 9, 2019; accepted June 17, 2019; previously published online August 30, 2019

Abstract

Background: Spindle and kinetochore associated complex subunit 1 (SKA1) is an essential component of SKA complex, which is required for the proper formation of kinetochore–microtubule attachment and timely mitotic progression. The aim of this study is to perform detailed analyses of SKA1 genomic and expression alterations in cancers and to assess SKA1 as a biomarker for predicting human cancers and patient prognosis.
Materials and methods: Missense mutations from human cancers were extracted, deleterious missense mutations were predicted and shown on 3D SKA1 protein. SKA1 expression and the effect of SKA1 expression on patient survival were investigated in human cancers.
Results and discussion: Most of the predicted deleterious mutations were detected on microtubule-binding domain of SKA1, suggesting mutations on microtubule-binding domain might be more relevant in human cancers. High SKA1 expression was detected in various cancers. In addition, patients with high SKA1 expression showed poor overall survival compared to patients with low SKA1 expression in breast, lung and gastric cancers.
Conclusion: These results suggest that high SKA1 expression might be a prognostic and predictive biomarker for several cancers and mainly mutations in the microtubule-binding domain of SKA1 might have a deleterious effect for SKA1.

Keywords: Mitosis; Missense mutation; Prediction; Gene expression; Patient survival.

Öz

Amaç: Spindle and kinetochore associated complex subunit 1 (SKA1), kinetochore-microtubule bağlantısının ve zamanlı mitotik ilerlemenin doğru oluşumu için gerekli olan SKA kompleksinin önemli bir bileşenidir. Bu çalışmanın amacı, kanserlerde SKA1'in genomik ve ekspresyon değişikliklerinin ayrıntılı analizlerini yapmak ve SKA1'i insan kanserlerini ve hasta prognozunu tahmin etmek için bir biyobelirteç olarak değerlendirmektir.
Gereç ve Yöntemler: İnsan kanserlerine ait yanlış anlamlı mutasyonlar çıkarıldı, patojenik yanlış anlamlı mutasyonlar tahmin edildi ve 3D SKA1 proteini üzerinde gösterildi. İnsan kanserlerinde SKA1 ekspresyonu ve bunun hastanın sağkalımı üzerindeki etkisi araştırıldı.
Bulgular ve Tartışma: Patojenik olduğu tahmin edilen mutasyonların çoğunun, SKA1'in mikrotübül bağlama bölgesi üzerinde tespit edilmesi bu bölgenin insan kanserlerinde daha önemli olabileceğini gösteriyor olabilir. Çeşitli kanserlerde yüksek SKA1 ekspresyonu tespit edildi. Ek olarak, yüksek SKA1 ekspresyonu olan hastalar, meme, akciğer ve mide kanserlerinde düşük SKA1 ekspresyonu olan hastalara kıyasla düşük genel sağkalım gösterdi.
Sonuç: Bu sonuçlar, yüksek SKA1 ekspresyonun çok sayıda kanser için prognostik ve tahmin edici bir biyobelirteç olabileceğini ve çoğunlukla SKA1'in mikrotübül bağlama bölgesindeki mutasyonların SKA1 için patojenik özellikte olabileceğini göstermiştir.

Anahtar kelimeler: Mitoz; Yanlış anlamlı mutasyon; Tahmin; Gen ekspresyonu; Hasta sağkalımı.

***Corresponding author: Ceren Sucularli,** Department of Bioinformatics, Institute of Health Sciences, Hacettepe University, Ankara 06100, Turkey, Phone: +90312 3053038, Fax: +90312 3051459, e-mail: ceren.sucularli@hacettepe.edu.tr.
https://orcid.org/0000-0003-0627-7900

Introduction

Mitosis, which is a critical process in cell cycle, includes separation of replicated chromosomes into daughter cells.

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

Proper spindle formation, depolymerization and connection of chromosomes to spindle microtubules are crucial for chromosome segregation in mitosis [1]. Mutations and aberrant expression of proteins, which function in microtubule dynamics and stability, have been associated with tumorigenesis, metastasis and response of cells to chemotherapeutic agents [2, 3]. In addition, some of those proteins and several centromere and kinetochore proteins have been proposed as markers for different cancers [4]. Involvement and prognostic value of these proteins in various cancers emphasize the importance of exploring additional proteins, which function in similar mechanisms, as cancer markers.

Chromosome segregation during cell division is achieved by the proper attachment of kinetochores, protein complexes on centromeres of the chromosomes to spindle microtubules [5, 6]. During microtubule polymerization and depolymerization at mitosis, kinetochores stay attached to microtubules and chromosomes are pulled apart from the kinetochore regions [1, 7]. In addition kinetochores regulate the order of mitotic events [7].

In humans, SKA complex, which consists of SKA1 (also known as C18orf24), SKA2 (also known as FAM33A) and SKA3 (also known as RAMA1 and C13orf3), is essential for the formation of proper kinetochore–microtubule attachment and timely mitotic progression [8, 9]. The microtubule binding activity of SKA1 is required for the interaction of kinetochores and microtubules, and kinetochore movement [10]. Depletion of SKA1 protein or inhibition of SKA1 microtubule binding activity causes a mitotic delay in human cells [9, 10].

