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Original Article

Comprehensive profiling of somatic alterations and HRD characteristics in Chinese germline BRCA-mutated breast cancer patients

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Abstract: Approximately 10% of breast cancer cases are hereditary and associated with germline BRCA1/2 mutations. To characterize the somatic alteration landscape and HRD-related genomic features, we analyzed next-generation sequencing and clinical data from 1,243 breast cancer patients treated at Tianjin Cancer Hospital Airport Hospital between October 2021 and November 2024. We compared mutation patterns and clinicopathological features between patients with and without germline BRCA (gBRCA) mutations and further assessed somatic alterations and homologous recombination deficiency (HRD) in those carrying pathogenic variants. PIK3CA mutations were significantly more frequent in the Non-Germline and non-gBRCA groups than in the Germline and gBRCA groups (49% vs. 6%; 47% vs. 0%; both $P < 0.001$), indicating mutual exclusivity with gBRCA mutations. Conversely, PTEN alterations co-occurred in 30% of gBRCA cases, while TP53 mutations were mutually exclusive with MDM2 and FGFR1. HER2 amplification was identified in 10% of gBRCA-mutated tumors, and somatic alterations in non-gBRCA tumors were enriched in endocrine-resistance pathways. HRD scores were markedly higher in gBRCA patients than in non-gBRCA patients (median 59 vs. 24.5, $P = 0.015$), driven by significant increases in large-scale state transitions (LST) and telomeric allelic imbalance (TAI). The overall gBRCA1/2 mutation frequency was 15.61%, and two previously unreported variants, BRCA1 NM_007294.3:c.4185G>A and BRCA2 NM_000059.3:c.439C>A, were identified in the Chinese population. These findings provide a biological rationale to explore AKT1/HER2-targeted combinations with PARP inhibition in future studies for gBRCA-mutated breast cancer and provide the first evidence of PIK3CA-gBRCA mutual exclusivity in Chinese patients. The elevated HRD scores further underscore the presence of homologous recombination deficiency in the gBRCA group.

Keywords: Breast cancer, germline mutations, somatic mutations, gBRCA, HRD characteristics

Introduction

Breast cancer is the most commonly diagnosed malignancy among women and the second most prevalent newly diagnosed cancer worldwide [1]. Despite advances in screening and therapy, breast cancer remains a major public health concern due to its high incidence and heterogeneity in clinical behavior and treatment response. Approximately 10% of breast cancer cases are classified as hereditary breast cancer, which is primarily driven by inherited mutations in high-penetrance susceptibility genes [2]. Among these, BRCA1 and BRCA2 are the most significant, accounting for a large proportion of hereditary breast cancer cases [3].

Women carrying pathogenic germline mutations in BRCA1 or BRCA2 have a substantially increased lifetime risk of developing breast and ovarian cancers. BRCA1/2 proteins are central components of the homologous recombination repair (HRR) pathway for DNA double-strand breaks. Loss-of-function mutations lead to homologous recombination deficiency (HRD), genomic instability, and a synthetic lethal vulnerability to poly (ADP-ribose) polymerase (PARP) inhibition [4-6]. PARP inhibitors are now approved for both metastatic and early-stage breast cancer in patients with pathogenic gBRCA1/2 mutations, making gBRCA status an essential biomarker for risk assessment and therapeutic decision-making.

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However, approximately 40%-50% of patients with germline BRCA mutations do not respond to PARP inhibitor therapy [7, 8]. Mechanisms of both primary and acquired resistance include restoration of HRR, replication fork protection, drug efflux, PARP1 alterations, and rewiring of major oncogenic pathways, such as PI3K/AKT and MAPK. These observations highlight the need for rational combination strategies, including PARP inhibitors with targeted agents, immune checkpoint inhibitors, or platinum-based chemotherapy [9, 10]. In parallel, targeted therapies directed at driver alterations such as HER2 amplification, PIK3CA mutations, and PTEN loss, as well as immunotherapy for tumors with high microsatellite instability (MSI-H), have further expanded the therapeutic landscape in advanced breast cancer [11].

The HRD score, which integrates genomic measures such as loss of heterozygosity (LOH), large-scale state transitions (LST), and telomeric allelic imbalance (TAI), has emerged as an important predictor of sensitivity to DNA-damaging agents, including platinum compounds and PARP inhibitors, particularly in ovarian cancer [12-14]. In breast cancer, however, a standardized threshold for defining HRD positivity remains lacking, and its integration with germline and somatic alterations remain less clearly established. Moreover, the biological interplay between PI3K/AKT pathway activation and HRD is increasingly recognized: PI3K signaling can modulate BRCA1/2 expression and RAD51 recruitment, thereby affecting HR proficiency and PARP inhibitor sensitivity, while PTEN loss has been shown to further compromise HRR and enhance genomic instability [5, 12].

Despite these advances, few studies have conducted large-scale, integrated analyses of germline BRCA mutations, somatic alterations, pathway-level changes, and HRD phenotypes in Chinese breast cancer populations. Given the documented ethnic differences in BRCA mutation spectra and co-mutational patterns, such data are important for improving molecular characterization and informing future precision-oncology studies in Chinese patients.

