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Association of Interleukin-enhanced factor 2 (ILF2) expression with prognosis and clinico-genomic features in breast cancer

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Background

Novel prognostic and predictive biomarkers beyond traditional histological subtypes are needed to better inform outcomes and enhance therapy guidance in breast cancer (BC). We have previously reported that ILF2 was overexpressed in TNBC cell lines and has a functional role in DNA and RNA metabolism, making it a promising biomarker for risk assessment and treatment decisions. Herein, we aim to leverage a large clinico-genomic dataset to further characterize ILF2 in BC patients (pts).

Methods

- A total of 9,456 BC tissue samples underwent molecular profiling at Caris Life Sciences (Phoenix, AZ).
- Analyses included next generation sequencing of DNA (592 Gene Panel, or Whole Exome Sequencing), and RNA (Whole Transcriptome Sequencing), and immunohistochemistry (IHC). Wilcoxon and Fisher's exact were used to determine statistical significance.
- Overall survival (OS) was obtained from insurance claims and Kaplan-Meier estimates were calculated.
- Spearman correlation was used to identify highly correlated genes (ρ>0.6) with ILF2 and significant genes that were subsequently analyzed via pathway analysis using STRING.
- BC pts were grouped into ILF2-High (H, top quartile) and ILF2-Low (L, bottom quartile) based on mRNA levels (TPM).

Results

- ILF2-H pts were significantly younger (73 vs 80% for pts >50), enriched in ductal histology (90.9 vs 77.7%), TNBC subtype (48.9 vs 18.9%), and had a higher CNS metastases rate (4.3 vs 1.4%) compared to ILF2-L pts (all q<0.0001; **Table 1**).

Table 1. Association between clinico-pathological features and *ILF2* mRNA levels.

Variables	ILF2 Q1 (2364)	ILF2 Q4 (2364)	q value
Age			
>50	1880 (79.53)	1718 (72.67)	<0.0001
<50	484 (20.47)	646 (27.33)	
Histology			
Ductal	760 (77.71)	916 (90.87)	<0.0001
Lobular	201 (20.55)	80 (7.94)	
Both	17 (1.74)	12 (1.19)	
Gender			
Female	2324 (98.31)	2349 (99.37)	<0.001
Male	40 (1.69)	15 (0.63)	
PAM50			
LumB	952 (41.12)	708 (30.01)	<0.0001
Basal	329 (14.21)	1197 (50.74)	
Her2	427 (18.44)	362 (15.35)	
LumA	607 (26.22)	92 (3.90)	
Molecular Sub			
HR+/HER2-	1453 (72.94)	917 (43.52)	<0.0001
TNBC	377 (18.93)	1031 (48.93)	
HR+/HER2+	105 (5.27)	75 (3.56)	
HR-/HER2+	57 (2.86)	84 (3.99)	
Sites			
Breast	889 (37.61)	998 (42.23)	<0.0001
Liver	323 (13.66)	378 (16.00)	
Axilla + Lymph	302 (12.77)	358 (15.15)	
Lung + Pleura	149 (6.30)	146 (6.18)	
Bone	200 (8.46)	65 (2.75)	
Chest	100 (4.23)	124 (5.25)	
Multiple Sites	90 (3.81)	49 (2.07)	
CNS	33 (1.40)	101 (4.27)	
Spine	73 (3.09)	26 (1.10)	
GYN	26 (1.10)	14 (0.59)	
Peritoneum + Omentum	21 (0.89)	13 (0.55)	

- N > 10 displayed

- ILF2 overexpression was associated with significantly inferior OS in all BC pts (HR 3.38, 95%CI: 2.97 – 3.84; **Fig. 1A**); when stratified into known BC hormonal receptor (HR) subtypes, ILF2 was prognostic in both HR+ BC (HR 1.7, 95 CI: 1.34-2.19; **Fig. 1B**) and TNBC (HR 3.8, 95 CI: 3.1-4.7, **Fig. 1C**), all p<0.0001.

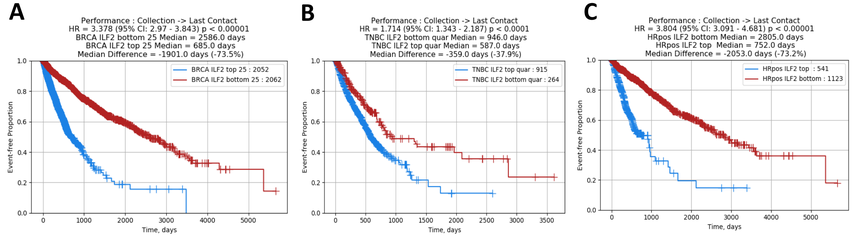

Figure 1. Prognostic value of *ILF2* mRNA levels in different breast cancer (BC) subtypes. A-C Kaplan-Meier curves for OS in all BC (A), HR+ (B), or TNBC (C) patients stratified based on *ILF2* mRNA levels.

- In TNBC patients (n=2,468), ILF2-H was associated with a higher frequency of *TP53* mutations (mt), lower rate of *PIK3CA* mt and higher amplification of *CCNE1* and *FGF23* (**Fig. 2A**); while in HR+/HER2- BC subtype (n=5,071), ILF2-H was associated with a higher rate of *TP53* mt, PD-L1 expression, *NOTCH2* and *CCND2* amplifications (**Fig. 2B**).

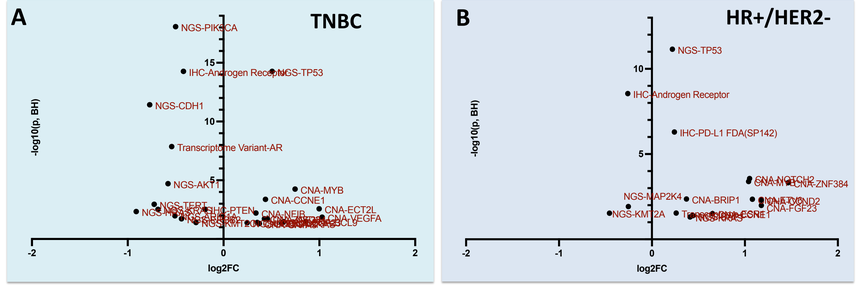

Figure 2. Genomic and proteomics co-alterations with *ILF2* mRNA overexpression in different molecular subtypes. The co-alteration were assessed in patient with TNBC (A) or HR+/HER2- (B) subtypes.

- In TNBC, *ILF2* mRNA levels were significantly correlated with genes involved in spliceosome, cell cycle and RNA transport pathways. In HR+/HER2- BC, ILF2-correlated genes were significantly enriched in mismatch repair and DNA replication pathways (p<0.05 for all factors individually; **Table 2**).

Table 2. Top enriched pathways in tumors with different molecular subtypes and ILF2 upregulation (strength: enrichment score; FDR: false discovery rate)

	Strength	FDR (*q-value*)
HR+/HER2-		
Mismatch Repair	1.42	<0.05
Proteasome	1.28	<0.01
DNA replication	1.23	<0.05
TNBC		
Spliceosome	1.26	<0.0001
Cell cycle	0.92	<0.05
RNA transport	0.88	<0.05

Conclusions

High levels of ILF2 mRNA are associated with a poorer prognosis independent of the BC subtype. Our study warrants further investigation on ILF2 as a prognostic and therapeutic target for BC patients.

References

1. Zhang et al., *Clinical and Translational Medicine*, 2021.
2. Goh et al., *Nature Medicine*, 2017.
3. Bustos et al., *Cancer Research (AACR abstract)*, 2020.