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Research article

Molecular profiling of nucleocytoplasmic transport factor genes in breast cancer

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ABSTRACT

Transport of functional molecules across the nuclear membrane of a eukaryotic cell is regulated by a dedicated set of transporter proteins that carry molecules into the nucleus or out of the nucleus to the cytoplasm for homeostasis of the cell. One of the categories of cargo molecules these transporters carry are the molecules for cell cycle regulation. Therefore, their role is critical in terms of cancer development. Any misregulation of the transport factors would means aberrant abundance of cell cycle regulators and might have consequences in cell cycle progression. While earlier studies have focussed on individual transport related molecules, a collective overview of how these molecules may be dysregulated in breast cancer is lacking.

Using genomic and transcriptomic datasets from TCGA (The Cancer Genome Atlas) and microarray platforms, we carried out bioinformatic analysis and provide a genetic and molecular profile of all the molecules directly related to nucleocytoplasmic shuttling of proteins and RNAs. Interestingly, we identified that many of these molecules are either mutated or have dysregulated expression in breast cancer. Strikingly, some of the molecules, namely, *KPNA2, KPNA3, KPNA5, IPO8, TNPO1, XPOT, XPO7 and CSE1L* were correlated with poor patient survival. This study provides a comprehensive genetic and molecular landscape of nucleocytoplasmic factors in breast cancer and points to the important roles of various nucleocytoplasmic factors in cancer progression. This data might have implications in prognosis and therapeutic targeting in breast cancer.

1. Introduction

One of the key attributes of eukaryotic cells is the existence of nuclear membrane that demarcates the nuclear and the cytoplasmic components from each other. While the existence of the nuclear membrane separates transcription and RNA processing from the cytoplasmic translation thus contributing significantly to the diversity of gene expression, it also necessitates the presence of a dedicated system for the localization of proteins in two compartments to maintain the unique composition of each [1]. This system consists of two sets of factors; one importing proteins into the nucleus after translation in the cytosol, and the other exporting RNAs and proteins from the nucleus to the cytosol [2]. A number of dedicated import/export receptor molecules are involved in these processes.

Import of protein cargoes into the nucleus involves either direct interaction of cargo with importin β, or via an adaptor molecule called importin α [3, 4]. Importin α binds an NLS (nuclear localization signal) and makes a trimeric complex with importin β that is targeted to the nuclear pore complexes (NPCs). After series of interactions with NPCs the complex is translocated to the nucleus [5, 6]. In the nucleus, due to an interaction of importin β1 (KPNB1) with RanGTP (RanGTP has higher concentration in the nucleus due to the action of RANGEF), the ternary complex is dissociated. The cargo is released to perform its function and the other transport factors are recycled for another transport cycle [7, 8]. The importin α (KPNAs) interacts with CAS for its export into the cytosol. The process of nuclear transport is complicated by the fact that there exist multiple importin α and beta family members [9, 10]. Interestingly, various specific cargo molecules have been documented for different family members of importin α and β, sometimes with mutual cross-talk [11]. The proteins molecules identified so far with nuclear import and export functions are Karyopherin α1 [12], Karyopherin α2 [13], Karyopherin α3 [14], Karyopherin α4 [15], Karyopherin α5 [16], Karyopherin α6 [16], Karyopherin α7 [17], Karyopherin β1 [18,19], Importin 4 [20], Importin 5 [21], Importin 7 [22], Importin 8 [22],

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Importin 9 [20], Importin 11 [23], Importin 13 [24], Transportin 1 [25], Transportin 2 [26], Transportin 3 [27], Exportin 1 [28,29], NXF1 [30,31] Exportin t [32, 33], Exportin 4 [34], Exportin 5 [35], Exportin 6 [36], Exportin 7 [37], and CAS [38]. This diversity within the transport system has been extensively investigated and it has been shown that multiple importin α proteins are capable of importing the same target cargoes; it is also known that different importin αs bind distinct cargoes by their respective NLSs supporting the notion that each importin α is uniquely a part of specific cellular pathways [9, 16, 39, 40, 41].

In addition to the well-known nuclear transport functions attributed to importin α and β, non-nuclear transport functions have been established for several of the factors that are traditionally associated with nuclear transport including functions associated with DNA repair, and Chromatin remodeling [42]. Moreover, their roles have been documented in various physiological processes, like differentiation [43, 44, 45], and pathological situations like cancer [46].

Nuclear transport receptors have also been associated with cell cycle regulation. The cell cycle associated functions may be either direct by interaction with chromatin and regulating the expression of genes related to cell cycle progression [47], by coordinating cell cycle events [48] or by regulating nucleocytoplasmic enrichment of cargo molecules implicated in cell cycle regulation [46]. The cargo molecules that are targeted by transport receptors with implications in cell cycle regulation include various tumor suppressors, oncogenes and chromatin remodeling factors among other important proteins. The nucleocytoplasmic shuttling of these molecules in a specific compartment by virtue of their NLSs and NESs (Nuclear Export Signals) maintains a sophisticated balance that, when perturbed, has ramifications in tumorigenesis. For instance, the nucleocytoplasmic shuttling, and thus activities, of P53 are regulated by importin α3 [49] and CRM1 [50,51]; the subcellular localization of BRCA2, an important tumor suppressor that directs RAD51 to ssDNA foci where they function in DNA repair, is regulated by CRM1 by binding to its NES [52]; Retinoblastoma (Rb) protein, a tumor suppressor known for its pivotal role cellular proliferation, is imported into the nucleus by importin α/β1 pathway [53]. Similarly, a battery of proteins that are critical regulators of cell cycle control is partly controlled by the nuclear transport machinery for their activities and any misregulation in subcellular localization may lead to proliferative defects in cells leading to transformation [54].

Based on critical roles of transport receptors in transporting cell cycle related cargoes, significance in mitosis regulation and chromatin remodeling, their pivotal roles in carcinogenesis has been suggested. Additionally, the roles of individual transporters in various cancers has been extensively studied. However, the comprehensive molecular analysis of nuclear transport encompassing all the transport receptors is lacking in the literature. We, therefore, carried out bioinformatic analysis to uncover the genetic and molecular profiles of all the nuclear transporters to unentangle the significance of the process of the nuclear transport in breast cancer. By using genomic and transcriptomic datasets, we identified nuclear transport receptors that undergo molecular aberrations. Furthermore, a subset of these proteins shows significance in breast cancer prognosis.