In this study, we aimed to: (1) compare the somatic mutational profiles between patients with and without gBRCA1/2 mutations; (2) identify mutually exclusive and co-occurring mutation patterns, and explore the molecular rationale for potential combination treatment regimens; (3) assess the enrichment of altered signaling pathways, with a focus on endocrine resistance; and (4) evaluate HRD scores and related genomic signatures, including LOH, LST, and TAI. Through this integrated approach, we seek to characterize the molecular landscape of hereditary breast cancer in Chinese patients and provide a stronger rationale for precision clinical management.

Materials and methods

Patients and study methods

This study included a total of 1,243 breast cancer patients who underwent next-generation sequencing (NGS) between October 2021 and November 2024 at Tianjin Cancer Hospital Airport Hospital. The inclusion criteria were: (1) a histopathologically confirmed diagnosis of breast cancer, and (2) completion of germline BRCA1/2 testing. Among the enrolled patients.

Among the enrolled patients, 1,137 underwent germline-only testing using a hereditary breast/ovarian cancer panel that only included BRCA1, BRCA2. The remaining 106 patients received dual testing, consisting of both germline analysis and comprehensive somatic genomic profiling using a broad cancer gene panel (≥ 139 cancer-related genes), which covered key oncogenic signaling pathways and DNA-damage response genes. The overall cohort (n = 1,243) comprised consecutive patients undergoing germline testing for hereditary risk assessment, whereas the paired cohort (n = 106) was a clinically selected subset who additionally received tumor profiling driven by treatment decision needs. This design enabled us to evaluate the germline BRCA (gBRCA) mutation frequency in the full cohort and to analyze detailed somatic mutational patterns, pathway alterations, and HRD characteristics in the subset with dual testing. In this study, the HRD score was calculated using a genomic-scar model consistent with previously published 3DMed-HRD methodology, where the HRD score is defined as the unweighted sum of LOH, TAI, and LST components derived from tumor copy-number profiling (with appropriate quality control and correction steps as applicable) [PMID: 36861447; PMID: 35156571] [15, 16].

Pathogenic and likely pathogenic germline variants were annotated according to the American College of Medical Genetics and Genomics (ACMG) criteria and current clinical practice guidelines. Variants of uncertain significance were not considered gBRCA-positive in this study. We conducted a retrospective analysis to investigate the somatic mutational landscape and HRD characteristics in patients carrying deleterious germline BRCA1/2 mutations, and to evaluate the mutation frequencies and clinicopathological features of patients with gBRCA versus those without gBRCA. The study was approved by the Ethics Committee of Tianjin Cancer Hospital Airport Hospital, and written informed consent or a waiver of consent was obtained in accordance with institutional and national regulations.

Statistical analysis

Differences in gene alteration frequencies between groups were evaluated using two-sided Fisher's exact tests, with statistical significance defined as $P < 0.05$. For the mutation waterfall plots (**Figures 2A** and **3A**), the top 30 genes with the highest mutation frequencies in at least one comparison group were displayed. To facilitate visual comparison, genes in each plot were ordered in descending order of mutation frequency within the corresponding group. Pathway enrichment analysis of differentially mutated genes was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, implemented via the clusterProfiler package in R [17]. Enrichment *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method, and pathways with a false discovery rate (FDR) < 0.05 were considered significantly enriched. To ensure sufficient genomic coverage for reliable KEGG enrichment, only the tumors analyzed with the 295-gene panel were included in the pathway analysis. To minimize panel-related detection bias, all gene-level frequency comparisons and co-occurrence/mutual-exclusivity analyses were restricted to the gene set covered by both panels (the 139-panel gene list). As a sensitivity analysis, panel-stratified tests were additionally performed to confirm robustness.

Comparisons of tumor mutational burden (TMB), HRD scores, and chromosomal instability (CIN) scores between gBRCA1/2 subgroups were conducted using the Wilcoxon rank-sum test. Pairwise Fisher's exact tests were used to assess co-occurrence or mutual exclusivity between somatic mutations, copy number alterations, and gene fusions. For the gene interaction network (**Figure 3C**), only gene pairs with Fisher's exact test $P < 0.05$ were included.

All statistical analyses were performed using R software (version 4.4.1) and RStudio.

Results

Analysis of BRCA1/2 mutations in breast cancer germline

Among the 1,243 breast cancer patients, the overall frequency of gBRCA mutations was 15.61%, with 10.38% carrying BRCA1 mutations and 5.23% carrying BRCA2 mutations. A total of 58 germline variants were identified in BRCA1, and 45 in BRCA2. Notably, two novel variants - BRCA1 NM_007294.3:c.4185G>A and BRCA2 NM_000059.3:c.439C>A - were not recorded in existing public databases, suggesting their potential uniqueness in the Chinese population.

Correlation analysis revealed mutual exclusivity between gBRCA1 and gBRCA2 mutations. Both mutation types were more commonly observed in patients older than 35 years (**Figure 1**), although the age-related difference was not statistically significant. Additionally, no significant differences were found between gBRCA1 and gBRCA2 carriers in terms of clinical stage, molecular subtype, the presence of bilateral breast cancer, or response to neoadjuvant therapy.