In different cancers, SKA1 expression has been shown to affect cell proliferation, cell invasion, apoptosis and cell cycle progression of cancer cells [11–15]. In addition to cell proliferation and invasion, association of SKA1 expression with metastasis and cancer progression has also been reported in non-small cell lung carcinoma cells [15].

Here, the occurrence of SKA1 mutations, CNVs and aberrant expression, as upregulation or downregulation, have been shown in several cancers and the possibility of SKA1 as a biomarker for predicting patient prognosis has been investigated by using bioinformatics approaches. Furthermore, in order to detect the deleterious mutations for SKA1 protein function and structure, missense mutations were selected and deleterious mutations have been predicted by using *in silico* prediction methods. The localization of amino acids, which carry the predicted deleterious mutations, was shown on 3D SKA1 structure.

Materials and methods

Extraction of mutations and CNVs from Catalogue of Somatic Mutations in Cancer (COSMIC) database

Mutation and CNV data for *SKA1* gene were downloaded from the COSMIC v82 (http://cancer.sanger.ac.uk/cosmic, [16]) database. COSMIC database provides information for coding and non-coding mutations, gene fusions, genome re-arrangements and CNVs in over a million tumor samples [16]. Missense mutations were selected from COSMIC database to investigate the effect of those mutations on SKA1 protein.

In silico evaluation of SKA1 missense mutations

The possible effect of missense mutations on SKA1 protein structure and function was assessed by using PredictSNP1.0 (http://loschmidt.chemi.muni.cz/predictsnp1/, [17]). For prediction analysis, human protein sequence of SKA1 (NP_659497.1) and missense mutation data, obtained from COSMIC v82 [16], were submitted to PredictSNP1.0 [17], and integrated tools were selected. PredictSNP1.0 is a consensus classifier, which combines the predictions of integrated tools. The consensus PredictSNP prediction and individual tool predictions for the effect of mutations were classified as neutral or deleterious and were provided with consensus and individual expected accuracies by PredictSNP1.0 [17].

Localization of predicted deleterious mutations on 3D SKA1 structure

To create the protein model of SKA1, the crystal structure of the Ska core complex, 4AJ5 [5] containing the coiled coiled region of SKA1, and crystal structure of Microtubule Binding Domain of SKA1, 4C9Y [1], were downloaded from the Protein Data Bank (www.rcsb.org, [18]). Protein models and mutations were visualized by using UCSF Chimera (https://www.cgl.ucsf.edu/chimera/, [19]).

Gene expression analysis in cancer datasets

SKA1 expression in different cancers was investigated by using Oncomine 4.5 Research Edition (http://www.

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

oncomine.org, [20, 21]). The threshold values to obtain SKA1 expression in cancers were selected as follows: p-value: 1E-5; fold change (FC): 2; gene rank: 10% and data type: mRNA. Cancers, which have significantly altered SKA1 expression, were further analyzed with Cancer vs. Normal Analysis. The p-value, FC and datasets with references [22–33] were reported.

Patient survival analysis

The effect of SKA1 expression on cancer patient survival was assessed with the Kaplan-Meier plotter tool (http://kmplot.com/analysis/index.php, [34–37]). Kaplan-Meier plotter provides mRNA gene chip data of breast, ovarian, lung and gastric cancer patients to assess cancer biomarkers. Patient cohorts, which had been divided into two groups based on quantile expressions, were compared by using Kaplan-Meier survival plot and hazard ratio with 95% confidence intervals and log rank p-value were calculated and provided with a survival curve. The log rank p-value <0.05 was used as significance threshold. According to selected cancer type, two groups were compared based on relapse free survival, overall survival, distant metastasis free survival, post progression survival, progression free survival and first progression (http://kmplot.com/analysis/index.php, [34–37]).

Results

SKA1 mutations and CNVs in human cancers

The occurrence of *SKA1* mutations and CNVs in human cancers were evaluated using COSMIC v82 [16]. According to COSMIC database search, *SKA1* had 47 mutations that were observed in different cancers. Of the 47 mutations, 32 mutations were missense mutations, which cause an amino acid change in the protein, and four mutations were nonsense mutations, which result in a premature stop codon. The remaining 10 mutations were coding silent substitutions and did not alter the amino acid sequence and the effect of one mutation was unknown on the amino acid level. There were no samples with inframe or frameshift insertions or deletions according to COSMIC v82.

The CNVs in *SKA1* were determined for high value (numeric) copy number data. The copy number segments were omitted if the total copy number and minor allele values were unknown. Sixteen copy number gains were detected in 15 cancer samples, while 58 cancer samples had copy number losses. When SKA1 expression was searched in the samples with copy number alterations, SKA1 overexpression was detected in nine samples with 10 copy number gains. Among the 58 samples, which had SKA1 copy number losses, two samples were reported to have SKA1 under-expression. As for the remaining samples, with copy number gains and losses, either they had normal expression or the expression status was not reported in COSMIC v82 database.