Table 1. Various import/export factors associated with nuclear transport mechanisms and genes encoding them.

Import/Export receptor	Gene name	Reference
KARYOPHERIN α1	*KPNA1*	Cortes et al., 1994 [12]
KARYOPHERIN α2	*KPNA2*	Weis et al., 1996 [13]
KARYOPHERIN α3	*KPNA3*	Takeda et al., 1997 [14]
KARYOPHERIN α4	*KPNA4*	Seki et al., 1997 [15]
KARYOPHERIN α5	*KPNA5*	Köhler et al., 1997 [16]
KARYOPHERIN α6	*KPNA6*	Köhler et al., 1999 [70]
KARYOPHERIN α7	*KPNA7*	Tejomurtula et al., 2009 [17]
KARYOPHERIN β1	*KPNB1*	Görlich et al., 1995 [19]
IMPORTIN 4	*IPO4*	Jäkel et al., 2002 [20]
IMPORTIN 5	*IPO5*	Yaseen and Blobel, 1997 [21]
IMPORTIN 7	*IPO7*	Görlich et al., 1997 [22]
IMPORTIN 8	*IPO8*	Görlich et al., 1997 [22]
IMPORTIN 9	*IPO9*	Jäkel et al., 2002 [20]
IMPORTIN 11	*IPO11*	Plafker and Macara, 2000 [23]
IMPORTIN 13	*IPO13*	Mingot et al., 2001 [24]
TRANSPORTIN 1	*TNPO1*	Pollard et al., 1996 [25]
TRANSPORTIN 2	*TNPO2*	Siomi et al., 1997 [26]
TRANSPORTIN 3	*TNPO3*	Lai et al., 2000 [27]
EXPORTIN 1	*XPO1*	Fornerod et al., 1997 [28]
NUCLEAR RNA EXPORT FACTOR 1	*NXF1*	Yoon et al., 1997 [30]
EXPORTIN T	*XPOT*	Kutay et al., 1998 [33]
EXPORTIN 4	*XPO4*	Lipowsky et al., 2000 [34]
EXPORTIN 5	*XPO5*	Brownawell and Macara, 2002 [35]
EXPORTIN 6	*XPO6*	Stüven et al., 2003 [36]
EXPORTIN 7	*XPO7*	Kutay et al., 2000 [37]
CAS	*CSE1L*	Brinkmann et al., 1995 [38]

2. Material and methods

2.1. Mutations detection

For mutations detection, we utilized TCGA (The Cancer Genome Atlas) data using cBioportal [55, 56]. Of the available datasets in cBioportal, we chose the latest TCGA Breast Invasive Carcinoma (Firehouse legacy). Out of 1108 patients in this category, 963 had both mutation and CNA (Copy number variation) data. Therefore, these 963 breast cancer patients' datasets were used for the detection of the following; 1) Mutation, 2) CAN (copy number variation).

2.2. Gene nomenclature

The genes and proteins for import/export receptors have adapted variety of names during the discoveries of individual molecules. In order to remain consistent with the nomenclature, all the gene names encoding proteins pertaining to nuclear import and export functions were obtained from HUGO gene nomenclature committee resource (https://www.genenames.org/). All the genes in the categories of importin, exportin, karyopherins were identified from this HUGO resource. The list of proteins encoded by respective genes are listed in Table 1.

2.3. Gene over/under expression compared with the normal tissue

TCGA data was used utilizing Xena [57] which incorporates data from GTEX for normal tissues and compares with breast cancer patients' datasets. Heat map was generated by incorporating the list of all the transport related genes along with TOP2A and CCND2 as control genes in Xena. After launching, the first variable phenotype “main category” was selected. In the second Genomic variable, Gene expression was selected, followed by incorporating the list of genes related to nuclear import/export. To generate heatmap pertaining to breast cancer TCGA GTEX datasets, the data was filtered down using “breast” filter. In the “view chart” box plots were also generated for the individual genes comparing gene expression between GTEX and TCGA breast cancer patients' datasets. Xena utilized the same pipeline for TCGA and GTEx samples, wherein they are re-analyzed (using UCSC Toil RNA-seq recompute compendium) to eliminate batch effects [57].

2.4. Patient survival plots

Meier-Kaplan plots were obtained from Kaplan-Meier Plotter that uses microarray expression data from 7462 breast cancer patients [58]. The plots were generated for patients' overall survival after splitting

