Structural Variants in Homologous Recombination Repair/DNA Damage Response Pathways as an Alternative Mechanism of Genomic Instability in Breast Cancer

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Background

Alterations in homologous recombination (HR) and DNA damage response (DDR) pathways drive genomic instability in a subset of breast cancers (BC), with associated therapeutic implications. While inactivating mutations in HR-deficiency (HRD)/DDR genes are well established, the role of structural variants (SVs) disrupting these pathway genes remains to be determined.

Aim

Through the analysis of a large cohort of BC, we sought to investigate SVs as a mechanisms of HRD/DDR gene inactivation and to assess their contribution to genomic instability through HRD genomic scars and mutational signatures.

Materials and Methods

- We interrogated 9,481 BCs (4,376 primary and 5,105 metastasis), previously subjected to clinical tumor/normal targeted sequencing (MSK-IMPACT), to identify SVs affecting the HRD/DDR core genes *BRCA1*, *BRCA2*, *PALB2*, *ATM* and *CHEK2*.
- The loss of heterozygosity (LOH) was assessed using FACETS.
- The driver probability of fusion genes was examined using Oncofuse.
- The mutational signatures were inferred using SigMA.
- The HRD status was assessed though evaluation of genomic scars by applying an algorithm tailored for MSK-IMPACT data.

Results

Frequency of structural variants affecting HRD/DDR genes in BC

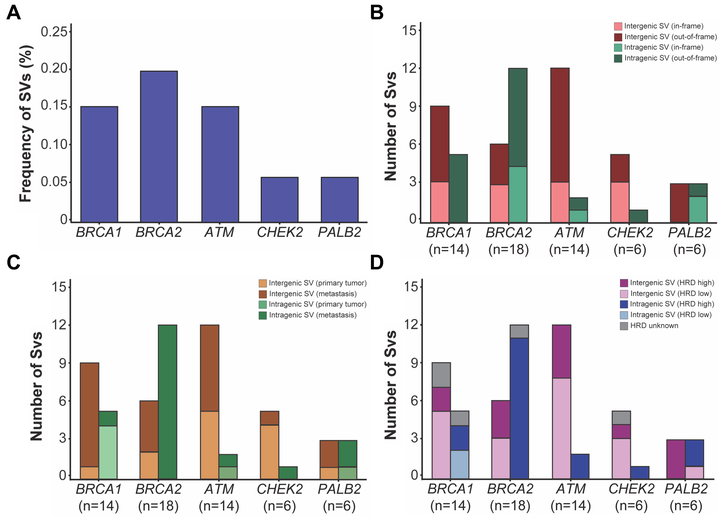


Fig. 1. Frequency of structural variants affecting HRD/DDR genes identified in this study. Vertical bar and stacked bar plots depict the frequency of structural variants (SVs) affecting HRD/DDR genes identified in breast cancer (**A**), and their distribution according to the frame status (**B**), sample type (**C**) and homologous recombination deficiency (HRD) scores (**D**). SV, structural variant.

SV breakpoint distribution according to HRD/DDR gene

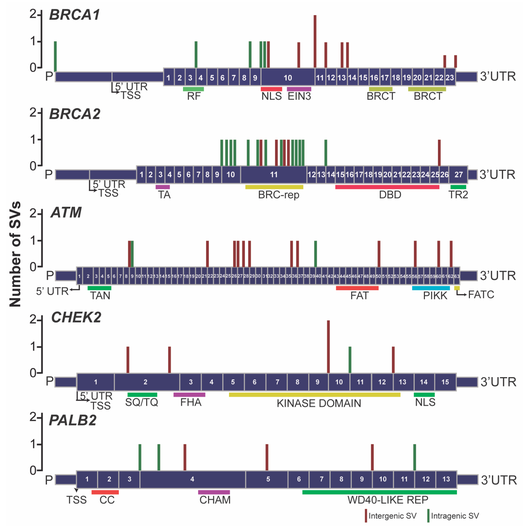


Fig. 2. Position of structural variant genomic breakpoint affecting core HRD/DDR genes. SV, structural variant; TSS, transcription start site; UTR, untranslated region.

Mutational signatures in BCs harboring SVs in HRD/DDR genes

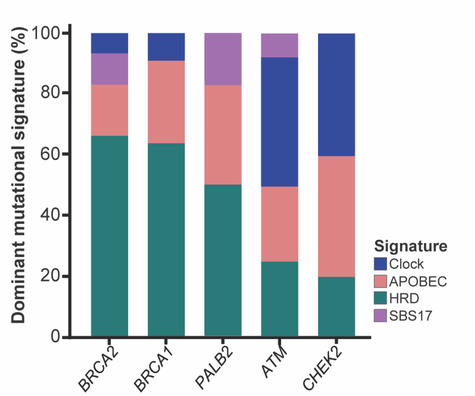


Fig. 4. Mutational signatures in breast cancers harboring structural variants in HRD/DDR genes. Stacked bar plots depicting the dominant mutational signatures present in BCs harboring SVs in HRD/DDR genes.

Molecular features of structural variants affecting HRR genes in BC

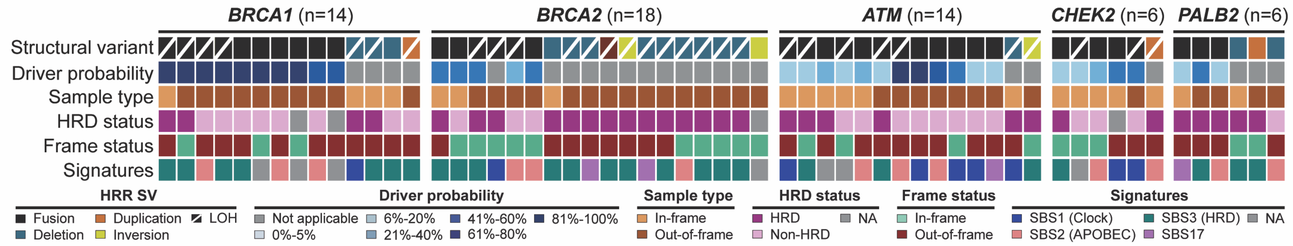


Fig. 3. Structural variants affecting HRD/DDR genes and associated molecular features. Heatmap depicting the molecular features of the structural variants affecting core HRD/DDR genes in breast cancer. Each column is a sample and each row is a molecular feature, color-coded according to the legend at the bottom of the heatmap. HRD, homologous recombination deficiency; HRR, homologous recombination repair; NA, not applicable; SBS, single base substitution; SV, structural variant.

Conclusions

- We demonstrate that although rare, SVs in core HRD/DDR genes represent an underrecognized mechanism of gene inactivation in a subset of BCs.
- Their associated HRD genomic scars and mutational signatures mirror those observed in cases harboring inactivating mutations in those genes, supporting the functional relevance of these SVs in shaping HRD/DDR related processes.
- Our findings highlight alternative mechanisms driving genomic instability and deepen our understanding of the HR/DDR pathways in BC.

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