The effect of missense mutations on SKA1 protein

The effect of 32 missense mutations on SKA1 protein was assessed by using PredictSNP1.0, which classifies the effect of missense mutations as neutral or deleterious. Among the 32 missense mutations, 15 mutations were predicted as deleterious by PredictSNP1.0 (Table 1).

The localization of 15 missense mutations, which were predicted as deleterious by PredictSNP, was then investigated on the crystal structure of SKA1, which is a 255 amino acid protein. While, the N terminal region of SKA1 (residues 1–130), which includes coiled-coil region, is sufficient for the formation of SKA complex and to interact with SKA2 and SKA3 [8], the C terminal region of SKA1 (residues 133–255) is the main microtubule-binding region for the SKA complex [1]. Of the 32 missense mutations, which were given to PredictSNP, 12 missense mutations were scattered between 1 and 130 amino acids and 20 missense mutations were between residues 133–255. After

Table 1: The prediction and expected accuracy results of 15 missense SKA1 mutations predicted as deleterious by PredictSNP.

AA Mutation	PredictSNP	
p.R27I	Deleterious	0.61
p.L70F	Deleterious	0.61
p.D83Y	Deleterious	0.65
p.E144G	Deleterious	0.76
p.F145L	Deleterious	0.51
p.P149L	Deleterious	0.87
p.S185Y	Deleterious	0.72
p.S188C	Deleterious	0.55
p.S188F	Deleterious	0.61
p.S188Y	Deleterious	0.61
p.R208C	Deleterious	0.65
p.R239W	Deleterious	0.76
p.R245Q	Deleterious	0.79
p.G246E	Deleterious	0.87
p.R251C	Deleterious	0.87

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

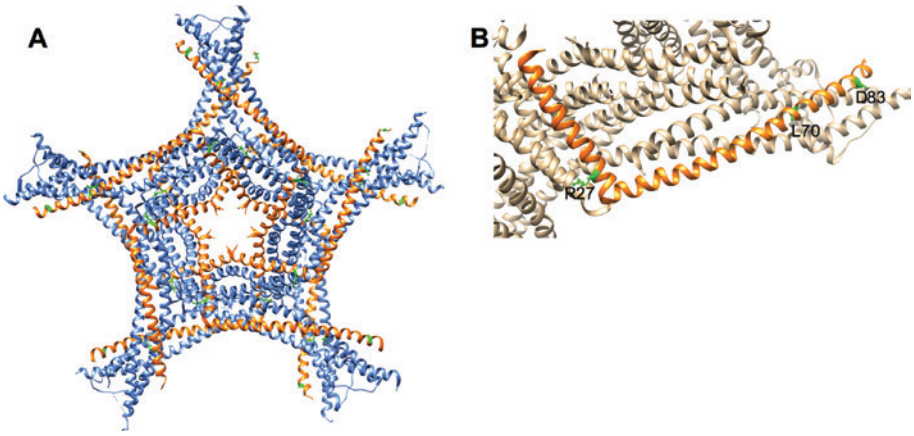


Figure 1: Localization of 3 predicted deleterious mutations on N terminal region of SKA1.
(A) Ten copies of $SKA1_{1-91}$, full length SKA2 and $SKA3_{1-101}$ form an oligomeric assembly (PDB: 4AJ5, [5]). The N terminal SKA1 chains and the three residues, which carry predicted deleterious mutations (ball and stick presentation), were displayed on SKA core complex.
(B) The three predicted deleterious mutations (ball and stick presentation) were shown on the SKA1 chain

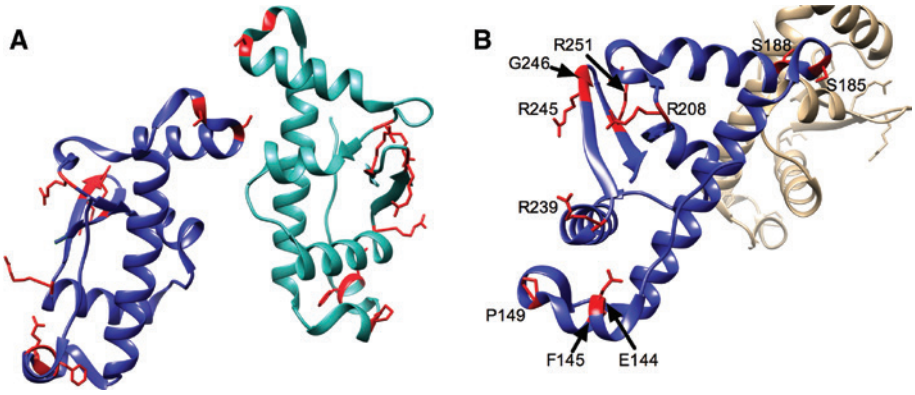


Figure 2: Localization of 12 predicted deleterious mutations on microtubule-binding region of SKA1.
(A) The residues, which carry predicted deleterious mutations (stick presentation) were shown on the chain A (right) and B (left) on the 3D model of microtubule binding domain of SKA1 (PDB: 4C9Y, [1]). (B) The mutated residues were shown in stick presentation on chain B.

prediction of deleterious mutations, only three mutations; R27I, L70F and D83Y, in the N terminal region were predicted as deleterious (Figure 1A, B), while 12 of the deleterious mutations were located in the microtubule-binding region of SKA1 (Figure 2A, B).