Differences in molecular characteristics of patients with germline-mutated breast cancer

Among the 106 patients who underwent both somatic and germline genomic sequencing, 17 patients were identified as carrying at least one pathogenic germline mutation (including BRCA1/2 and other cancer susceptibility genes) and were therefore classified into the germline mutation group, while the remaining 89 patients, in whom no pathogenic germline mutations were detected, were classified into the non-germline mutation group.

It should be noted that in subsequent analyses, patients are further stratified into gBRCA and non-gBRCA groups according to the presence

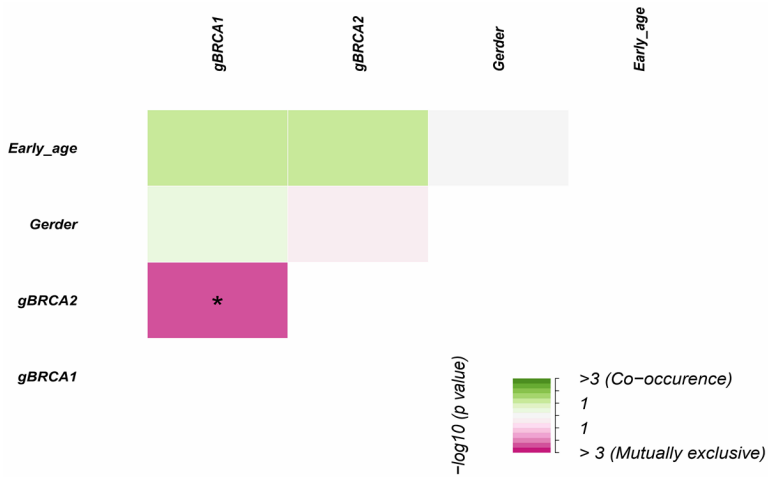

Figure 1. Correlation between germline BRCA (gBRCA) status and clinical features.

or absence of germline BRCA1/2 variants classified as pathogenic or likely pathogenic. Because these two classification strategies are not identical, mutation frequencies reported across these analyses, including those for PIK3CA, are not directly comparable.

In the germline mutation group, the most frequently altered genes were TP53 (65%), MYC (35%), and KMT2C, PTEN, AR, and MET (each at 18%). In contrast, the non-germline group exhibited high-frequency mutations in TP53 (63%), PIK3CA (49%), and MYC (25%) (**Figure 2A**). The mutation frequency of PIK3CA was significantly higher in the non-germline group compared to the germline group (49% vs. 6%, P < 0.001), whereas MET mutations were significantly enriched in the germline group (18% vs. 2%, P < 0.05) (**Figure 2B**). Among the PIK3CA mutations observed in the non-germline group, the most common variants were p.H1047R (54.55%), p.E545K (11.36%), and p.H1047L (9.09%).

Somatic mutation profiles in gBRCA vs. non-gBRCA groups

Further stratification based on germline BRCA status showed that in the gBRCA group (n = 10), the most common somatic mutations were TP53 (60%), MYC (50%), and PTEN (30%). In the non-gBRCA group (n = 96), the most frequently mutated genes were TP53 (64%), PIK3CA (47%), and MYC (24%) (**Figure 3A**). The PIK3CA mutation rate was significantly higher in the non-gBRCA group than in the gBRCA group (47% vs. 0%, P < 0.001), while PTEN mutations were significantly more frequent in the gBRCA group (30% vs. 4%, P < 0.05) (**Figure 3B**). Additionally, among 10 patients with gBRCA mutations, one exhibited HER2 amplification, suggesting that 10% of patients with gBRCA may be candidates for combined PARP inhibitor and anti-HER2 targeted therapy. Meanwhile, among 96 patients without germline BRCA mutations, 19 cases showed HER2 variations, and statistical analysis revealed no significant difference in HER2 variations between the two patient populations (P = 0.7425). In the whole cohort, there were not MSI-H found through NGS test and 106 patients were all MSS. Gene interaction analysis revealed that PIK3CA mutations were mutually exclusive with gBRCA mutations, PTEN mutations significantly co-occurred with gBRCA mutations, and TP53 mutations were mutually exclusive with MDM2 and FGFR1 alterations (**Figure 3C**). Among the 10 gBRCA-positive tumors, 5 were sequenced using a 295-gene panel and 5 using a 139-gene panel. Because KEGG pathway enrichment requires sufficient genomic coverage to reliably capture pathway-level alterations, only the 5 cases sequenced with the 295-gene panel were included in the pathway analysis. Additionally, pathway enrichment analysis of genes mutated exclusively in the 64 non-gBRCA patients (63 genes) relative to the five gBRCA patients included in the pathway analysis showed significant enrichment of the endocrine resistance pathway (FDR < 0.05). These genes involved recurrent alterations in canonical endocrine resistance-related genes, including ESR1, PIK3CA, PIK3R1, AKT2, MTOR, CDK4, ERBB3, FGFR2, FGFR3, FGF19, KRAS, NRAS, HRAS, RAF1, NRG1, and RARA, as well as related co-regulators (**Figure 3D**). These comparisons were conducted using the shared 139-panel gene set to ensure comparable genomic coverage across cases.