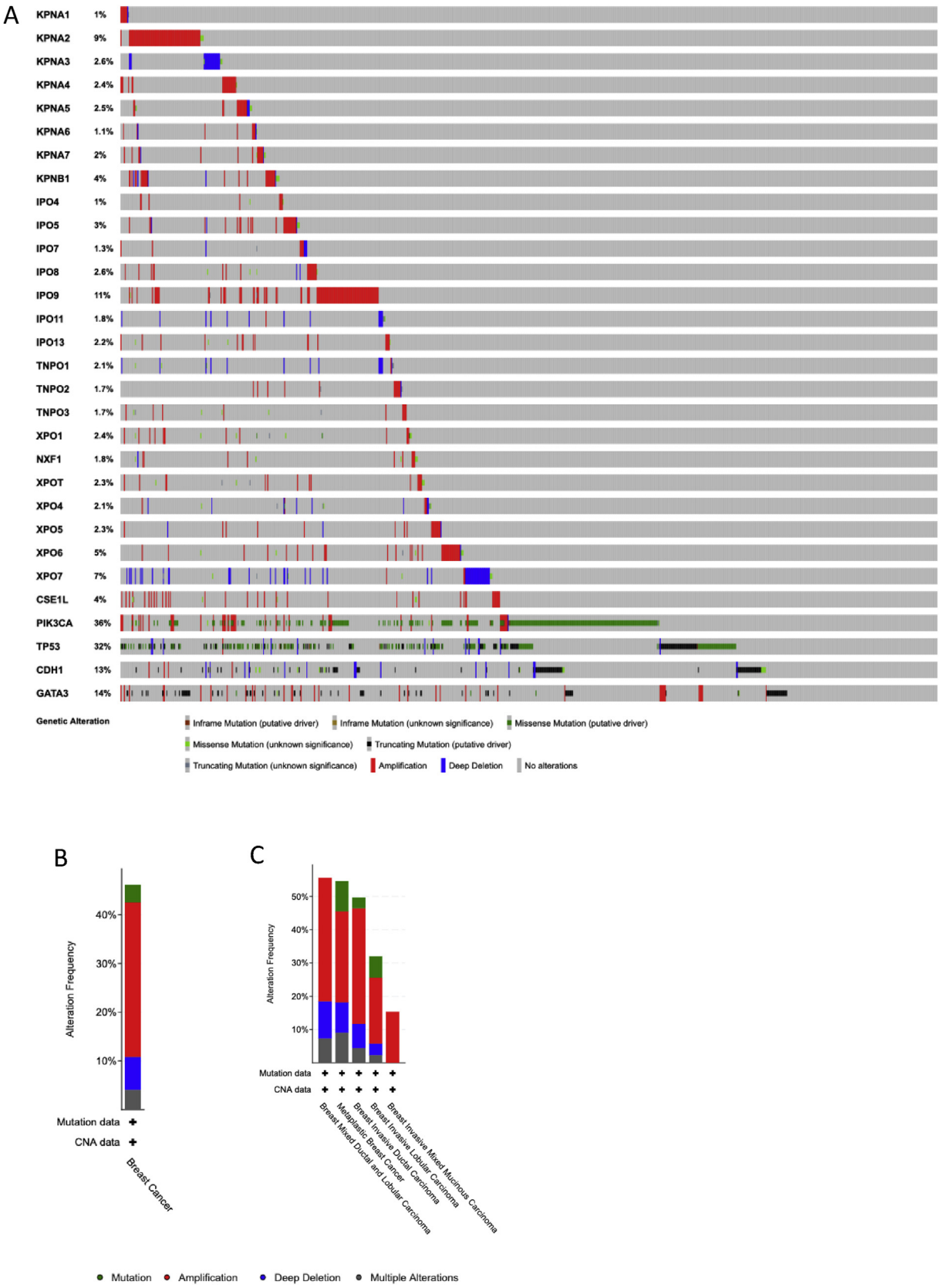

Figure 1. Genes encoding nuclear transport receptors are mutated in breast cancer. **(A)** Various genetic alterations are detected in breast cancer. Various color schemes representing amplification, deep deletion, in frame mutation, missense mutation and truncating mutations are shown. Amplification is the top mutation type detected among the nuclear transport family. PIK3CA, TP53, CDH1 and GATA3 are shown as positive controls from previous studies. **(B)** Overall mutation frequency in the nuclear transport group. **(C)** Spectrum of mutations in different breast cancer subtypes.

