Comprehensive molecular characterization of patients with metastatic invasive lobular carcinoma (ILC): Using real-world data to describe this unique clinical entity

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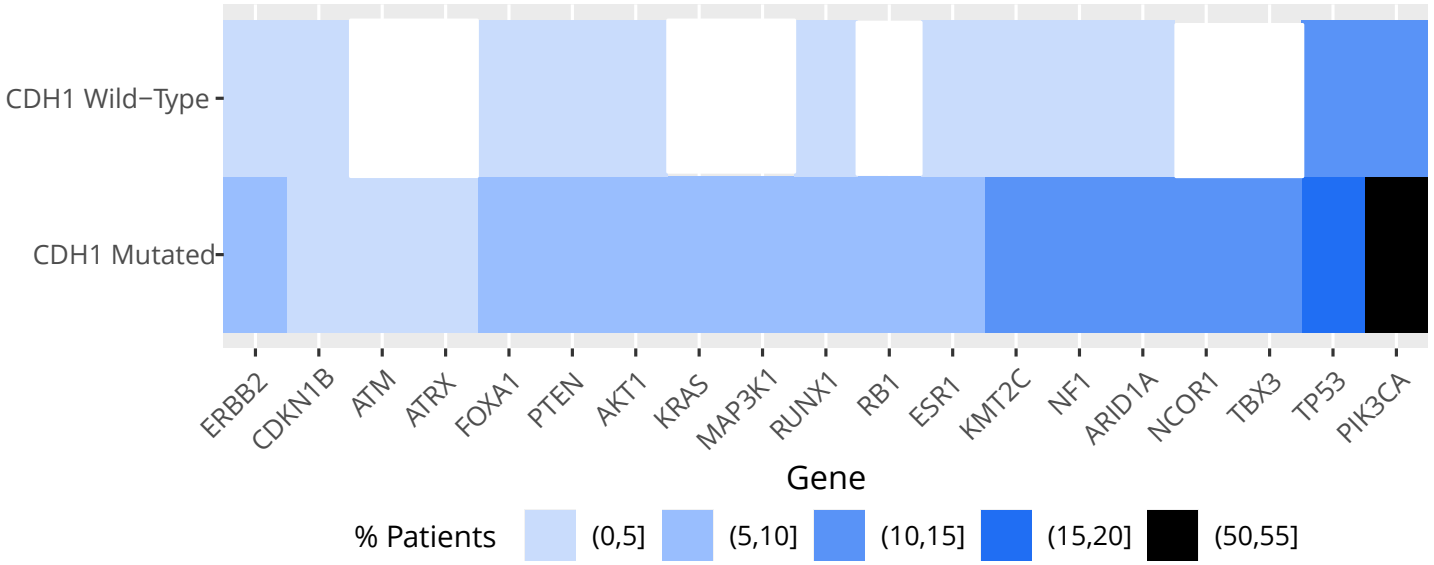
Background

- The genomic landscape of primary ILCs is well described, but less is known about metastatic ILC (mILC).
- We used de-identified next-generation sequencing data to examine the co-mutational landscape of *CDH1*-mutant mILC.
- Additionally, we investigated transcript-level expression variation between *CDH1*-wildtype (WT) and *CDH1*-mutant mILC and mixed lobular/ductal histology cohorts.
- Better characterization of the genomic and transcriptomic landscape of mILC is critical to provide new insights into ILC tumor biology and improve long-term outcomes in patients with mILC.