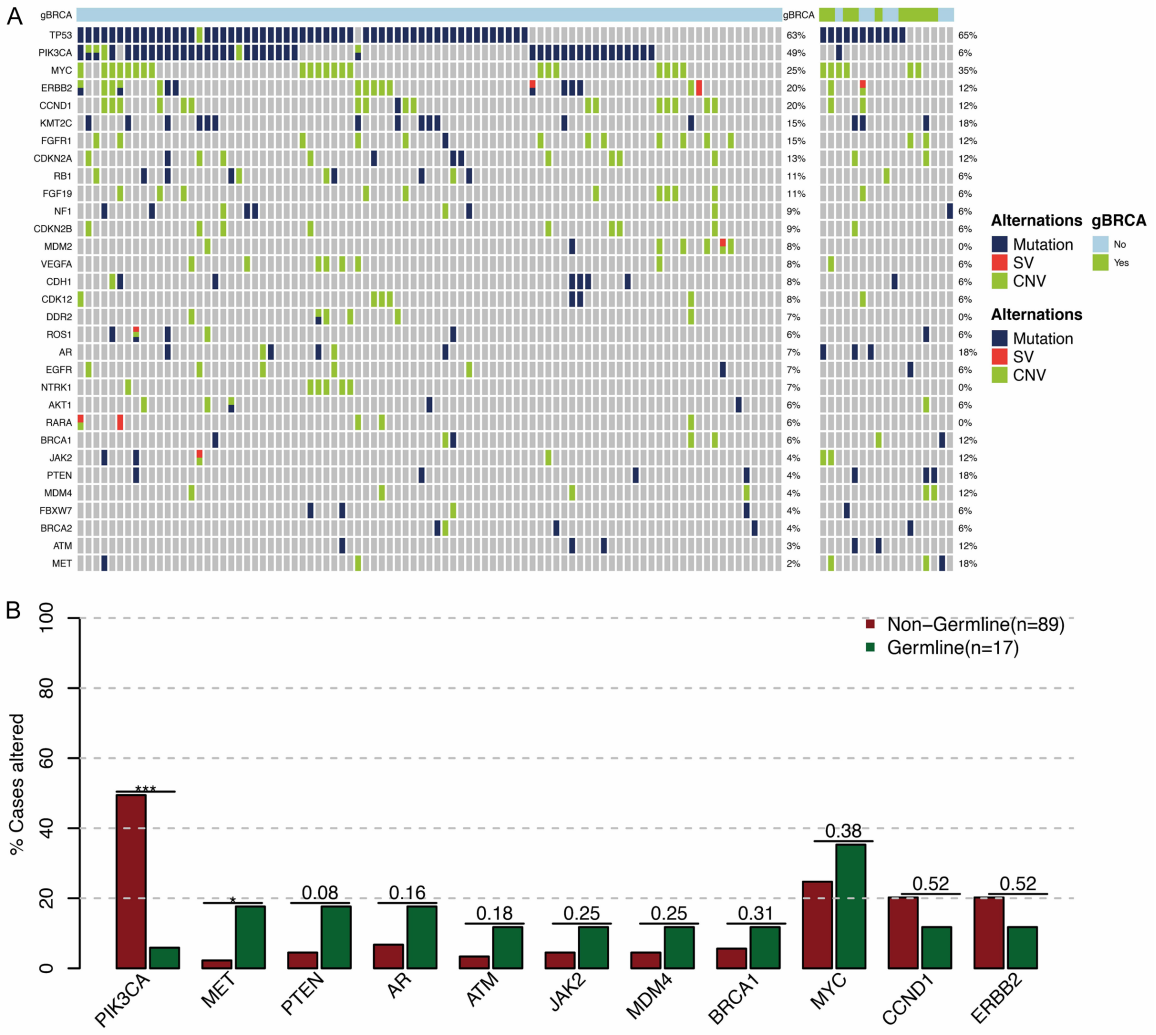

Figure 2. Molecular features associated with germline mutation-related breast cancer. A. Waterfall plot illustrating the mutation spectrum in the Non-Germline and Germline cohorts. B. Genes exhibiting significantly different mutation frequencies between the Non-Germline and Germline groups.

HRD characteristics of germline mutant breast cancer patients

Among the 106 patients, tumor mutational burden (TMB) analysis showed a trend toward higher TMB in the gBRCA group compared to the non-gBRCA group, although the difference did not reach statistical significance (median: 8.38 vs. 5.59 mutations/Mb, P = 0.056) (**Figure 4A**). In contrast, both the homologous recombination deficiency (HRD) scores and chromosomal instability scores (CIS) were significantly higher in the gBRCA group than in the non-gBRCA group (HRD median: 59 vs. 24.5, P = 0.015; CIS median: 45 vs. 20, P = 0.016) (**Figure 4B**, **4C**).

Further analysis of the three genomic instability components contributing to the HRD score revealed no significant difference in the LOH score between the two groups. However, the LST and TAI scores were significantly elevated in the gBRCA group compared to the non-gBRCA group (**Figure 4D**). These findings suggest that patients with germline BRCA mutations exhibit greater genomic instability, particularly in chromosomal structural alterations, consistent with impaired homologous recombination repair.