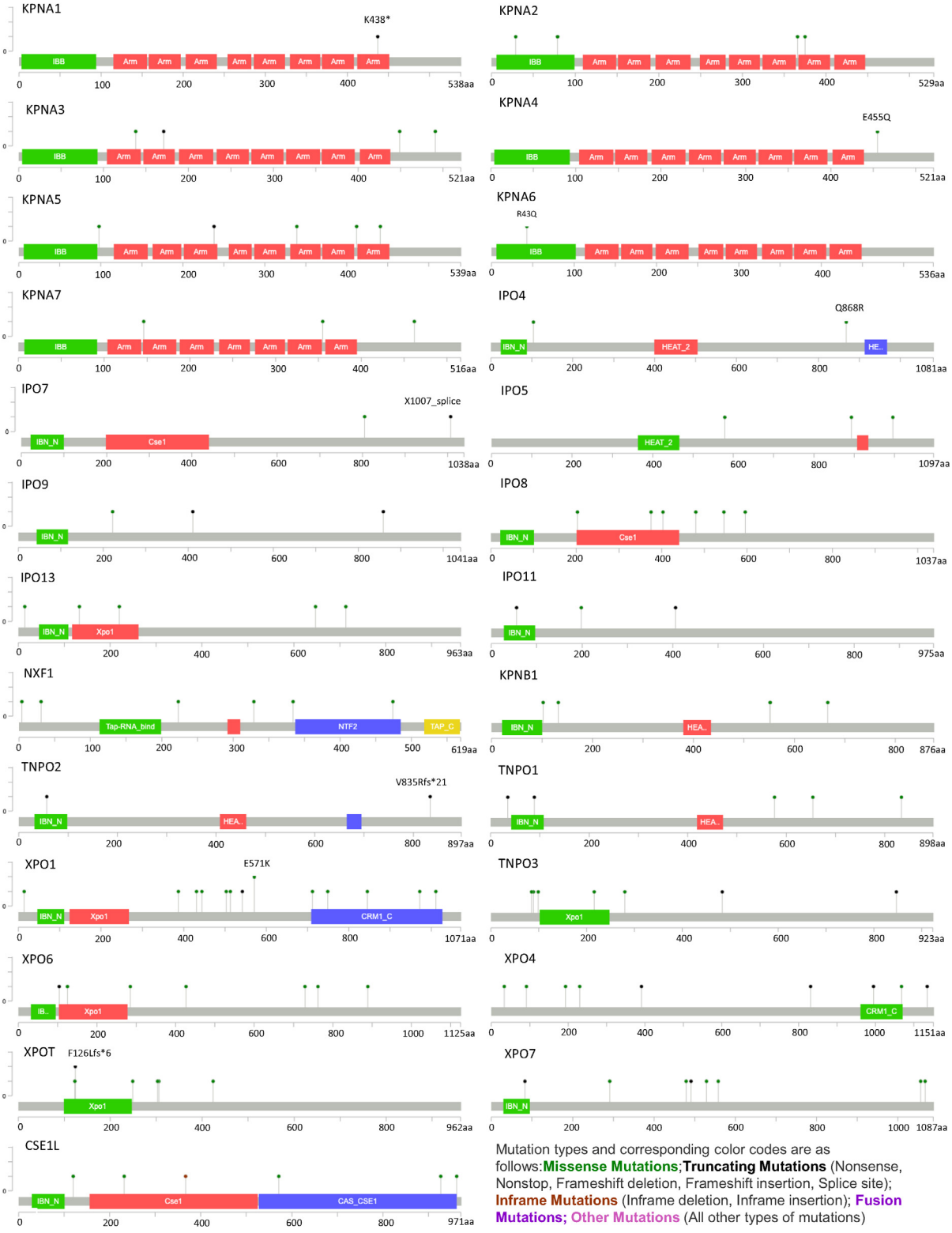

Figure 2. Mutation types and corresponding color codes in breast cancer are indicated in the figure, representing Missense Mutations; Truncating Mutations (Nonsense, Nonstop, Frameshift deletion, Frameshift insertion, Splice site); Inframe Mutations (Inframe deletion, Inframe insertion); Fusion Mutations; Other Mutations (All other types of mutations).

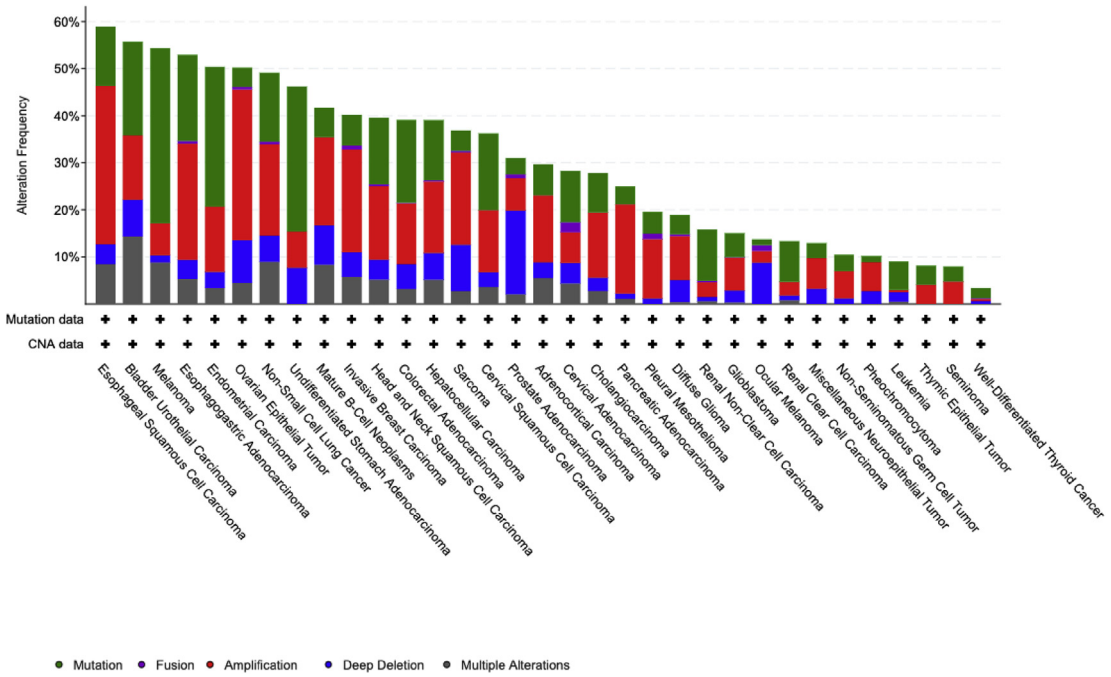

Figure 3. Genes encoding nuclear transport receptors are mutated in a variety of cancers. Spectrum of mutations in different cancer types using TCGA PanCancer Atlas datasets.

patients by median and using jetset for the best probe selection for the indicated time periods. The generated p value does not include correction for multiple hypothesis testing by default [58].

2.5. Statistics

The statistical tools were embedded in the resources we used. Briefly, in cBioportal, a Fisher's exact test was used to determine whether the identified relationship is significant for each gene pair, while examining a tendency of co-occurrences and mutual exclusivity [56]. Xena [57] employs Welch's t-test to calculate the p values while comparing individual transporter genes expression in normal vs breast cancer patients as shown in Figure 2B.

3. Results

3.1. Majority of nuclear transporters are mutated in breast cancer

Considering the importance of cataloguing the spectrum of mutations and gene expression changes, TCGA was established to document genetic alterations in various cancers. We made use of the data and analyzed the mutational landscape of the breast cancer patients. Interestingly, a

Table 2. Co-occurrence and mutual exclusivity of gene mutations in breast cancer.

A	B	Neither	A Not B	B Not A	Both	Log2 Odds Ratio	p-Value	q-Value	Tendency
IPO11	TNPO1	938	5	8	12	>3	<0.001	<0.001	Co-occurrence
TP53	CDH1	540	294	116	13	-2.280	<0.001	<0.001	Mutual exclusivity
KPNA2	KPNB1	854	73	20	16	>3	<0.001	<0.001	Co-occurrence
XPO7	TP53	630	26	269	38	1.775	<0.001	<0.001	Co-occurrence
PIK3CA	GATA3	509	319	108	27	-1.326	<0.001	0.001	Mutual exclusivity
KPNA2	CSE1L	845	76	29	13	2.317	<0.001	0.003	Co-occurrence
KPNA1	KPNA4	934	6	19	4	>3	<0.001	0.003	Co-occurrence
KPNA6	IPO13	935	7	17	4	>3	<0.001	0.003	Co-occurrence
IPO5	TP53	644	12	286	21	1.978	<0.001	0.007	Co-occurrence
KPNA7	TP53	651	5	293	14	2.637	<0.001	0.008	Co-occurrence
KPNA4	PIK3CA	611	6	329	17	2.396	<0.001	0.008	Co-occurrence
KPNB1	NXF1	915	31	12	5	>3	<0.001	0.009	Co-occurrence
XPO5	TP53	649	7	292	15	2.252	<0.001	0.014	Co-occurrence
TNPO1	TP53	650	6	293	14	2.372	<0.001	0.014	Co-occurrence
KPNA2	XPO1	859	81	15	8	2.500	<0.001	0.017	Co-occurrence
KPNA7	XPO1	925	15	19	4	>3	<0.001	0.021	Co-occurrence
KPNA5	IPO5	911	19	28	5	>3	<0.001	0.024	Co-occurrence
KPNA5	IPO13	922	20	17	4	>3	0.001	0.030	Co-occurrence
KPNA2	GATA3	762	66	112	23	1.245	0.001	0.030	Co-occurrence
KPNA5	KPNB1	908	19	31	5	2.946	0.001	0.030	Co-occurrence
IPO5	CSE1L	894	27	36	6	2.464	0.002	0.045	Co-occurrence

