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BRIEF COMMUNICATION

Examining the prevalence of homologous recombination repair defects in ER+ breast cancers

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Abstract

Purpose Homologous recombination deficiency (HRD) is well characterized in triple-negative breast cancer (TNBC), but its prevalence in the hormone-receptor-positive breast cancer subtypes is not as clearly defined. It is estimated that around 50–60% of TNBC cases are deficient in HR. We sought to identify HRD cases in ER+/Her2− patients using various mutational HRD signatures.

Methods We abstracted published HRD genomic signatures from the Pan-Cancer Analysis of Whole Genomes (PCAWG) database and compared the prevalence of HRD in ER+/Her2− breast cancer, comparing this to the control of set of triple-negative breast cancers.

Results In 78 patients with ER+/Her2− breast cancer, 13 patients have over a 70% probability of being HRD as measured by HRDetect, while 18 qualify as HRD based on HRD score, with an approximate prevalence of HRD ranging between 14 and 20% of cases.

Conclusion Our analyses suggest that 14% of ER+/Her2− patients may be HRD and therefore potentially eligible for treatments with HRD-directed therapies such as platinum agents and PARP inhibitors. As the ER+/Her2− subtype is the most common breast cancer subtype, this group of HRD patients is likely more sizable than that of HRD TNBC patients.

Keywords HRD · Genomic signatures · PARP inhibition · ER+ breast cancer

Introduction

Cancers with defects in homologous recombination repair (HRD) exhibit increased sensitivity to platinum agents and PARP inhibitors (PARPi). HRD can occur secondary to germline or somatic acquired genetic alterations in HR genes or *BRCA1* promoter methylation, but a plurality of HRD cancers do not have known explanatory mechanisms. HRD is relatively frequent in triple-negative breast cancers (TNBCs) [1], but the prevalence in hormone-receptor-positive/Her-2 negative (ER+/Her2−) is not well defined. Furthermore, current germline testing guidelines are appropriately more restrictive in this group relative to TNBCs. We sought to determine the frequency of HRD, defined by genomic signatures, in ER+/Her2− breast cancers, the largest segment of the overall breast cancer population.

The Pan-Cancer Analysis of Whole Genomes (PCAWG) Consortium has made the whole-genomes of 2658 cases available for analysis. We used the available breast cancer cases and identified 78 TNBC cases and 92 ER+/Her2− cases (contributed to PCAWG by the EU, US, and UK breast cancer cohorts). We then computationally abstracted features that have been described as inferences for HRD, including the HRD score (unweighted sum of the scores for three ultrastructural features: large-scale state transitions (LST), telomere allelic imbalances (TAI), and loss-of-heterozygosity (LOH)), HRDetect, single base substitution signature 3 (SBS3), and indel signature 6 (ID6). These scores are associated with responsiveness to systemic therapy, platinum agents, or PARP inhibitors, consistent with their use as surrogates for HRD [1–4]. We dichotomized these signatures based on previously published thresholds when available as follows: HRD score ≥ 42, HRDetect ≥ 0.7,