SKA1 expression in cancers

The mRNA expression alterations of SKA1 were investigated in several cancer types with cancer vs. normal analyses by using Oncomine 4.5 Research Edition. SKA1 expression was found to be significantly higher in 20 analyses, while it was significantly lower only in two analyses in cancers when compared to normal tissues (Table 2).

Accordingly, SKA1 was overexpressed in different types or subtypes of cancers including lung, liver, colorectal, gastric, kidney and breast cancers (Table 2). Only in two analyses, one from breast cancer and one from brain and CNS cancer, SKA1 expression has been detected to be significantly under-expressed (Table 2).

Survival analysis in cancer patients

SKA1 is represented with a single probe id, which is 217640_x_at, in the Kaplan-Meier plotter mRNA gene chip section (on the date of April 2019). According to Kaplan-Meier plotter analysis, breast, lung and gastric cancer patients with high SKA1 expression showed poor overall survival compared to patients with low SKA1 expression, while SKA1 expression showed no association with overall survival of ovarian cancer patients (Figure 3 and Table 3). The results also showed that high expression of SKA1 was

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

Table 2: SKA1 mRNA expression in different cancers.

Type	p-Value	FC	Dataset, [Reference]
Over-expression			
Gastric Cancer			
Gastric Intestinal Type Adenocarcinoma vs. Normal	2.71E-7	3.095	DErrico Gastric, [25]
Lung Cancer			
Lung Adenocarcinoma vs. Normal	8.50E-9	2.379	Garber Lung, [27]
Squamous Cell Lung Carcinoma vs. Normal	2.00E-6	3.162	Garber Lung, [27]
Large Cell Lung Carcinoma vs. Normal	1.05E-6	2.427	Hou Lung, [28]
Kidney Cancer			
Chromophobe Renal Cell Carcinoma vs. Normal	4.83E-11	3.921	Jones Renal, [29]
Papillary Renal Cell Carcinoma vs. Normal	1.78E-18	10.491	Jones Renal, [29]
Renal Pelvis Urothelial Carcinoma vs. Normal	5.73E-17	10.380	Jones Renal, [29]
Breast Cancer			
Invasive Ductal Breast Carcinoma vs. Normal	3.48E-6	7.501	Turashvili Breast, [33]
Ductal Breast Carcinoma vs. Normal	2.43E-7	2.431	Richardson Breast 2, [31]
Invasive Breast Carcinoma vs. Normal	1.18E-23	3.770	TCGA Breast, [23]
Invasive Ductal Breast Carcinoma vs. Normal	4.31E-40	4.441	TCGA Breast, [23]
Invasive Lobular Breast Carcinoma vs. Normal	3.72E-12	2.456	TCGA Breast, [23]
Male Breast Carcinoma vs. Normal	5.77E-6	2.118	TCGA Breast, [23]
Colorectal Cancer			
Colon Adenoma vs. Normal	1.92E-11	3.204	Sabates-Bellver Colon, [32]
Cecum Adenocarcinoma vs. Normal	2.24E-10	2.340	TCGA Colorectal, [22]
Colon Adenocarcinoma vs. Normal	1.45E-12	2.161	TCGA Colorectal, [22]
Colon Mucinous Adenocarcinoma vs. Normal	2.32E-11	2.463	TCGA Colorectal, [22]
Rectal Adenocarcinoma vs. Normal	3.26E-12	2.107	TCGA Colorectal, [22]
Rectal Mucinous Adenocarcinoma vs. Normal	1.13E-12	2.500	TCGA Colorectal, [22]
Liver Cancer			
Hepatocellular Carcinoma vs. Normal	1.85E-12	2.534	Chen Liver, [24]
Under-expression			
Breast Cancer			
Invasive Breast Carcinoma Stroma vs. Normal	4.69E-23	−7.644	Finak Breast, [26]
Brain and CNS Cancer			
Glioblastoma vs. Normal	1.45E-8	−8.707	Lee Brain, [30]

Oncomine 4.5 Research Edition [20, 21], thresholds: p-value: 1E-5; fold change (FC): 2; gene rank: 10% and data type: mRNA, Cancer vs. Normal Analysis.

significantly associated with a relapse free survival (RFS), distant metastasis free survival (DMFS) and post progression survival (PPS) in breast cancer patients (Table 3). High SKA1 expression also significantly associated with PPS and first progression (FP) in lung cancer patients and with FP in gastric cancer patients (Table 3).

