Research Square

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Clinicopathological and genetic analysis of 55 male patients with invasive breast cancer

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Abstract

Aims

To explore the clinical and pathological characteristics, immunophenotypes, and molecular genetic features of invasive male breast cancer.

Methods

The clinicopathological data of 55 male patients with invasive breast cancer were analyzed. Molecular subtyping of all patient samples was performed using immunohistochemistry (IHC) to determine the expression of ER, PR, HER2, and Ki-67. Next-generation sequencing (NGS) of 511 genes was analysed

Results

Among the 55 patients, the median age was 67 years (24–86 years). The common manifestation was a retroareolar mass, with a median tumor size of 1.7 cm (1.2–5.5 cm). Twenty-three patients (41.82%) had stage I pTNM, 27 patients (49.09%) had stage II, and 5 patients (9.09%) had stage III. Most of the tumors were invasive carcinoma of no special type (92.72%) and grade 2 tumors (81.82%). The molecular subtype was mainly luminal type (98.18%). 32 patients had gene mutation. Pathogenic somatic mutations of the PIK3CA gene was detected in 6 cases (18.75%). Germline pathogenic mutations of the BRCA2 and CHEK2 gene in 4 cases(12.50%) and 2 cases(6.25%). Amplifications of the FGFR1, ERBB2, MYC, CCND1 and FGFR2 gene in our cohort were 12.50%), 6.25%, 6.25%, 3.13%, 3.13%.

Conclusions

In males, invasive breast cancer is a rare malignancy that predominantly affects elderly individuals. The most common histological type was invasive carcinoma of no special type, and most cases were luminal type according to molecular subtyping. PIK3CA and BRCA2 gene mutations and FGFR1 gene amplification were the most common pathogenic genetic changes in invasive male breast cancer.

Introduction

Male breast cancer is an extremely rare malignant tumor that accounts for approximately 1% of all breast cancer cases[1]. Compared with female breast cancer, male breast cancer is associated with significant differences in clinicopathological characteristics, molecular biological behavior, and prognosis. Patients often present at advanced stages with delayed diagnosis, which may be attributed to insufficient awareness of breast diseases among men and the lack of early screening programs[2].

Recent advances have been made in the study of the clinicopathological characteristics of male patients with breast cancer. Research has demonstrated that male breast cancer predominantly presents histologically as invasive ductal carcinoma, comprising more than 90% of cases[1]. In terms of molecular subtypes, male breast cancer presents a distinctive distribution pattern—nearly 90% of cases are luminal A or luminal B subtypes—reflecting significantly higher hormone receptor positivity rates compared to female breast cancer; however, triple-negative breast cancer is extremely rare among male patients, accounting for only 2.3% of cases[3,4].

Despite increasing international research on male breast cancer, clinicopathological and molecular genetic data from large patient cohorts in the Chinese population remain limited. Studies on genetic testing for breast cancer in China suggest that the Chinese population may exhibit ethnic-specific mutation spectra in key genes such as BRCA1/2 and PIK3CA[5,6]. In the era of precision medicine, a thorough understanding of the molecular characteristics of male patients with breast cancer is crucial for developing individualized treatment strategies. Traditional treatment regimens are largely based on protocols for female breast cancer patients; however, the unique molecular biological characteristics of male breast cancer suggest the need for more precise therapeutic approaches[7].

The aim of this study is to systematically elucidate the clinicopathological characteristics of male invasive breast cancer through retrospective analysis of 55 patients, investigate immunophenotypic and molecular subtyping features, and reveal key molecular genetic alterations through multigene detection technology, thereby providing scientific evidence for the precise diagnosis and treatment of male breast cancer in the Chinese population.

MATERIALS AND METHES

Case Selection

Clinical data of male breast cancer patients diagnosed in the Department of Pathology at Fudan University Shanghai Cancer from January 2021 to December 2023 were included in this study. All cases were confirmed by histopathological examination, and complete clinicopathological data and follow-up information were available. Tumor tissues were obtained from surgical resection, fixed in formalin, embedded in paraffin, stained with H&E, and evaluated using a microscope. The histological diagnosis was made according to the fifth edition of the WHO classification. Through the hospital information system and medical records management system, the basic clinical data of all the enrolled patients were systematically collected.

Immunohistochemical

Immunohistochemical studies included the following stains: estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67, and androgen receptor (AR). All staining was performed with a Ventana

Bench Mark Ultra autostainer (Ventana Medical System Inc., Roche, Tucson, Arizona, USA). Antibodies for ER, PR and HER2 were purchased from Roche. Antibodies for AR and Ki-67 were sourced from Dako. In accordance with the 2020 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, nuclear ER/PR staining in 1% or more of samples was defined as ER/PR-positive. HER2 status was assessed as proposed in the 2023 ASCO/CAP guidelines and considered positive if the patient had a HER2 immunohistochemistry (IHC) score of 3 + or HER2 gene amplification.