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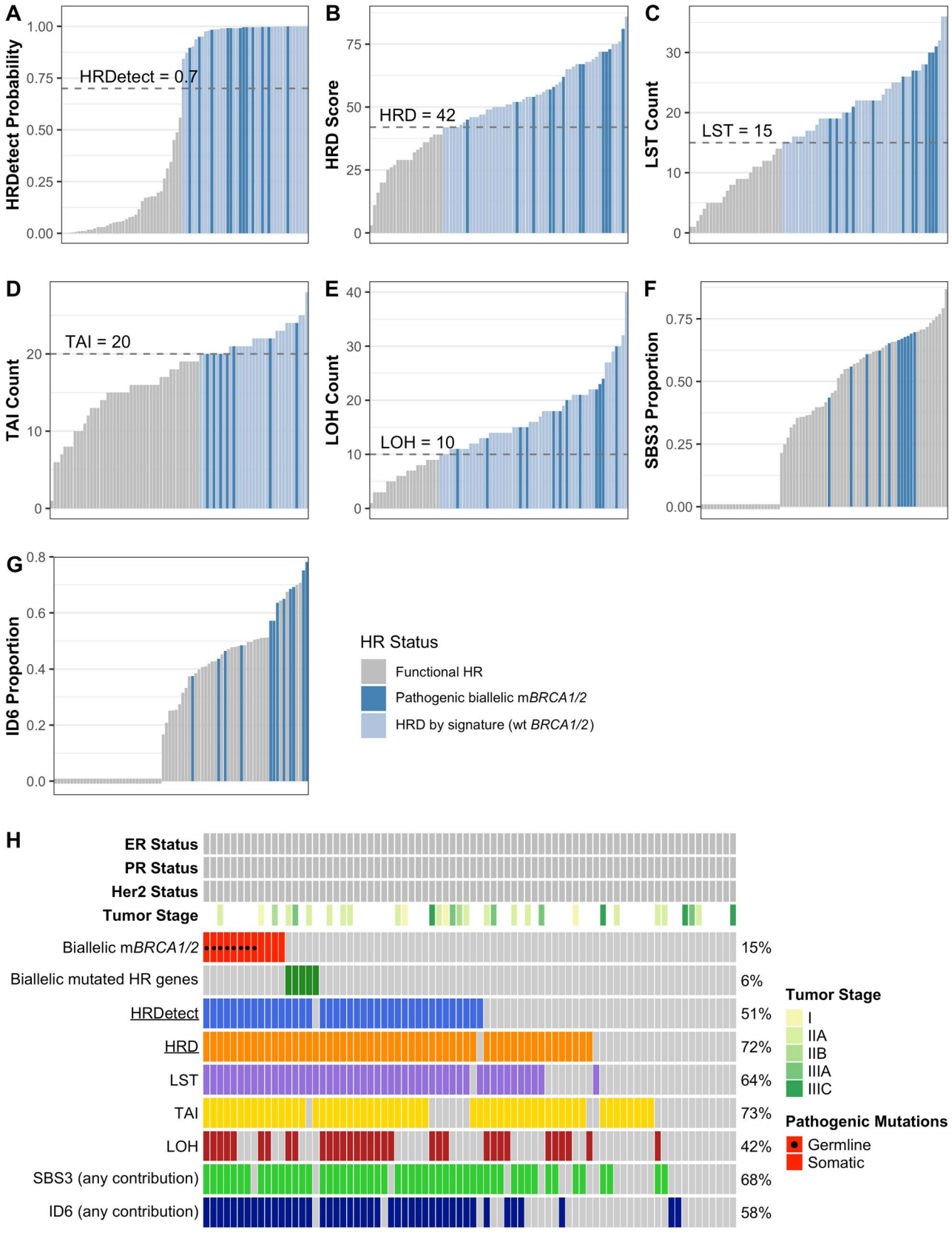
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HRDetect Probability
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TAI Count
TAI = 20
E
LOH Count
LOH = 10
F
SBS3 Proportion
G
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Functional HR
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PR Status
Her2 Status
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Tumor Stage
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Germline
Somatic

◂**Fig. 1** **A–G** Distribution of genomic features across 78 TNBC breast cancer patients (HRDetect, HRD score, LST, TAI, LOH, SBS3, and ID6, respectively). Samples classified as HRD by feature cut-off colored in based on *BRCA*-status. **H** Clinical and genomic features for each patient. Genomic features included if they are classified as HRD by feature cut-off (HRDetect, HRD score, LST, TAI, LOH) or if the signature is present (SBS3, ID6). White boxes for PR status and tumor stage indicate lack of available data. HR genes checked for biallelic mutations include RAD51B, RAD51C, and PALB2, but only a RAD51C mutation was identified