Discussion

BRCA1 and BRCA2 are central components of the HRR pathway. Loss-of-function mutations

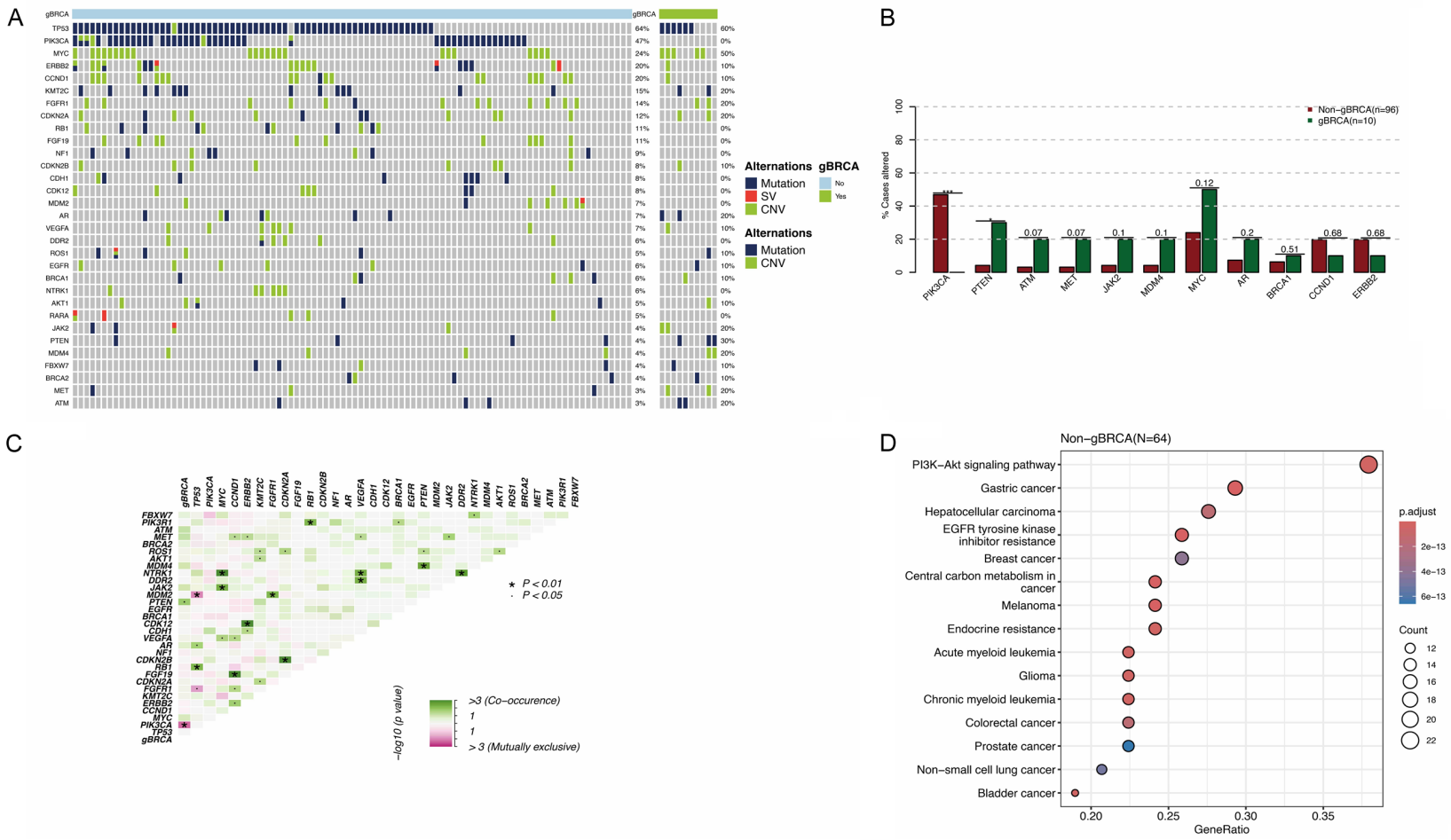

Figure 3. Molecular characteristics of breast cancers with and without germline BRCA (gBRCA) mutations. A. Waterfall plot showing the somatic mutation landscape in the non-gBRCA and gBRCA groups. B. Differentially mutated genes between the non-gBRCA and gBRCA groups. C. Gene-gene interaction network of gBRCA-associated alterations, illustrating significant co-occurrence and mutual exclusivity (Fisher's exact test, $P < 0.05$). D. Signaling pathways uniquely enriched in the non-gBRCA group.

