Homologous Recombination Deficiency and DNA-Damage Response in Breast Invasive Lobular Carcinoma

Christopher J. Schwartz[1], Daniel Muldoon[1], Andrea Gazzo[1], Matteo Repetto[2], Higino Dopeso[1], Panieh Terraf[1] ,Dara Ross[1] , Hong Zhang[1], Larry Norton[2], Diana Mandelker[1], Hannah Wen[1], Britta Weigelt[1], Edi Brogi[1], Sarat Chandarlapaty[2], Anita Mamtani[3], Sherry Shen[2] Chaitanya Bandlamudi[1], Fresia Pareja[1]

[1]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY USA, [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY USA, [3]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY USA.

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Background

Identification of genetic alterations in homologous recombination deficiency (HRD) and DNA damage response (DDR) genes in breast cancer (BC) is key for prognostication and potential selection for targeted therapies, such as PARP inhibitors. While HRD/DDR somatic oncogenic alterations are generally associated with ductal BCs, their roles in invasive lobular carcinoma (ILC) remain unclear.

Aim

We aim to investigate the spectrum of HRD/DDR somatic genetic alterations in ILC and their histologic features of these BCs.

Materials and Methods

We analyzed targeted sequencing data from 1,076 ILCs using the FDA-cleared MSK-IMPACT assay to identify oncogenic somatic alterations in HRD/DDR genes.

Clinicopathologic features were retrieved from the electronic medical records.

Histopathologic review of ILC cases was performed for variant subclassification according to WHO criteria by two breast pathologists (CS & FP).

Loss of heterozygosity (LOH) was assessed using FACETS.

Mutational signatures were analyzed using SigMA, for tumor samples with at least five single nucleotide variants (SNVs).

HRD status was determined using an algorithm optimized for MSK-IMPACT, with a threshold of 50 for the IMPACT-HRD score to classify tumors as HRD.

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Results

Spectrum of somatic HRD/DDR genetic alterations in ILC

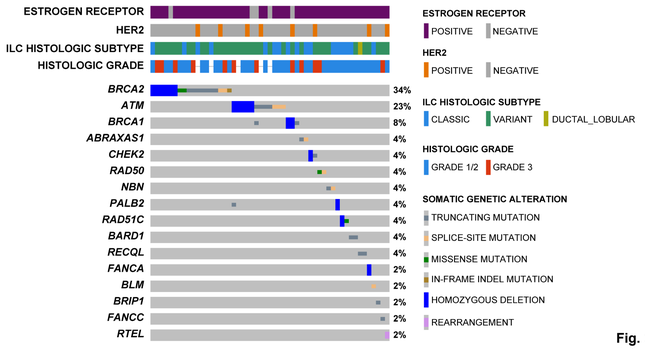


Fig. 1. Somatic genetic alterations in HRD/DDR genes in ILC and clinicopathologic features

Morphologic spectrum

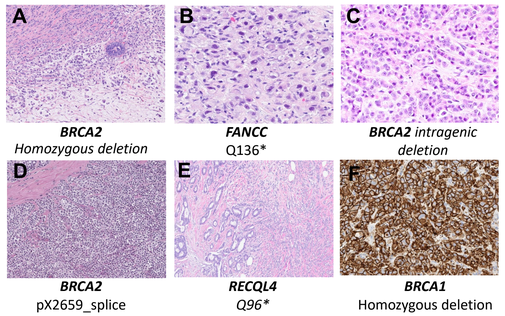


Fig. 2. Histologic spectrum of ILC with somatic HRD/DDR alterations. (**A**) Pleomorphic ILC with extracellular mucin, (**B**) pleomorphic apocrine ILC, (**C**) pleomorphic ILC, (**D**) solid ILC, (**E**) mixed ductal-lobular carcinoma, (**F**) HER2 overexpression (3+) in pleomorphic ILC

Analysis of HRD features in ILC with somatic alterations in HRD/DDR genes

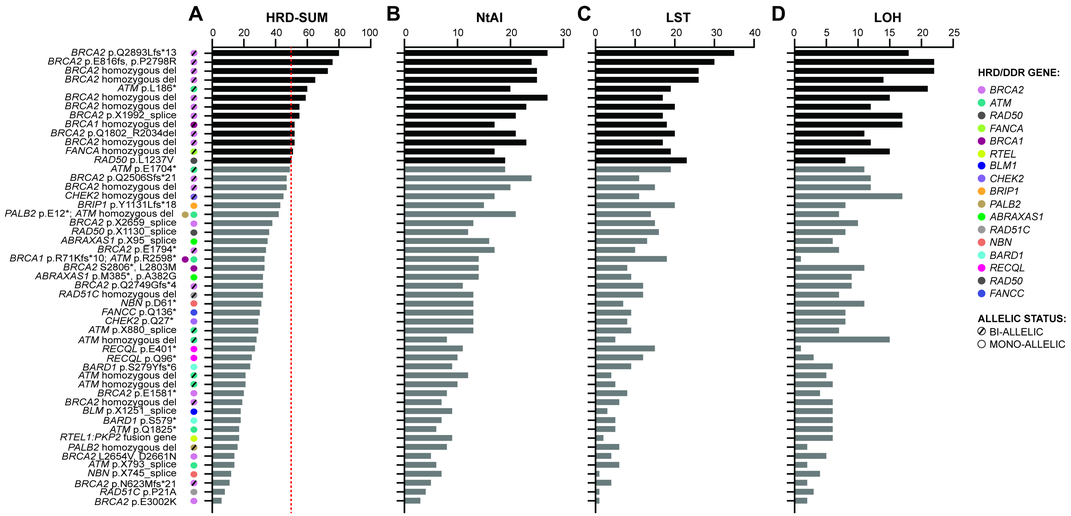


Fig. 3. HRD assessment in ILCs harboring somatic genetic alterations in HRD/DDR genes. (**A**) HRD-SUM, (**B**) NtAI, (**C**) LST and (**D**) LOH scores derived from MSK-IMPACT targeted sequencing data. HRD/DDR genes and allelic status are shown to the left. The red dashed line depicts the HRD threshold.

ILC with biallelic inactivation of HRD/DDR genes



Fig. 4. Clincopathologic characteristics, repertoire of somatic mutations, mutational signature and HRD assessment in of ILCs with biallelic inactivation of HRD/DDR genes

Conclusions

- Our findings demonstrate that, although less frequent than in ductal breast cancer (BC), somatic alterations in HRD/DDR genes occur in a subset of invasive lobular carcinoma (ILC) (5%) with *BRCA2* and *ATM* being the most frequently altered .
- ILC with HRD/DDR show significant heterogeneity.
- High HRD scores and/or the presence of Signature 3 in HRD/DDR genes are predominantly observed in ILC with biallelic *BRCA2* alterations. These cases typically exhibit variant histology, mostly in the form of pleomorphic/pleomorphic features.

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