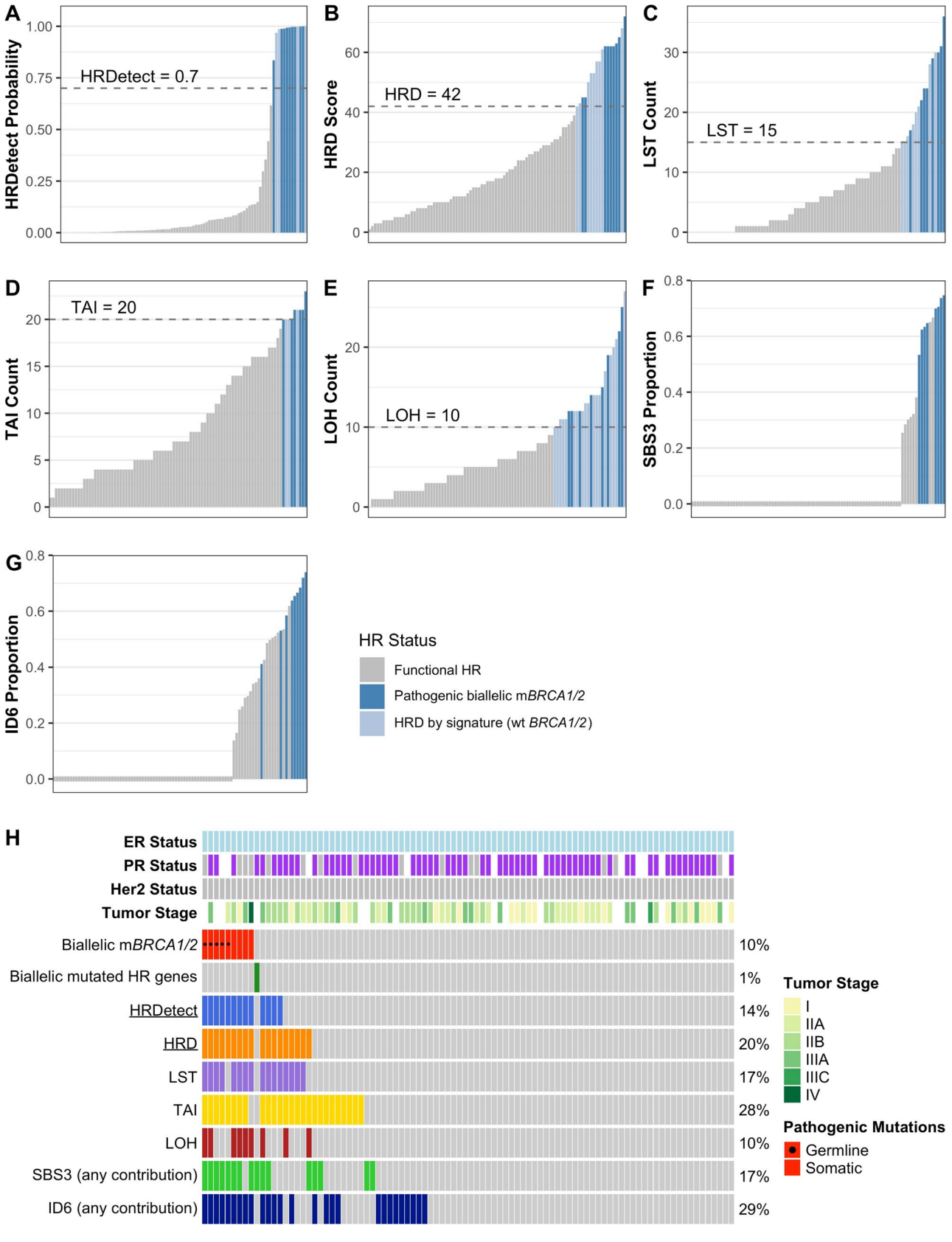
LST ≥ 15, TAI ≥ 15, and LOH ≥ 10 as suggestive of HRD [1].