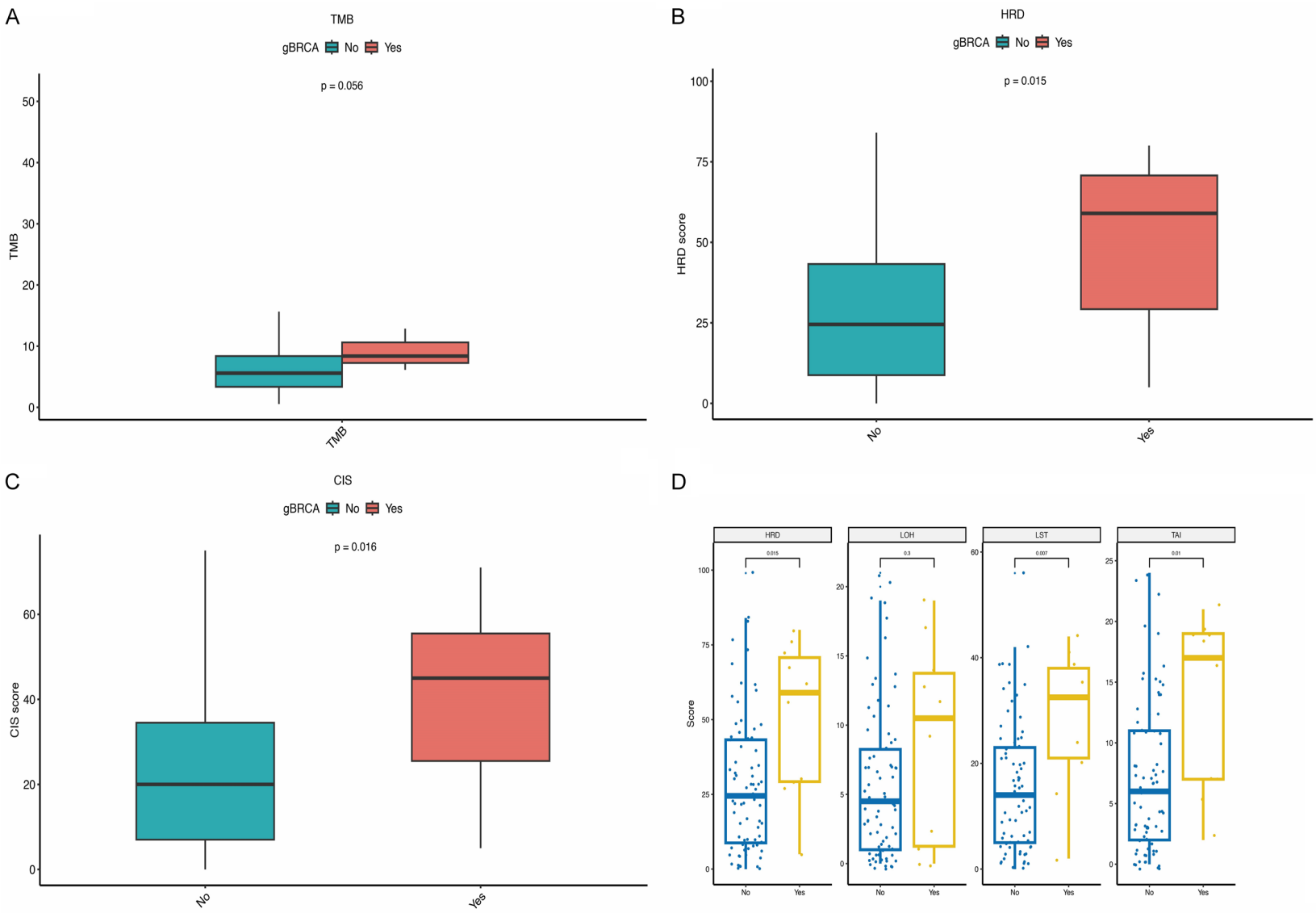

Figure 4. Features of TMB and HRD in non-gBRCA and gBRCA groups. A. Comparison of tumor mutational burden (TMB) between non-gBRCA and gBRCA groups. B. Comparison of homologous recombination deficiency (HRD) scores between non-gBRCA and gBRCA groups. C. Comparison of chromosomal instability score (CIS) between non-gBRCA and gBRCA groups. D. Comparison of HRD components, including loss of heterozygosity (LOH), large-scale state transitions (LST), and telomeric allelic imbalance (TAI), between non-gBRCA and gBRCA groups.

in these genes impair the repair of DNA double-strand breaks, leading to genomic instability. This defect induces a synthetic lethality mechanism that renders tumor cells particularly sensitive to PARP inhibitors. PARP inhibitors have been approved for breast cancer patients with pathogenic germline BRCA1/2 mutations [18-20]. Comprehensive analysis of somatic alterations in gBRCA-mutant breast cancers is valuable for understanding tumor biology, treatment response, and potential resistance mechanisms.

Consistent with previous studies, our data demonstrated a significantly lower frequency of PIK3CA mutations in gBRCA patients compared with non-gBRCA patients, suggesting a mutually exclusive relationship [21], our study demonstrated a significantly lower frequency of PIK3CA mutations in gBRCA patients compared to non-gBRCA patients, suggesting a mutually exclusive relationship. The most frequent PIK3CA variants in our cohort - p.H1047R, p.E545K, p.H1047L, and p.E542K - are classical activating mutations [22]. Previous studies, such as by Guo et al. [23], have shown that the PIK3CA H1047R mutation is associated with reduced pathological complete response rates, further highlighting its clinical relevance. Previously several studies have reported a mutually exclusive relationship between PIK3CA and gBRCA in Caucasus breast cancer patients [24-26]. However, to our knowledge, no studies have yet explored the correlation between PIK3CA variants and gBRCA in the Chinese breast cancer population. Given that significant differences exist in BRCA mutation rates and characteristics between Caucasus and Asian patients, our findings add important population-specific data.