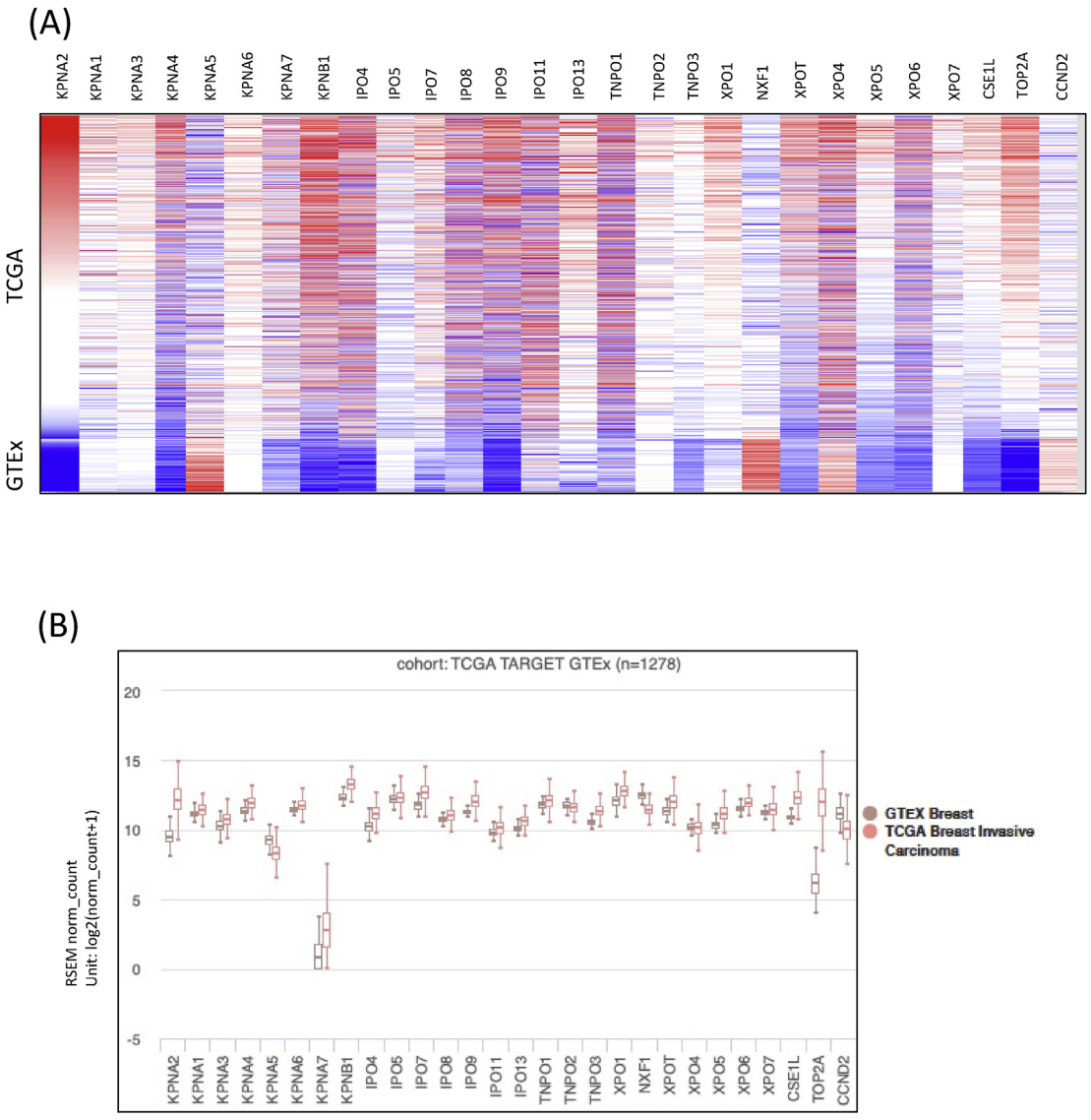

Figure 4. Expression profiling of genes that encode proteins responsible for nuclear import/export functions. (A) Over/under expression of all the genes is depicted in red/blue bars respectively. The data from GTEx is used to compare the expression of normal breast tissue with breast cancer samples. (B) Comparisons of individual transporter genes expression in normal vs breast cancer patients. Welch's t-test calculates the p values shown for individual genes. KPNA1, p = 3.856e-23 (t = -10.58), KPNA2, p = 7.971e-158 (t = -48.65), KPNA3, p = 7.834e-33 (t = -13.37), KPNA4, p = 1.825e-67 (t = -21.89), KPNA5, p = 0.000 (t = 23.77), KPNA6, p = 3.097e-33 (t = -12.92), KPNA7, p = 3.866e-59 (t = -19.83), KPNB1, p = 9.299e-112 (t = -33.34), IPO4, p = 3.041e-64 (t = -23.09), IPO5, p = 0.0001531 (t = -3.823), IPO7, p = 3.613e-93 (t = -27.28), IPO8, p = 1.922e-39 (t = -14.10), IPO9, p = 1.820e-155 (t = -35.12), IPO11, p = 3.657e-18 (t = -9.109), IPO13, p = 4.495e-66 (t = -22.33), TNPO1, p = 7.398e-24 (t = -10.65), TNPO2, p = 0.007802 (t = 2.677), TNPO3, p = 3.277e-130 (t = -34.82), XPO1, p = 1.598e-49 (t = -18.81), NXF1, p = 0.000 (t = 39.34) XPOT, p = 3.844e-56 (t = -18.86), XPO4, p = 0.1158 (t = 1.576), XPO5, p = 8.350e-98 (t = -27.35), XPO6, p = 1.350e-60 (t = -19.71), XPO7, p = 5.369e-19 (t = -9.179), CSE1L, p = 1.967e-282 (t = -56.07), TOP2A, p = 6.588e-156 (t = -58.62), CCND2, p = 0.000 (t = 20.99). s = significant, ns = non-significant.