Discussion

SKA1, as an essential member of SKA complex, is an important part of cell division, carries the major microtubule binding part of the SKA complex and is required for proper function of the complex [1]. SKA1 is critical for the formation of the robust interactions between kinetochores and microtubules, proper kinetochore movement and proper mitotic progression [1, 9, 10]. In addition to SKA2 and SKA3, SKA1 interacts with other proteins, such as PP1 [7], Aurora B and Hec1 [38]. As a necessary part of mitosis, SKA1 expression affects cell proliferation, apoptosis and cell cycle progression of cancer cells [11–14], which highlights the potential of SKA1 as a biomarker for human cancers. From this point of view, in this study genomic and trancriptomic alterations of SKA1 have been investigated in a wide range of cancers. Genomic alterations, particularly missense mutations, which cause production of an altered amino acid in the protein, were selected and

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

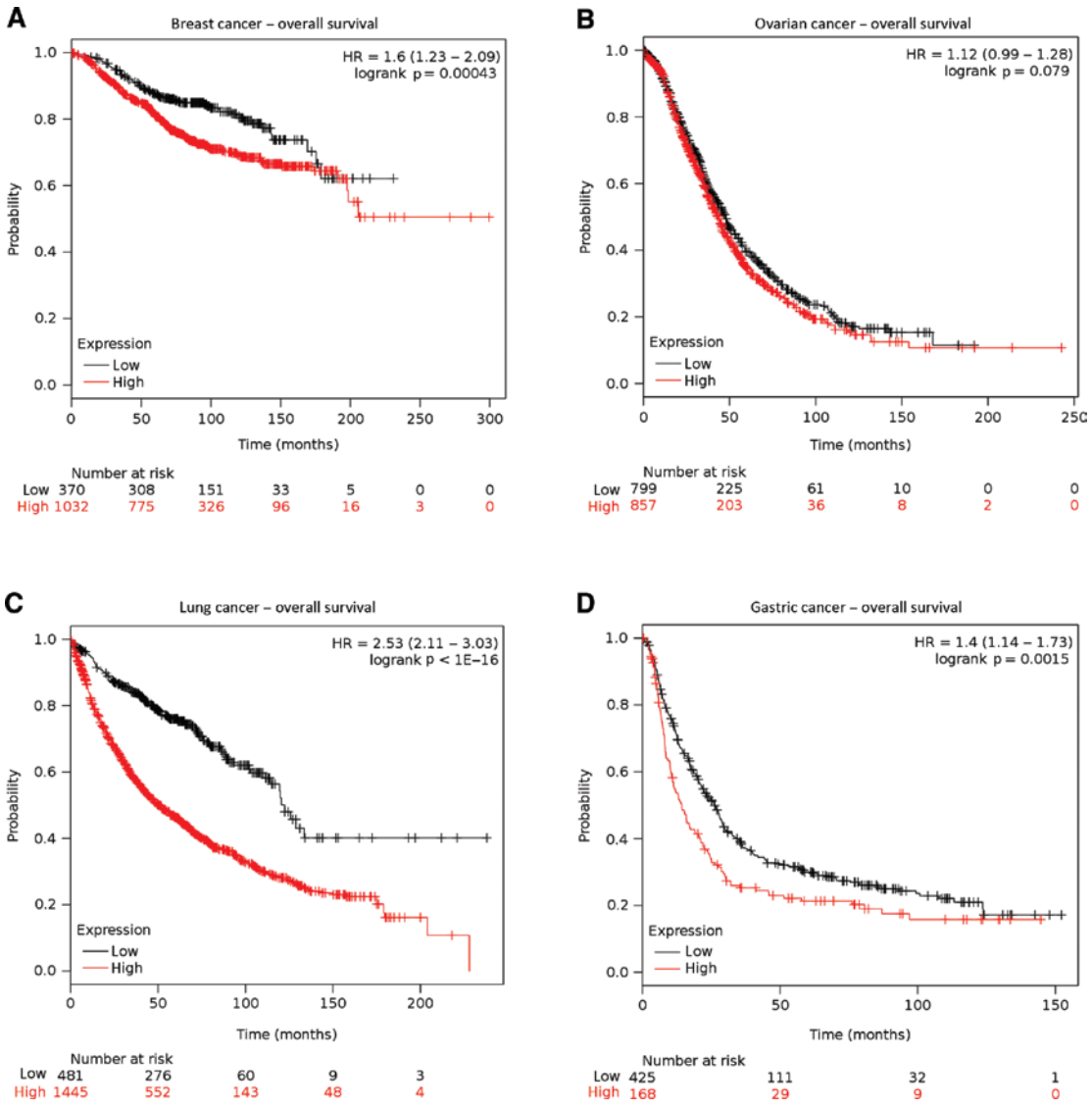


Figure 3: Correlation of SKA1 expression with overall survival.
Kaplan-Meier survival plots showing overall survival in (A) breast, (B) ovarian, (C) lung and (D) gastric cancers.

Table 3: Correlation of SKA1 with survival outcomes in cancer patients.