From a biological perspective, activating mutations in PIK3CA result in hyperactivation of the PI3K/AKT/mTOR signaling pathway, which can upregulate HRR components and partially restore homologous recombination capacity, thereby reducing selective pressure for BRCA loss in some contexts [27, 28]. In contrast, PTEN functions as both a negative regulator of PI3K signaling and a guardian of genomic stability. PTEN loss has been reported to impair RAD51 recruitment and further compromise HRR, leading to increased chromosomal instability and HRD [5, 7]. In our study, PIK3CA mutations were mutually exclusive with gBRCA, whereas PTEN mutations significantly co-occurred with gBRCA. This pattern supports a model in which PIK3CA-driven tumors are less likely to acquire or retain gBRCA-mediated HRD, while PTEN loss may synergize with gBRCA to exacerbate genomic instability, which is consistent with the higher HRD, LST, and TAI scores observed in the gBRCA group.

Beyond these findings, our analysis of the non-gBRCA cohort identified a broad set of unique somatic alterations - including AKT2, ATR, BARD1, FANCA, FANCD2, FANCL, ERCC2, ERCC3, MLH1, MLH3, MSH2, PMS1, PMS2, POLD1 and POLE - involved in diverse DNA damage repair pathways. However, despite the presence of these repair-related mutations, the overall HRD, LST and TAI scores in non-gBRCA tumors remained significantly lower than those in gBRCA carriers, suggesting that many of these alterations are monoallelic or subclonal and insufficient to produce a BRCA-like HRD phenotype. This highlights that not all DDR mutations are functionally equivalent to BRCA loss and reinforces the central role of germline BRCA in shaping genomic instability.

Additionally, non-gBRCA tumors exhibited multiple alterations in PI3K/AKT/mTOR and metabolic regulators (AKT2, MTOR, PIK3R1, STK11, TSC1, TSC2), receptor tyrosine kinases (FGFR2, FGFR3, ERBB3, NTRK1/2, KIT, FLT3, NRG1), and RAS/RAF components (KRAS, NRAS, HRAS, BRAF, RAF1). These alterations indicate that BRCA-proficient tumors rely more on proliferative and endocrine-resistance signaling, consistent with our KEGG enrichment analysis showing endocrine resistance pathway activation uniquely in the non-gBRCA group. Altogether, these findings reveal that non-gBRCA breast cancers adopt fundamentally different oncogenic programs than gBRCA tumors, with greater heterogeneity and multiple potentially targetable pathways such as FGFR, NTRK and MAPK.

In March 2025, the PI3Kα inhibitor inavolisib was approved in China for patients with PIK3CA-mutated, HR+/HER2- advanced breast cancer. Since PIK3CA mutations and gBRCA mutations are mutually exclusive in our research, this drug is unlikely to be combined with PARP inhibitors for breast cancer patients with gBRCA mutations. However, another AKT1 inhibitor, capiv-

asertib, was approved in China in April 2025 for HR+/HER2- advanced breast cancer with PI3KCA/AKT1/PTEN alterations. Our study found that 30% of gBRCA-mutated breast cancers concurrently harbor pathogenic alterations in the PTEN gene, suggesting potential clinical value for combination therapy with AKT1 inhibitors and PARP inhibitors in this biomarker-defined subgroup. Although we did not generate in vitro or in vivo experimental data in this study, our observations are consistent with preclinical and clinical evidence that inhibition of the PI3K/AKT pathway can sensitize HRR-deficient tumors to PARP inhibition and delay or overcome PARP inhibitor resistance [5, 7-9].

Additionally, HER2 amplification was detected in 10% of patients with gBRCA variants, indicating that a small proportion of the gBRCA-mutated breast cancer population may benefit from combining classic anti-HER2 therapy with PARP inhibitors. Preclinical models have suggested that HER2 signaling interacts with DNA damage response pathways, and dual targeting of HER2 and PARP has shown synergistic antitumor effects in HER2-positive breast cancer [9]. In our cohort, these HER2-amplified gBRCA tumors represent a distinct molecular subgroup that warrants further investigation in future combination trials.

Consistent with previous reports, the incidence of MSI-H in breast cancer patients was low [29], and all 106 patients enrolled in this study belonged to the MSS population. In our cohort, gene interaction analysis revealed that PIK3CA mutations were mutually exclusive with gBRCA mutations, while PTEN mutations co-occurred with gBRCA mutations. Moreover, TP53 mutations were found to be mutually exclusive with MDM2 and FGFR1, consistent with known biological relationships among these genes. Pathway enrichment analysis indicated that somatic mutations unique to the non-gBRCA group were significantly enriched in endocrine resistance pathways, potentially reflecting the emergence of therapy-resistant clones in hormone receptor-positive breast cancers following endocrine treatment. These findings underscore the importance of comprehensive genomic profiling at both baseline and disease progression to better guide individualized therapy [30]. Together, these observations underscore the importance of comprehensive genomic profiling at both baseline and disease progression to better guide individualized therapy.