number of genes related to karyopherin functions were found to be mutated. Among all the genes tested, the mutational percentage ranged from 1% (in KPNA1 and IPO4) to 11% (in IPO9) (Figure 1A). Analysis of mutation types indicated that gene amplification was the most prevalent mutation in majority of the genes under study. This included KPNA2, IPO9, XPO6, IPO5 and other factors with variable rates (Figure 1). However, in a small subset of genes, deep deletions were also detected. This category included KPNA3, IPO11, TNOP1 and XPO7. Looking at the overall alteration frequency, gene amplifications had the highest percentage, followed by deep deletion and other mutations and multiple alterations (Figure 1B). We then compared the mutational landscape of transport related genes in multiple breast cancer types. This included breast mixed ductal and lobular carcinoma, metaplastic breast cancer, breast invasive ductal carcinoma, breast invasive locular carcinoma, and breast invasive mixed mucinous carcinoma. Alteration frequency remained the same topped by amplification followed by deep deletions and other multiple mutations. Somatic mutations had relatively little representation in overall genetic mutations. Somatic mutations including missense Mutations, truncating mutations (Nonsense, Nonstop, Frameshift deletion, Frameshift insertion, Splice site), inframe mutations (Inframe deletion, Inframe insertion), fusion Mutations and all other Mutations in all the transporters are shown in Figure 2. Additional analysis involving datasets from a variety of cancer from TCGA Pan-Cancer Atlas Studies identified similar trends in majority of the cancers showing that dysregulated nuclear import pathways span a spectrum of cancers (Figure 3). Importantly, we included PIK3CA, TP53, CDH1, and GATA3, already identified to be top mutated driver genes in earlier studies, in our analysis. Consistent with the literature, these candidate genes had high mutation rates confirming the validity of our analysis (Figure 1A). Moreover, we found co-occurrences and mutual exclusivities

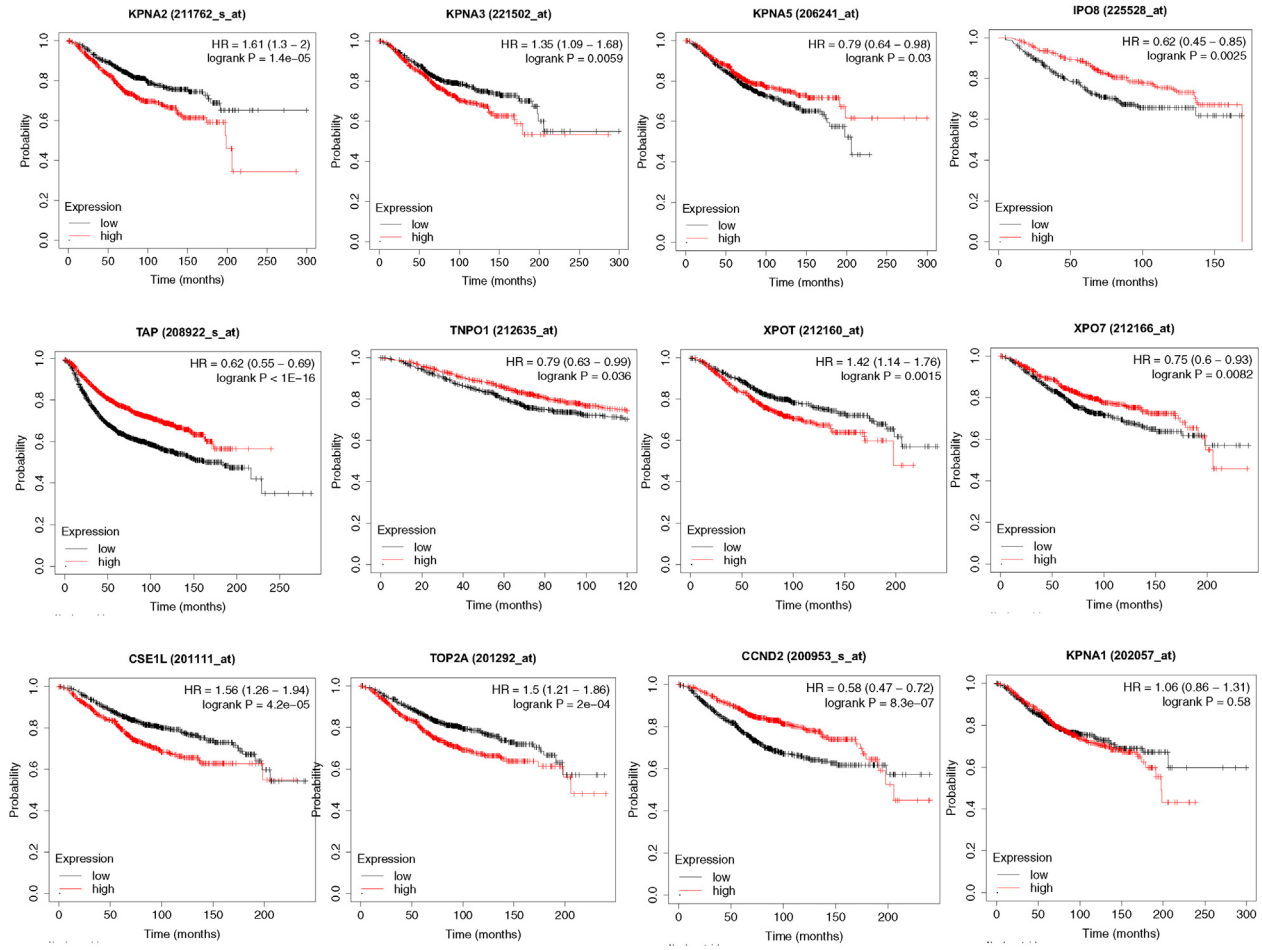

Figure 5. Meier-Kaplan plots showing overall patient survival. X axis shows Overall survival percentage, and Y axis shows Months after the diagnosis. Red indicates high expression group, while the black indicates the low expression group. The patients (n = 1402) were split by median. p-values were determined using the Log-Rank test.

amongst several transport receptors and these top mutated genes (Table 2).

