Multiomic landscape of LRCC15 in Triple Negative Breast Cancer

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Poster #
Abstract #

Background

- Leucine-rich repeat-containing protein 15 (LRRC15) has emerged as a potential biomarker and therapeutic target for various cancers due to its high expression in cancer-associated fibroblasts (CAFs) and role in tumor progression.
- High LRRC15 expression is associated with poor prognosis in Triple Negative Breast Cancer (TNBC).
- This study aims to define the multiomic profile of LRRC15 in TNBC.

Methods

- 3,038 TNBC samples were analyzed via Next-Generation Sequencing (592, NextSeq; Whole Exome Sequencing, NovaSeq) and Whole Transcriptome Sequencing (NovaSeq; Caris Life Sciences, AZ).
- Immune cell fractions were estimated using WTS deconvolution (Quantiseq). Stromal cell abundance in the tumor microenvironment (TME) was estimated from RNA expression profiles using MCP Counter.
- LRRC15-high (H) and -low (L) tumors were classified by RNA expression above or below the 25th percentile.
- Real-world overall survival (OS) and treatment-related survival were derived from insurance claims and calculated from tissue collection or treatment initiation to last contact using Kaplan-Meier.
- Statistical significance was determined using chi-square, Mann Whitney U and adjusted for multiple comparisons where applicable (q< 0.05).

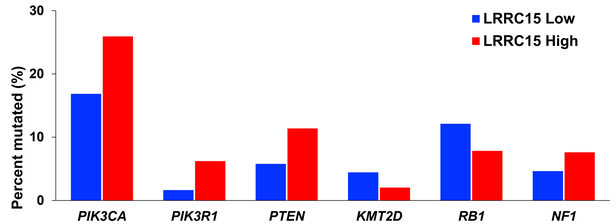
Table 1. Patients' demographic information

		LRRC15 low (25th percentile)	LRRC15 high (25th percentile)
Count (N)		735	735
Median age [range]		59 (23 - >89)	61 (24 - >89)
Race	**White**	60.07% (346/576)	62.95% (350/556)
	Black	28.99% (167/576)	26.08% (145/556)
	Asian/Pacific Islander	3.47% (20/576)	4.5% (25/556)
	Other	7.47% (43/576)	6.47% (36/556)
Ethnicity	**Not Hispanic or Latino**	85.23% (456/535)	80.56% (431/535)
	Hispanic or Latino	14.77% (79/535)	19.44% (104/535)
Tumor site	**Primary**	19.46% (143/735)	58.1% (427/735)
	Metastatic	80.54% (592/735)	41.9%(308/735)

Race and ethnicity data is self reported.

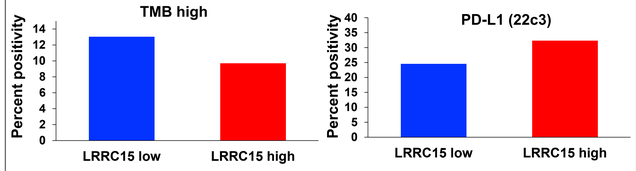
Results

Figure 1. Mutation analysis of *LRRC15*-low vs high TNBC



LRRC15-H TNBC had higher frequency of *PIK3CA* (25.9% vs 16.8), *PIK3R1* (6.2% vs1.6%), *PTEN* (11.3% vs 5.8%), but lower frequency of *RB1* (7.8% vs 12.1%) and *KMT2D* (2%vs 4.4%) compared to *LRRC15*-L, all q<0.05.

Figure 2. TMB High and PD-L1 positivity analysis



LRRC15-H had lower frequency of TMB-high (13% vs 9.7%, p<0.05), but higher PD-L1 positivity (32.3%vs 24.5%, q < 0.05)

Figure 3. Immune cell infiltration

quanTIseq

	Median %	
	LRRC15 Low	LRRC15 High
B cell	3.59	4.23
Macrophage M1	2.09	4.38
Macrophage M2	2.52	4.06
Neutrophil	3.92	4.95
NK cell	2.91	2.85
DC	3.01	2.57
T cell CD8+	0.18	0.4
Tregs	1.14	1.98

MCP counter

	Median	
	LRRC15 Low	LRRC15 High
CAF	93.78	576.64
Endothelial cell	3.77	7.36
B cell	90.40	286.83
Macrophage	11.40	26.08
Neutrophil	7.87	12.20
NK cell	0.62	0.91
DC	0.96	1.99
T cells	1.95	3.50
T cell CD8+	1.39	2.31

LRRC15-H TNBC had higher median % infiltration of B cells, M1 Mϕ, M2 Mϕ, Tregs, neutrophils, CD8 T cells, but lower dendritic cells, all q<0.05. *LRRC15*-H tumors had greater median abundance of CAFs and endothelial cells, all q<0.05.