Somatic landscape of *CDH1*-mutant vs. *CDH1*-WT mILC cohorts



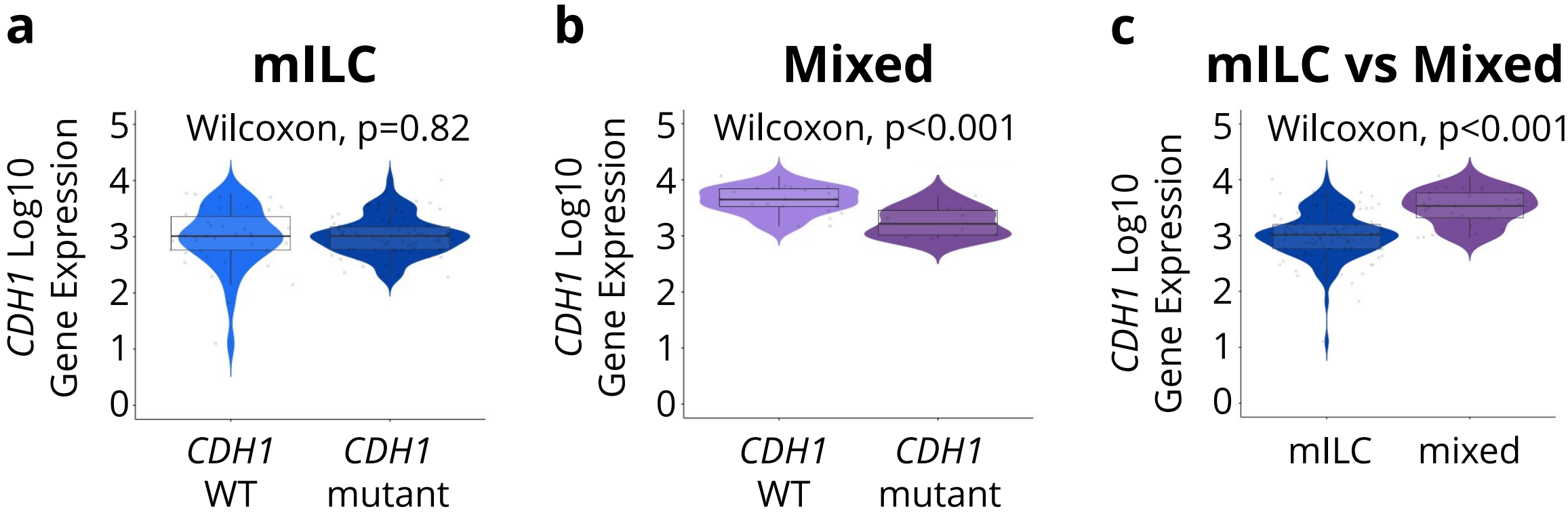
- *PIK3CA* mutations were enriched in *CDH1*-mutant mILC compared to *CDH1*-WT mILC.
- *TBX3* and *NCOR1* mutations were mildly enriched in *CDH1*-mutant mILC, but these results were not significant when correcting for multiple testing.
- The median tumor mutational burden (TMB) score was significantly higher in *CDH1*-mutant mILC samples

Table 1: Frequency of co-mutations and TMB comparison in *CDH1*-mutant vs. WT mILC cohorts

Genes/ Biomarkers	***CDH1*-mutant (n=98)**	***CDH1* WT (n=52)**	**p-value[1]**	**q-value[2]**
	n (%)	**n (%)**		
PIK3CA	53 (54%)	6 (12%)	<0.001	<0.001
TBX3	13 (13%)	0 (0%)	0.004	0.13
NCOR1	11 (11%)	0 (0%)	0.009	0.2
High TMB[3]	10 (10%)	3 (6.2%)	0.5	N/A
Median TMB	3.4	2.1	0.010	N/A

[1]Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank-sum test
[2]False discovery rate correction for multiple testing
[3]High TMB defined as ≥10 mutations/MB

Comparing *CDH1* gene expression between mILC and mixed histologies



- *CDH1*-mutant mixed histology patients had lower median log10 *CDH1* expression than WT patients (3.21 vs. 3.65, p <0.001).

- Median log10 *CDH1* expression across all mILC patients was lower than in mixed histology patients (3.01 vs. 3.53, p<0.001).

Conclusions

- Our real-world dataset illustrates that the molecular landscape of *CDH1*-mutant mILC patients is distinct from *CDH1*-WT patients.
- mILC differs from mixed histology at a transcriptional level, with lower *CDH1* expression regardless of *CDH1* mutational status.
- *CDH1* RNA levels in *CDH1*-mutant mixed histology patients more closely resemble those seen in mILC patients, suggesting a use for *CDH1* RNA expression levels in reclassifying mixed histology samples as mILC.
- Because *PIK3CA* mutations are more common in *CDH1*-mutant than in *CDH1*-WT disease, therapies targeting *PIK3CA* may be further investigated for their actionability in *CDH1*-mutant mILC cases.