The prevalence of HRD in TNBC was found to be around 50–60% by the different inference methods consistent with what is known about the distribution of HRD in this subtype (Fig. 1). Additionally, there were 12 TNBC patients with biallelic *BRCA1/2* mutations, of which eight were germline mutations. Thus, our findings in the TNBC cohort are concordant with existing data on HRD in TNBC, and serves as a validation of our methods. In patients with ER+/Her2− breast cancer, 13 patients have over a 70% probability of being HRD as measured by HRDetect, while 18 qualify as HRD based on HRD score (Fig. 2). The SBS3 and ID6 lack defined thresholds for HRD but were present to some degree in 16 and 27 patients, respectively (Fig. 2). Nine ER+/Her2− patients had biallelic mutations in *BRCA1/2*, of which five patients had a germline mutation.

Our work suggests that HRD may be as prevalent as 14% in ER+/Her2− breast cancers. To our knowledge, there are very few published estimates; in one previous study of 981 breast cancer exomes included in the TCGA project, the prevalence of SBS3 as the first signature in luminal A and B subtypes appears consistent with our finding (estimating from their figure) [5]. In another report of 215 breast tumor samples, HRD score was calculated as the mean value of LST, LOH, and TAI [6]. While there is no reported HRD threshold for this metric, comparing the TNBC results with the ER+/Her2−, there is a similar distribution of patients with high mean HRD scores as seen in our analysis (estimating from their figure).

While there is some discordance between individual HRD signatures, we found that 13/92 (14%) of ER+/Her2− cancer genomes are likely to be HRD, even when applying the very stringent criteria of HRDetect. Farkkila et al. similarly used different inferences of HRD signatures in a report on ovarian cancer patients treated with niraparib and pembrolizumab [4]. SBS3 was present in 50% of cases. In contrast, Myriad HRD and the BROCA panel (targeted sequencing of 84 DNA repair genes plus methylation analysis of BRCA1 and RAD51C) were suggestive of HRD in 40% of cases; BRCA mutations were present in 18% of cases. These findings are consistent with our report in that (1) computational inferences of HRD are approximations without perfect concordance, and (2) these inferences can potentially detect tumors with HRD that are not BRCA mutants.

Given the preponderance of ER+ breast cancer, women with ER+ breast cancer with HRD likely outnumber the 50–60% of women with TNBC with HRD. Based on data from the SEER report, TNBC makes up around 10% of breast cancer cases, while the ER+/Her2− subtype occurs in 68% of cases [7]. Using these numbers, HRD ER+/Her2− patients could be around twice as common as HRD TNBC patients. In a future with rapid, clinical-grade assays for HRD, many more breast cancer patients may be eligible for synthetically lethal combination therapies (such as PARP and/or ATR inhibitors) than previously anticipated.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PR Status
Her2 Status
Tumor Stage
Biallelic mBRCA1/2
Biallelic mutated HR genes
HRDetect
HRD
LST
TAI
LOH
SBS3 (any contribution)
ID6 (any contribution)
10%
1%
14%
20%
17%
28%
10%
17%
29%
Tumor Stage
I
IIA
IIB
IIIA
IIIC
IV
Pathogenic Mutations
Germline
Somatic

◂**Fig. 2** **A–G** Distribution of genomic features across 92 ER+/Her2− breast cancer patients (HRDetect, HRD score, LST, TAI, LOH, SBS3, and ID6, respectively). Samples classified as HRD by feature cut-off colored in based on *BRCA*-status. **H** Clinical and genomic features for each patient. Genomic features included if they are classified as HRD by feature cut-off (HRDetect, HRD score, LST, TAI, LOH) or if the signature is present (SBS3, ID6). White boxes for PR status and tumor stage indicate lack of available data. HR genes checked for biallelic mutations include RAD51B, RAD51C, and PALB2, but only a RAD51C mutation was identified

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Author contributions GMM: Conceptualization; formal analysis, investigation, visualization, writing-original draft; SNP: Formal analysis, writing-review&editing; DSH: Conceptualization, formal analysis, visualization; writing-original draft; AJK: Conceptualization, formal analysis, visualization; writing-original draft.

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Data availability All data used in this study are available from PCAWG. Controlled PCAWG data can be obtained after applying for access through ICGC DACO and dbGaP (https://docs.icgc.org/pcawg/data/).

Declarations

Conflict of interest All authors declares that they have no conflict of interest to disclose.

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