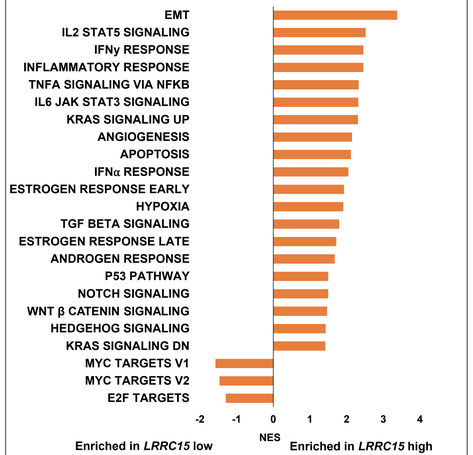
Figure 4. Immune checkpoint gene expression

	LRRC15 Low	*LRRC15* High
CD274	3.02	5.28
PDCD1	0.33	0.60
PDCD1LG2	0.82	2.08
CTLA4	0.89	2.06
LAG3	2.64	4.11
HAVCR2	12.90	27.45
FOXP3	1.62	3.74
IDO1	1.22	2.79
TNFSF14	0.37	0.45
TIGIT	0.64	1.51
BTLA	0.90	1.78
CEACAM1	22.34	28.27
CD47	44.73	63.88
CD80	2.69	6.44
CD86	5.70	12.57
CD160	2.98	4.15

LRRC15-H had higher expression of immune checkpoint genes, all q < 0.05

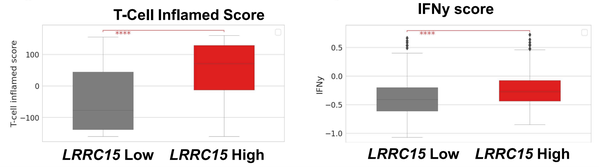
Low TPM (Median)
High TPM (Median)

Figure 5. Gene set enrichment analysis



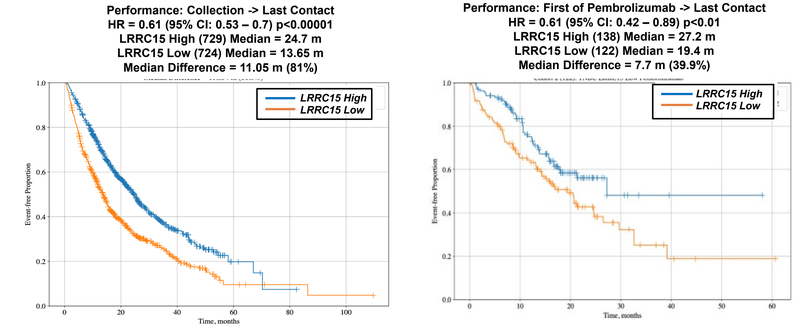
LRRC15-H TNBC had enrichment several cancer-related pathways, all FDR<0.25.

Figure 6. T-cell inflamed score and IFNy score



LRRC15-H had higher T-cell inflamed score (71.5 vs -77) and *IFNy* score (-0.14 vs -1.72), all q < 0.05.

Figure 7. *LRRC15* high vs low TNBC patient survival



LRRC15-H was associated with better OS (mOS: 24.7 vs 13.6 months; HR 0.61, 95% CI 0.53-0.7, p <0.001).Post-pembrolizumab survival was longer for *LRRC15*-H patients (mOS: 27.2 vs 19.4 months; HR 0.61, 95% CI 0.42-0.89, p = 0.01).

Conclusions

- LRRC15-H TNBC exhibited better outcomes with pembrolizumab, likely due to higher immune cell fractions and increased CAFs.
- These findings highlight TNBC heterogeneity and position LRRC15 as a potential biomarker for tumor stratification, a possible adverse prognostic biomarker and a positive predictive biomarker.
- Ongoing phase I trials targeting LRRC15 show promise. Combining LRRC15-targeted therapies with immunotherapy may improve TNBC outcomes, warranting further validation in breast cancer models.

Contact Information

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