Cancer Type	Survival outcome	Number of patients	Cutoff value	HR	95% CI	Log rank p-value
Breast Cancer	OS	1402	42	1.6	1.23–2.09	[a]4.3E-04
	RFS	3951	50	1.53	1.36–1.72	[a]5.5E-13
	DMFS	1746	48	1.79	1.43–2.23	[a]2.2E-07
	PPS	414	44	1.42	1.06–1.91	[a]1.9E-02
Ovarian Cancer	PFS	1435	94	1.08	0.95–1.23	2.4E-01
	OS	1656	74	1.12	0.99–1.28	7.9E-02
	PPS	782	59	1.19	0.99–1.43	6.1E-02
Lung Cancer	FP	982	44	2.08	1.7–2.53	[a]1.4E-13
	OS	1926	31	2.53	2.11–3.03	[a]<1E-16
	PPS	344	43	1.81	1.38–2.37	[a]1.1E-05
Gastric Cancer	FP	359	106	1.67	1.31–2.14	[a]3.6E-05
	OS	593	116	1.4	1.14–1.73	[a]1.5E-03

HR, hazard ratio; CI, confidence interval; OS, overall survival; RFS, relapse free survival; DMFS, distant metastasis free survival; PPS, post progression survival; PFS, progression-free survival; FP, first progression. [a]$p < 0.05$.

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

the deleterious missense mutations for SKA1 structure and function were predicted. The prognostic and predictive potential of SKA1 expression have been searched in different cancer types and subtypes.

Missense mutations are particularly important in cancer research, since missense mutations may alter the physicochemical properties of amino acids or protein-protein interactions [39]. Therefore, it is important to evaluate the effect of missense mutations on protein structure and function, and to define the pathogenicity of missense mutations. In this study, the effect of 32 missense mutations on SKA1 structure and function was assessed and of the 32 mutations, 15 missense mutations were identified as deleterious (Table 1). Localization of predicted mutations were searched on protein structure, since pathogenic missense mutations may accumulate in certain critical sites of proteins. Accordingly, most of the deleterious mutations were located in the microtubule-binding region (Figure 2) and only three mutations were located in the N terminal region, including coiled-coiled region of SKA1 (Figure 1). The N terminal region of human SKA1 (residues 1–130) functions in the formation of SKA complex [8]. One of the three mutations, R27I, which were predicted as deleterious in this study, lied in region of SKA1 that forms the short bundle, while L70F and D83Y located in region that forms the long bundle of SKA complex (Figure 1B). The short and long bundles consist of three parallel helices of SKA1, SKA2 and SKA3. R27 is particularly important for short bundle, since it is one of the interaction sites, which stabilize the coiled-coil structure of the SKA complex [5]. Therefore, mutation on this site might affect the interaction of SKA1 with the complex.

The C terminal region of the SKA1 provides the main microtubule binding properties of SKA complex [5, 10]. The region including amino acids 133–255 is the microtubule-binding site (MTBD) of the SKA1 and the principal microtubule-binding component of the SKA complex; in addition, deletion of the C terminal region of SKA1 (residues 92–255) completely eliminates the microtubule binding activity of the complex [1, 5]. In this study, most of the predicted deleterious mutations were found to be located in MTBD of SKA1 (Figure 2). Therefore, 12 missense mutations in this region might be more relevant in cancer formation or progression. One critical site might be S185, one of the conserved Aurora B phosphorylation sites. Aurora B negatively regulates SKA complex localization at kinetochores [38]. According to results presented here S185Y has been predicted as deleterious (Table 1). Particularly, another mutation in R245 to R245A (arginine to alanine), one of the residues predicted to have a deleterious mutation in this study, has previously been reported to be critical for microtubule binding; this mutation abolished microtubule-binding activity and caused a mitotic delay in human cells [1, 10]. However, prediction results presented here proposed that the mutation of arginine to glutamine on this site (R245Q) was also deleterious (Table 1).

Previously, it has been suggested that over expression of SKA1 is more relevant with the oncogenic function of SKA1, since SKA1 genomic alterations observed at low frequency in cancers [40]. From this point of view, the expression level of SKA1 mRNA has been investigated in cancers. According to Oncomine analysis results presented here, a significant increase in SKA1 mRNA expression has been observed in datasets from several cancers (Table 2). Increased expression of SKA1 in has been shown in cancers, such as gastric cancer [12], hepatocellular carcinoma [11] and non-small cell lung carcinoma [15]. Accordingly, different types of kidney, colorectal, breast and lung cancers showed high expression of SKA1 (Table 2). However, in two datasets, Finak Breast [26] and Lee Brain [30], SKA1 expression has been found to be decreased. The high SKA1 expression has been observed in datasets of invasive ductal and lobular carcinomas (Table 2), while SKA1 expression was lower in breast tumor stroma (Table 2). Therefore, the expression difference of SKA1 in breast cancer datasets may be related with the breast part of the carcinoma.