Molecular Subtyping

Molecular subtyping was performed on the basis of the following immunohistochemical results: luminal A type (ER and/or PR positive, HER2-negative, Ki-67 < 14%), luminal B type (ER and/or PR positive, Ki-67 ≥ 14% or HER2-positive), HER2-overexpressing type (ER and PR negative, HER2-positive), and triple-negative (ER, PR, and HER2 all negative). When the assessment results between the two pathologists were inconsistent, a consensus was reached through discussion.

Next-Generation Sequencing

Next-generation sequencing (NGS) of 511 genes was performed for all 32 tumors. DNA from paired tumor tissue and blood samples from 32 patients was extracted. The absorbances of the DNA at 260 nm (A260) and 280 nm (A280) were measured using a NanoDrop 2000 spectrophotometer to evaluate the purity and quantity of the total DNA. DNA with an A260/A280 ratio within the range of 1.6–1.9 was regarded as pure and suitable for further experiments. All tumor samples were subjected to next-generation sequencing in the laboratory using the FUSCC-BC panel—which included the 484-gene version 1 panel and the 539-gene version 2 panel—with the goal of detecting mutations, small insertions/deletions, and copy number alterations. Internal-generated RNA baits were employed to capture all protein-coding exons of the target genes. The RNA baits were produced by converting the oligo pool synthesized by Suzhou Synbio Technologies into double-stranded DNA, integrating the T7 promoter site into the amplicon, transcribing the DNA into biotinylated RNA, and then purifying, quantifying, and using the biotinylated RNA for target enrichment. Each DNA sample exceeding 10 ng after SYBR green quantification was fragmented using a Covaris M220, followed by end repair, A-tailing, and adapter ligation using the KAPA HyperPlus kit according to the manufacturer's recommended protocol. Prepared DNA (750 ng) in a volume of 3.4 μL was captured by RNA baits, and the captured library was purified and amplified with indexes. After quantification using a Multi-Mode Reader (BioTek), the libraries were pooled and sequenced using the Illumina HiSeq X TEN platform (Illumina Inc., San Diego, CA, USA). For the collection of genomic data, targeted sequencing was performed on the Illumina NovaSeq 6000 platform. Bases were called using the following software from Illumina: Nova-Seq control software v1.7.5 and Illumina bcl2fastq v2.20. Variant calling and coverage analysis of each capture region were performed using an in-house bioinformatics pipeline in accordance with the general variant calling pipeline. Reads were aligned to the human reference genome (GRCh37/hg19) using the Burrows–Wheeler Aligner (BWA, v0.7.17-r1188) with the BWA-MEM algorithm and default parameters. The

Genome Analysis Toolkit (GATK, v4.0.1.2.0) was used to locally realign the BAM files at intervals that included indel mismatches and recalibrate the base quality scores of the reads in the BAM files.

RESULT

Clinical and Pathological Characteristics

A total of 55 male patients with invasive breast cancer were included in this study. The median age was 67 years (24–86 years), which is consistent with the epidemiological pattern that male breast cancer predominantly affects elderly men. The median tumor size was 1.7 cm (0.12–5.5 cm). Analysis of tumor location revealed that the retroareolar region was the most frequent site, accounting for 20.0% (11/55) of cases. Modified radical mastectomy was the predominant surgical approach and was performed in 47.3% (26/55) of the patients.

Histopathologically, invasive carcinoma of no special type (IBC-NST) was the predominant type, accounting for 92.7% (51/55) of the cases. Other histological subtypes included invasive micropapillary carcinoma (2 cases, 3.6%), invasive lobular carcinoma (1 case, 1.8%), and solid papillary carcinoma with invasion (1 case, 1.8%). Histological grading revealed that 81.8% (45/55) were grade 2 tumors and 18.2% (10/55) were grade 3 tumors. No grade 1 tumors were identified in this cohort.

Staging analysis revealed that the majority of the patients presented at early stages: 41.8% (23/55) presented with stage I disease, 49.1% (27/55) with stage II disease, and 9.1% (5/55) with stage III disease, indicating that 90.9% of patients presented with early-stage disease. Lymphovascular invasion was present in 36.4% (20/55) of the patients, whereas axillary lymph node metastasis was detected in 27.3% (15/55) of the patients. The detailed clinicopathological characteristics are summarized in Table 1.

Table 1
Clinicopathological Characteristics of 55 Male Breast Cancer Patients

Characteristics	Total Cohort (n = 55)	Luminal A (n = 39)	Luminal B (n = 15)	HER2+ (n = 1)
Demographics				
Age, years				
Median (range)	67 (24–86)	68 (28–86)	65 (24–82)	69
≤ 65 years, n (%)	24 (43.6)	16 (41.0)	7 (46.7)	0 (0.0)
> 65 years, n (%)	31 (56.4)	23 (59.0)	8 (53.3)	1 (100.0)
Tumor Characteristics				
Tumor size, cm				
Median (range)	1.7 (0.12–5.5)	1.6 (0.12–5.5)	1.8 (0.8–4.2)	2.1
≤ 2.0 cm, n (%)	35 (63.6)	26 (66.7)	8 (53.3)	1 (100.0)
> 2.0 cm, n (%)	20 (36.4)	13 (33.3)	7 (46.7)	0 (0.0)
Tumor location, n (%)				
Retroareolar	11 (20.0)	8 (20.5)	3 (20.0)	0 (0.0)
Central/areolar	13 (23.6)	9 (23.1)	4 (26.7)	0 (0.0)
Upper outer quadrant	7 (12.7)	5 (12.8)	1 (6.7)	1 (100.0)
Other sites	17 (30.9)	12 (30.8)	5 (33.3)	0 (0.0)
Unspecified	7 (12.7)	5 (12.8)	2 (13.3)	0 (0.0)
Histopathological Features				
Histological type, n (%)				
Invasive carcinoma (NST)	51 (92.7)	36 (92.3)	14 (93.3)	1 (100.0)
Invasive micropapillary carcinoma	2 (3.6)	2 (5.1)	0 (0.0)	0 (0.0)
Invasive lobular carcinoma	1 (1.8)	1 (2.6)	0 (0.0)	0 (0.0)
Solid papillary carcinoma with invasion	1 (1.8)	0 (0.0)	1 (6.7)	0 (0.0)
Histological grade, n (%)				