In ovarian cancer, HRD positivity is defined by either BRCA1/2 mutations or a genomic instability score (GIS) of ≥ 42 [31-33], and PARP inhibitors such as olaparib and niraparib are approved in both BRCA-mutant and HRD-positive patients [34-36]. However, there remains no universally accepted threshold for defining HRD positivity in breast cancer. Moreover, the commonly cited GIS ≥ 42 cutoff was established using a specific commercial assay in ovarian cancer and is not directly applicable to the custom NGS panel and scoring algorithm used in our study. For this reason, we did not dichotomize patients according to this ovarian cancer - based threshold, but instead focused on comparative analyses between gBRCA and non-gBRCA tumors. Our study found that HRD scores were significantly higher in gBRCA patients than in non-gBRCA patients (median 59 vs. 24.5, P = 0.015), primarily driven by elevated LST and TAI scores, whereas LOH scores did not show significant differences between the two groups. This HRD profile in **Figure 4D** clearly indicates that germline BRCA-mutated breast cancers in our cohort are characterized by a more pronounced pattern of genomic instability compared with BRCA-proficient tumors. However, PARP inhibitor treatment and outcome data were not available; therefore, we could not evaluate HRD as a predictive biomarker of PARP inhibitor benefit in this study.

From a mechanistic perspective, these findings are consistent with the notion that BRCA deficiency predominantly leads to chromosomal structural alterations rather than widespread clonal LOH. LST reflects the accumulation of large-scale chromosomal breakage and rejoining events, and TAI captures allelic imbalance extending to telomeric regions; both are tightly linked to defects in homologous recombination repair. In contrast, LOH can arise through multiple biological processes, not all of which are directly dependent on HRR, and may therefore be less sensitive for distinguishing gBRCA from non-gBRCA tumors in a relatively small cohort. The **Figure 4D** plot in **Figure 4** highlights this pattern: while HRD, LST and TAI are markedly shifted upwards in the gBRCA group, the distribution of LOH overlaps substantially between

groups. Together, these observations support the use of composite HRD scoring and its structural components, particularly LST and TAI, to capture BRCA-associated genomic instability in breast cancer and provide a biological rationale for the potential sensitivity of gBRCA tumors to PARP inhibitors and other DNA-damaging therapies.

The frequencies of gBRCA1 and gBRCA2 mutations in our cohort were 10.38% and 5.23%, respectively, consistent with previous studies in Chinese populations [37]. We also identified two novel variants - BRCA1 NM_007294.3:c.4185G>A and BRCA2 NM_000059.3:c.439C>A - not previously recorded in public databases, which contribute to expanding the BRCA mutation spectrum in Chinese breast cancer patients. This study has several limitations. First, the germline gene panels used were not standardized across all patients, which limited our ability to assess other hereditary cancer genes beyond BRCA1/2. Because this is a real-world, single-center study and the paired cohort represents a treatment decision - driven subset, molecular associations observed in the 106 paired cohort may not be fully generalizable to the entire 1,243 cohort. Second, the sample size for patients who underwent both somatic and germline testing was relatively small. Third, survival data were not available, precluding evaluation of the prognostic implications of our findings. What's more, although two somatic panels were used, restricting analyses to the shared gene set and performing panel-stratified sensitivity analyses suggested minimal panel-related bias; nevertheless, residual bias cannot be fully excluded. Future studies with larger cohorts and long-term clinical follow-up are necessary to validate these results.

In summary, our study reveals distinct somatic mutational profiles and elevated genomic instability in breast cancer patients with germline BRCA1/2 mutations. The mutual exclusivity of PIK3CA and gBRCA mutations, the co-occurrence of PTEN with gBRCA, and the enrichment of endocrine resistance - related genes in non-gBRCA patients provide insight into the molecular heterogeneity of breast cancer. Furthermore, significantly higher HRD scores in the gBRCA group - primarily driven by LST and TAI - highlight the functional impact of homologous recombination deficiency. Importantly, the presence of multiple RTK-RAS-PI3K pathway alterations, partial DNA Damage Response (DDR) gene defects, and chromatin remodeling abnormalities uniquely in the non-gBRCA group further emphasizes that BRCA-proficient tumors follow alternative oncogenic trajectories distinct from BRCA-driven HRD tumors.

These findings support the clinical value of integrated germline and somatic genomic profiling, as well as HRD assessment, in guiding precision treatment strategies for breast cancer. Expanding the BRCA variant database through novel mutation discovery also enhances our understanding of the hereditary landscape in the Chinese population. Nonetheless, validation in larger, multi-center cohorts with survival data is warranted to further establish the clinical implications of these molecular features.

Conclusion

This study revealed the potential clinical application of combining AKT1 inhibitors or HER2 inhibitors with PARP inhibitors in Chinese breast cancer patients with gBRCA mutation. This research is also the first to demonstrate a significant mutually exclusive relationship between PIK3CA mutations and gBRCA mutations in Chinese breast cancer patients. Significantly higher HRD scores driven by LST/TAI in the gBRCA group underscore homologous recombination deficiency.

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Disclosure of conflict of interest

None.

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