High SKA1 expression may contribute to cell proliferation and invasion of cancer cells, since the knock down of SKA1 expression resulted in cell cycle arrest and a significant decrease in cell proliferation in different cancers [11–14]. In addition to cell proliferation and invasion, SKA1 expression also affected metastasis in non-small cell lung carcinoma cells [15]. SKA 1 expression may also be required for cell survival, since SKA1 inhibition caused apoptosis in human oral adenosquamous carcinoma cell line [14] and hepatocellular carcinoma cells [11].

In this study, high expression of SKA1 has been shown to be significantly associated with overall survival, RFS, DMFS and PPS in breast cancer patients (Figure 3 and Table 3), with overall survival, FP and PPS in lung cancer patients and with overall survival and FP in gastric cancer patients (Figure 3 and Table 3). SKA1 expression did not show any significant correlation with survival of ovarian cancer patients (Figure 3 and Table 3). Consistently, altered SKA1 expression has not been detected in ovarian cancer datasets in Oncomine analysis. The findings suggest that high SKA1 expression might be a prognostic marker for breast, lung and gastric cancers.

In conclusion, mutations in the microtubule-binding domain of SKA1 might be particularly important for cancer

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

research, since most of the predicted deleterious mutations scattered in this region. High SKA1 expression has been observed in several cancers and correlated with poor overall survival rate in breast, lung and gastric cancers. Therefore SKA1 might be predictive and prognostic marker for those cancers. However, it must be noted that further follow up experimental studies, such as sequencing for mutations and RT-qPCR for gene expression, are needed to test the potential of SKA1 as biomarker in cancers.

Acknowledgement: The author is grateful to Hacettepe University, Institute of Health Sciences and Department of Bioinformatics for providing facilities for this study.

Conflict of interest: There is no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Abad MA, Medina B, Santamaria A, Zou J, Plasberg-Hill C, Madhumalar A, et al. Structural basis for microtubule recognition by the human kinetochore Ska complex. Nat Commun 2014;5:2964.
2. Bhat KM, Setaluri V. Microtubule-associated proteins as targets in cancer chemotherapy. Clin Cancer Res 2007;13:2849–54.
3. Tala, Xie S, Sun X, Sun X, Ran J, Zhang L, et al. Microtubule-associated protein Mdp3 promotes breast cancer growth and metastasis. Theranostics 2014;4:1052–61.
4. Zhang W, Mao JH, Zhu W, Jain AK, Liu K, Brown JB, et al. Centromere and kinetochore gene misexpression predicts cancer patient survival and response to radiotherapy and chemotherapy. Nat Commun 2016;7:12619.
5. Jeyaprakash AA, Santamaria A, Jayachandran U, Chan YW, Benda C, Nigg EA, et al. Structural and functional organization of the Ska complex, a key component of the kinetochore-microtubule interface. Mol Cell 2012;46:274–86.
6. Walczak CE, Cai S, Khodjakov A. Mechanisms of chromosome behaviour during mitosis. Nat Rev Mol Cell Biol 2010;11:91–102.
7. Sivakumar S, Janczyk PL, Qu Q, Brautigam CA, Stukenberg PT, Yu H, et al. The human SKA complex drives the metaphase-anaphase cell cycle transition by recruiting protein phosphatase 1 to kinetochores. Elife 2016;5:e12902.
8. Gaitanos TN, Santamaria A, Jeyaprakash AA, Wang B, Conti E, Nigg EA. Stable kinetochore-microtubule interactions depend on the Ska complex and its new component Ska3/C13Orf3. EMBO J 2009;28:1442–52.
9. Hanisch A, Sillje HH, Nigg EA. Timely anaphase onset requires a novel spindle and kinetochore complex comprising Ska1 and Ska2. EMBO J 2006;25:5504–15.
10. Schmidt JC, Arthanari H, Boeszoermenyi A, Dashkevich NM, Wilson-Kubalek EM, Monnier N, et al. The kinetochore-bound Ska1 complex tracks depolymerizing microtubules and binds to curved protofilaments. Dev Cell 2012;23:968–80.
11. Qin X, Yuan B, Xu X, Huang H, Liu Y. Effects of short interfering RNA-mediated gene silencing of SKA1 on proliferation of hepatocellular carcinoma cells. Scand J Gastroenterol 2013;48:1324–32.
12. Sun W, Yao L, Jiang B, Guo L, Wang Q. Spindle and kinetochore-associated protein 1 is overexpressed in gastric cancer and modulates cell growth. Mol Cell Biochem 2014;391:167–74.
13. Tian F, Xing X, Xu F, Cheng W, Zhang Z, Gao J, et al. Downregulation of SKA1 gene expression inhibits cell growth in human bladder cancer. Cancer Biother Radiopharm 2015;30:271–7.
14. Zhang B, Li KY, Chen HY, Pan SD, Jiang LC, Wu YP, et al. Spindle and kinetochore associated complex subunit 1 regulates the proliferation of oral adenosquamous carcinoma CAL-27 cells in vitro. Cancer Cell Int 2013;13:83.
15. Shen L, Yang M, Lin Q, Zhang Z, Miao C, Zhu B. SKA1 regulates the metastasis and cisplatin resistance of non-small cell lung cancer. Oncol Rep 2016;35:2561–8.
16. Forbes SA, Beare D, Boutselakis H, Bamford S, Bindal N, Tate J, et al. COSMIC: somatic cancer genetics at high-resolution. Nucleic Acids Res 2017;45:D777–83.
17. Bendl J, Stourac J, Salanda O, Pavelka A, Wieben ED, Zendulka J, et al. PredictSNP: robust and accurate consensus classifier for prediction of disease-related mutations. PLoS Comput Biol 2014;10:e1003440.
18. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The protein data bank. Nucleic Acids Res 2000;28:235–42.
19. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera – a visualization system for exploratory research and analysis. J Comput Chem 2004;25:1605–12.
20. Rhodes DR, Kalyana-Sundaram S, Mahavisno V, Varambally R, Yu J, Briggs BB, et al. Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles. Neoplasia 2007;9:166–80.
21. Rhodes DR, Yu J, Shanker K, Deshpande N, Varambally R, Ghosh D, et al. ONCOMINE: a cancer microarray database and integrated data-mining platform. Neoplasia 2004;6:1–6.
22. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330–7.
23. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.
24. Chen X, Cheung ST, So S, Fan ST, Barry C, Higgins J, et al. Gene expression patterns in human liver cancers. Mol Biol Cell 2002;13:1929–39.
25. D'Errico M, de Rinaldis E, Blasi MF, Viti V, Falchetti M, Calcagnile A, et al. Genome-wide expression profile of sporadic gastric cancers with microsatellite instability. Eur J Cancer 2009;45:461–9.
26. Finak G, Bertos N, Pepin F, Sadekova S, Souleimanova M, Zhao H, et al. Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 2008;14:518–27.
27. Garber ME, Troyanskaya OG, Schluens K, Petersen S, Thaesler Z, Pacyna-Gengelbach M, et al. Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci USA 2001;98:13784–9.
28. Hou J, Aerts J, den Hamer B, van Ijcken W, den Bakker M, Riegman P, et al. Gene expression-based classification of non-small cell lung carcinomas and survival prediction. PLoS One 2010;5:e10312.

