Whole transcriptome sequencing reveals diagnostic and molecular complexity of lobular carcinoma associated with *CDH1* alteration

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Background

- Invasive lobular carcinoma (ILC), defined by its lobular morphology, is characteristically accompanied by E-cadherin loss due to *CDH1* inactivation.
- Despite its distinct clinico-biological features compared to invasive breast carcinoma of no special type (IBC-NST), discrepancies among morphology, immunohistochemistry (IHC), and molecular findings can complicate diagnosis.

AIM: To clarify the molecular basis of diagnostic discrepancies in ILC, we performed whole transcriptome sequencing (WTS) on selected breast cancer cases exhibiting variable E-cadherin expression patterns and morphology, including cases with and without *CDH1* mutations detected by prior targeted DNA sequencing.

Method

- WTS was performed on 11 formalin-fixed, paraffin-embedded (FFPE) tissues, including 8 tumors and 3 normal breast tissues.
  - NovaSeq 6000 (Illumina), generating 100-base pair paired-end reads
  - Transcript-level variant calling was performed to identify *CDH1* alterations
  - Only potentially protein-altering variants (missense, frameshift, stop-gained) were included
- All tumor cases had previously undergone targeted sequencing for clinical practice by*Trusight Oncology* 500 (Illumina)
  - *CDH1* variants reviewed per ACMG criteria
  - Included only tier 1-2 Clinically significant variants
- Based on morphology, *CDH1* mutation status, and E-cadherin IHC results, cases were stratified into three groups

Table 1. Grouping according to morphology, *CDH1* mutation status, and E-cadherin pattern

	Morphology	*CDH1* mutation*	E-cadherin IHC	No. of cases
Group 1	Non lobular (ductal or others)	Present	Positive (membranous)	4 cases
Group 2	Lobular	Not detected	Loss	4 cases
Group 3	Normal	Not performed	Not performed	3 cases

**CDH1* mutation status was determined by targeted DNA sequencing using the TruSight Oncology 500 assay (Illumina).

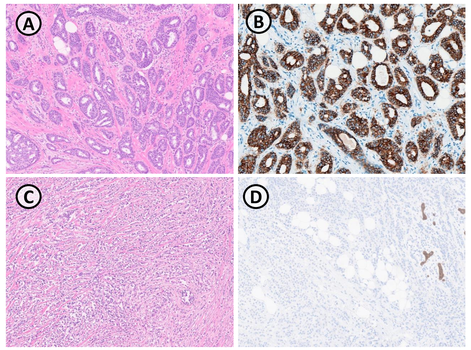


Figure 1. Representative H&E and IHC images for group 1 and group 2
(A, B) A Group 1 case of invasive carcinoma of no special type (IBC-NST) showing distinct gland-forming morphology and membranous E-cadherin expression. Despite these features, a *CDH1* mutation (L630V) was identified by targeted sequencing. **(C, D)** A Group 2 case of ILC showing classic lobular morphology and complete loss of E-cadherin staining, findings typical of ILC. However, a *CDH1* mutation was not detected by targeted sequencing.

Results

- WTS confirmed previously detected *CDH1* mutations from targeted sequencing
- It also revealed additional transcript-level variants missed by targeted DNA based analysis

Table 2. Comparison of *CDH1* mutations identified by targeted DNA sequencing and whole transcriptome sequencing (WTS)

	CDH1 mutation on Targeted DNA sequencing	*CDH1* mutation on Whole transcriptome sequencing	Key findings
Group 1 (n=4)	p.E880K	p.E880K+ p.D756Y	- WTS validated prior findings and identified one additional variant (p.D756Y)
	p.E880K	p.E880K	
	p.E880K	p.E880K	
	p.L630V	p.L630V	
Group 2 (n=4)	Not detected	p.Q610*	- WTS revealed previously undetected mutations
		p.F69Y, p.S70P, p.I584V, p.I707T	
		p.D476fs	
		Intronic alteration†	
Group 3 (n=4)	Not performed	- Intronic and 3'UTR variants only - No other pathogenic mutations	- Served as normal controls

†intronic alteration near a canonical splice site (c.163+19330C>G) was identified, suggesting potential splicing disruption.

Discussion & Conclusion

- WTS detected *CDH1* mutations in tumors lacking lobular morphology, indicating that molecular alterations can arise independently of classic morphologic features.
- WTS revealed pathogenic *CDH1* variants missed by targeted sequencing in tumors with lobular morphology and E-cadherin loss, highlighting its higher sensitivity.
- Together, these finding underscore the diagnostic and molecular complexity of ILC and support an expanded role for RNA-level profiling in its classification.

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