3.2. Gene expression dysregulation in breast cancer is frequently observed in genes encoding nuclear transporters

As dysregulated gene expression is another key attribute of cancer development in addition to the accumulation of mutations, we looked at the gene expression changes in the genes encoding proteins involved in nuclear transport process. We incorporated GTEx data for expression in normal breast tissue and compared with TCGA datasets and found that there were massive expression differences in majority of nuclear transport gene family members (Figure 4). Interestingly, compared with the normal tissue, the gene expression patterns were reversed in several genes encoding nuclear transport receptors. KPNA2 has been reported to be dysregulated in breast cancer and may serve as an important biomarker. In our analysis, we also observed overexpression of KPNA2 in breast cancer. Additionally, several other transporters were also over expressed in breast cancer in the heatmap shown in the Figure 4A. It is interesting to note that KPNA5 showed significant downregulation in breast cancer (Figure 4A, B). Massive expression changes were also identified in proliferation related genes, TOP2A and CCND2, as described before [58]. Our analysis also showed concordance with the previous studies and we found significant over expression of TOP2A and down regulation of CCND2 in breast cancer (Figure 4A, B). This data show that genes encoding nuclear transporters are dysregulated in breast cancer.

3.3. Nuclear transporter genes with roles in patients' prognosis

After establishing that many of the nuclear transport factors are not only genetically mutated but also show expression differences, the next question was if these are associated with patients' prognosis. To address this, we carried out overall survival analysis in breast cancer patients' samples using Meier-Kaplan (KM) plotter [58]. Interestingly, we found that some of the members showed a significant correlation with the patients' survival. Importantly, KPNA2, already shown to be an important biomarker in a variety of cancers including breast cancer [59], appeared to be an important molecule for patients' prognosis. Its overexpression correlated with poor patient overall survival (Figure 5). Additionally, overexpression of KPNA3, XPOT, CSE1L also correlated with poor patient survival, while overexpression of KPN5, IPO8, TNPO1, and XPO7 was correlated with better patient survival (Figure 5). We also included TOP2A and CCND2 in our analysis that are important molecules for breast cancer prognosis [60, 61]. KM plot for KPNA1 is also displayed in Figure 5 which does not show any correlation with the overall survival. The rest of the transporters that do not shown significant correlation with the patient survival are shown in Figure 6.

4. Discussion

Owing to its critical role in regulating subcellular localization of critical molecules, nuclear transport has been implicated in a number of scenarios within the cell including cell motility, cell cycle regulation and apoptosis etc. [42]. Moreover, their role in various pathological