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM

29. Jones J, Otu H, Spentzos D, Kolia S, Inan M, Beecken WD, et al. Gene signatures of progression and metastasis in renal cell cancer. Clin Cancer Res 2005;11:5730–9.
30. Lee J, Kotliarova S, Kotliarov Y, Li A, Su Q, Donin NM, et al. Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. Cancer Cell 2006;9:391–403.
31. Richardson AL, Wang ZC, De Nicolo A, Lu X, Brown M, Miron A, et al. X chromosomal abnormalities in basal-like human breast cancer. Cancer Cell 2006;9:121–32.
32. Sabates-Bellver J, Van der Flier LG, de Palo M, Cattaneo E, Maake C, Rehrauer H, et al. Transcriptome profile of human colorectal adenomas. Mol Cancer Res 2007;5:1263–75.
33. Turashvili G, Bouchal J, Baumforth K, Wei W, Dziechciarkova M, Ehrmann J, et al. Novel markers for differentiation of lobular and ductal invasive breast carcinomas by laser microdissection and microarray analysis. BMC Cancer 2007;7:55.
34. Gyorffy B, Lanczky A, Eklund AC, Denkert C, Budczies J, Li Q, et al. An online survival analysis tool to rapidly assess the effect of 22,277 genes on breast cancer prognosis using microarray data of 1809 patients. Breast Cancer Res Treat 2010;123:725–31.
35. Gyorffy B, Lanczky A, Szallasi Z. Implementing an online tool for genome-wide validation of survival-associated biomarkers in ovarian-cancer using microarray data from 1287 patients. Endocr Relat Cancer 2012;19:197–208.
36. Gyorffy B, Surowiak P, Budczies J, Lanczky A. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small-cell lung cancer. PLoS One 2013;8:e82241.
37. Szasz AM, Lanczky A, Nagy A, Forster S, Hark K, Green JE, et al. Cross-validation of survival associated biomarkers in gastric cancer using transcriptomic data of 1,065 patients. Oncotarget 2016;7:49322–33.
38. Chan YW, Jeyaprakash AA, Nigg EA, Santamaria A. Aurora B controls kinetochore-microtubule attachments by inhibiting Ska complex-KMN network interaction. J Cell Biol 2012;196:563–71.
39. Nishi H, Tyagi M, Teng SL, Shoemaker BA, Hashimoto K, Alexov E, et al. Cancer missense mutations alter binding properties of proteins and their interaction networks. PLoS One 2013;8:e66273.
40. Li J, Xuan JW, Khatamianfar V, Valiyeva F, Moussa M, Sadek A, et al. SKA1 over-expression promotes centriole over-duplication, centrosome amplification and prostate tumourigenesis. J Pathol 2014;234:178–89.

Brought to you by | Turkish Biochemical Society (TBD)
Authenticated
Download Date | 12/7/19 1:55 PM