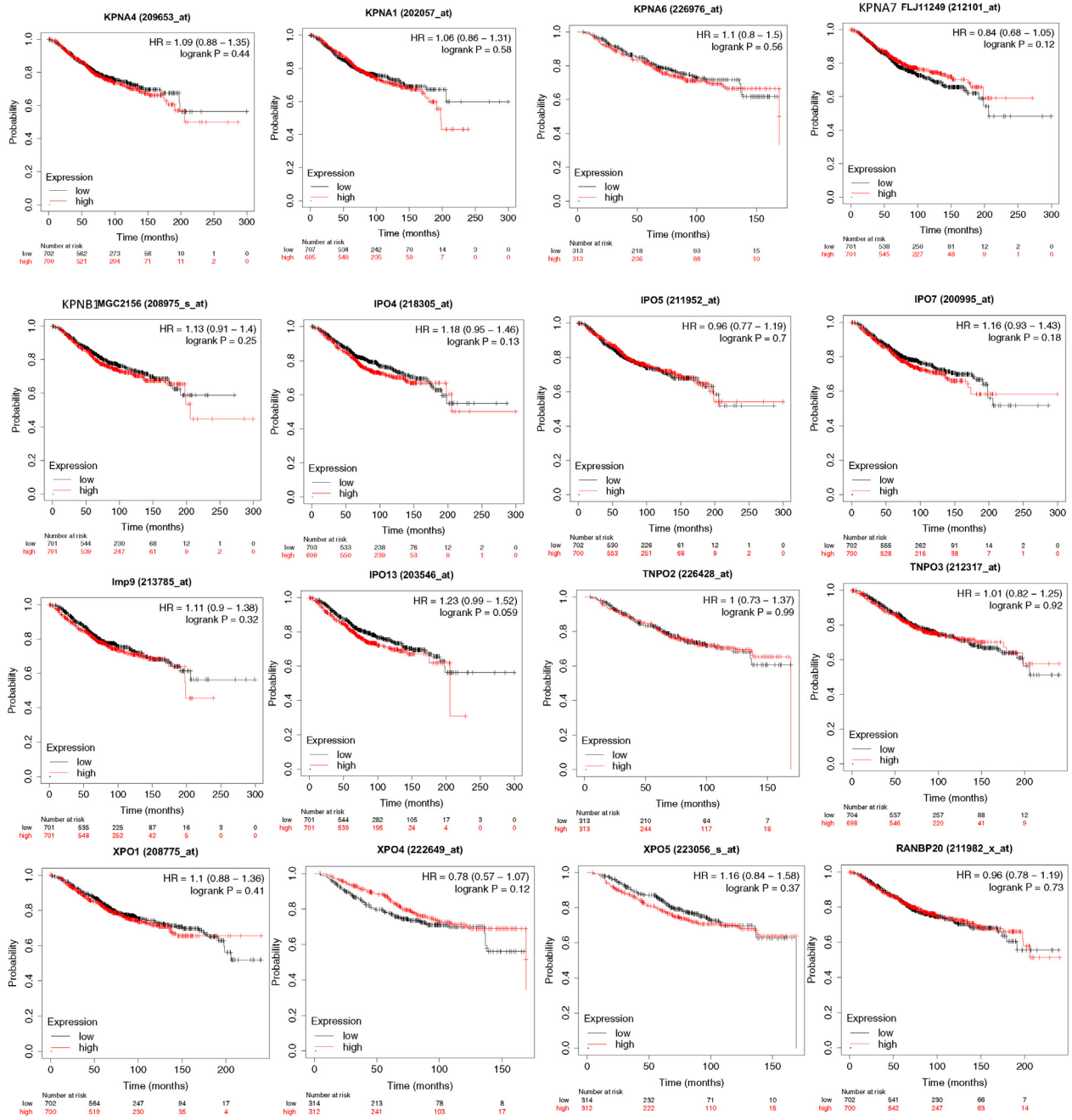

Figure 6. Meier-Kaplan plots showing overall breast cancer patient survival. X axis shows Overall survival percentage, and Y axis shows Months after the diagnosis. Red indicates high expression group, while the black indicates the low expression group. The patients (n = 1402) were split by median. p-values were determined using the Log-Rank test.

conditions is under investigation including its well-described role neurological conditions [62]. In the current study, using bioinformatic approaches, we, for the first time, examined the entire set of transporters in breast cancer by analyzing genomic and transcriptomic data. We found that majority of transport receptors are mutated albeit at variable rates (1%–11%). Interestingly, there was a little overlap of multiple transporters in the patients. Therefore, the anomalies in the transport process are presented in 46% of the patients (Figure 1). Understandably, some of the transporters have overlapping cargoes, but it is widely accepted that different transporters have unique cargoes and play roles in a wide variety of independent pathways [9, 39, 40, 41]. Considering this scenario, nuclear transport is one of the major pathways deregulated in breast cancer. Additionally, transcriptomic analysis also found massive deregulation of mRNA levels of majority of transporters in comparison with the normal tissues. Intriguingly, Meier-Kaplan plots clearly show the prognostic potentials of various members of transport receptors in breast cancer.

Clinically, genetic amplifications are implicated in prognosis and diagnosis of tumors in addition to providing a mechanism for drug resistance [63]. We found that gene amplification was the major genetic aberration that contributed to the genetic alterations of the majority of the transport receptors. Except for KPNA3, IPO11, TNOP1 and XPO7, all other members showed gene amplification. Interestingly, gene amplification along with deep deletions and other genetic alterations were observed in different types of breast cancer encompassing breast cancers of various cells of origin (Figure 1C). While gene amplifications were already reported for some of the transport receptors, we detected additional members with high mutation rates. For instance, KPNA2 was

already reported to be highly amplified in cancers and also considered to be a strong biomarker for breast cancer [59]. It promotes tumor formation and progression by participating in a number of physiological processes, like cell differentiation, proliferation, apoptosis, immune response [64]. Our analysis also identified similar trend for KPNA2 as it was found to be amplified and its overexpression had poor patient survival. Interestingly, IPO9 appeared to be another molecule with high mutation rate, mainly amplification. The role of IPO9 in breast cancer warrants further investigations considering a diversity of proteins that might be its cargo.

In contrast to gene amplification which was most predominant mutation, only a little prevalence of deep deletions was observed in most of the transporters. The only few exceptions were KPNA3, IPO11, TNPO1 and XPO7 with deep deletion as the major mutation (2.6 %, 1.8%, 2.1% and 7% respectively). KPNA3 was also down-regulated in B-cell chronic lymphocytic leukemia (B-CLL) [65]. Surprisingly, loss of KPNA3 expression led to better overall patient survival. It will be interesting to find out cargoes that are selectively transported by KPNA3 that might be mislocalized due to its loss. Such loss of nuclear localization of P53 was observed in cells with truncated form of importin α [66]. Deep deletions were also observed for XPO7. Recently a battery of proteins has been identified that might be possible cargoes for XPO7 including HDAC8 [67]. Contrary to KPNA3, however, XPO7 down regulation was correlated with poor patient survival. This contrasting difference in outcome might indicate cargo specificity of the two transport receptors.

Another exciting result of the current study is the identification of multiple transport factors with respect to their correlation with patient survival. Out of all the transporters studied, 9 showed significant correlation. While overexpression of KPNA2 and KPNA3 had poor patient survival, opposite scenario was observed for KPNA5 which had better overall survival. One possible action of KPNA5 might be its role in promoting differentiation [43] or by regulating the nuclear transport of an anti-proliferative factor, PHB2 [68]. RNA export factors, NXF1 (TAP) and XPOT, importing mRNA and tRNA respectively exhibited reverse trends in expression in cancer tissues compared with the normal. The reverse trends persisted even in KM plot for the overall survival. This shows critical roles of RNA transport in breast cancer. Looking at KM plots of various transport receptors, we see significance of nuclear transport process in patient prognosis.

Collectively, our data provide strong evidence regarding the pivotal role of nuclear transporters in cancer development and prognosis. Can this process be targeted in cancer therapeutics? The need to identify novel drug targets remains a did not dwindle considering the limited efficacy of available drugs against this recalcitrant cancer, tumor heterogeneity and high frequency of relapsed cases. As our analysis shows genes implicated in the nuclear transport process are mutated in 46% of breast cancer patients in addition to deregulated expression. Interestingly, the abnormal localization of P53, FoxO and IκB has been reversed by treating cells with EXPORTIN 1 inhibitor [69]. However, paradoxically, various oncogenic molecules are also exported by EXPORTIN 1, warranting caution. Moreover, as various members of KPNA family with high similarity are selectively amplified or expressed in breast cancer, finding specific inhibitors for the individual members presents a formidable challenge. In the nutshell, targeting nuclear transport pathway provides a promising but challenging avenue for future breast cancer therapeutics.

Declarations

Author contribution statement

Noriko Yasuhara: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Rashid Mehmood: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kazuya Jibiki, Noriko Shibazaki: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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