HER2+: HER2-overexpressing subtype (n = 1)

NST: No special type

Characteristics	Total Cohort (n = 55)	Luminal A (n = 39)	Luminal B (n = 15)	HER2+ (n = 1)
Demographics				
Grade 2	45 (81.8)	35 (89.7)	9 (60.0)	1 (100.0)
Grade 3	10 (18.2)	4 (10.3)	6 (40.0)	0 (0.0)
TNM stage, n (%)				
Stage I	23 (41.8)	18 (46.2)	5 (33.3)	0 (0.0)
Stage II	27 (49.1)	18 (46.2)	8 (53.3)	1 (100.0)
Stage III	5 (9.1)	3 (7.7)	2 (13.3)	0 (0.0)
Lymphovascular invasion, n (%)				
Positive	20 (36.4)	12 (30.8)	7 (46.7)	1 (100.0)
Negative	35 (63.6)	27 (69.2)	8 (53.3)	0 (0.0)
Lymph node metastasis, n (%)				
Positive	15 (27.3)	9 (23.1)	5 (33.3)	1 (100.0)
Negative	40 (72.7)	30 (76.9)	10 (66.7)	0 (0.0)
Treatment Modalities				
Surgical approach, n (%)				
Local excision	7 (12.7)	5 (12.8)	2 (13.3)	0 (0.0)
Simple mastectomy	18 (32.7)	13 (33.3)	4 (26.7)	1 (100.0)
Simple mastectomy + lymph node	1 (1.8)	1 (2.6)	0 (0.0)	0 (0.0)
Modified radical mastectomy	26 (47.3)	18 (46.2)	8 (53.3)	0 (0.0)
Post-neoadjuvant modified radical mastectomy	3 (5.5)	2 (5.1)	1 (6.7)	0 (0.0)
HER2+: HER2-overexpressing subtype (n = 1)				
NST: No special type				

Luminal Subtype Distribution

Molecular subtyping based on immunohistochemical expression patterns revealed a striking predominance of luminal subtypes in male patients with breast cancer. Luminal-type tumors accounted for 98.2% (54/55) of all cases, with the luminal A subtype representing 70.9% (39/55) and the luminal B

subtype constituting 27.3% (15/55) of the cohort. Only one case (1.8%) was classified as the HER2-overexpressing subtype. Notably, no triple-negative breast cancer cases were identified in this series. This distribution pattern demonstrates the highly hormone-dependent nature of male breast cancer, with nearly universal expression of hormone receptors.

Next-Generation Sequencing Results

Comprehensive genomic profiling using a 511-gene panel was performed using the data of 32 patients. Pathogenic genetic alterations were detected in 12 patients (37.5% of the sequenced cohort). Among them, the somatic mutation rate of PIK3CA was 18.75%. BRCA2 and CHEK2 were germline mutations, with mutation rates of 12.50% and 6.25%, respectively. FGFR1, ERBB2, MYC, CCND, and FGFR2 exhibited gene amplification, with amplification rates of 12.50%, 6.25%, 6.25%, 3.13%, and 3.13%, respectively(Fig. 2).

Additionally, high-frequency variants of uncertain significance were observed in key cancer-related genes. TP53 variants were detected in 26 patients (81.25%), BRCA2 variants in 27 patients (84.38%), and BRCA1 variants in 20 patients (62.50%)(Fig. 2). While these variants do not represent pathogenic mutations, their high prevalence may indicate increased genetic variation at these critical loci in male patients with breast cancer.

Discussion

Compared with female breast cancer, male invasive breast cancer is a rare malignancy that has significant differences in clinicopathological characteristics. This study revealed a median patient age of 67 years, which is consistent with the findings of previous epidemiological studies indicating that male breast cancer primarily affects elderly men and typically occurs 5–10 years later than breast cancer in female patients[8,9]. This age-related pattern may be attributed to hormonal changes in elderly men, where testosterone levels gradually decrease and aromatase activity increases, creating an elevated estrogen/androgen ratio that establishes a favorable endocrine environment for breast cancer development[9].

The clinical presentation patterns observed in this cohort reveal important diagnostic implications. The retroareolar region was the most common tumor location, accounting for 20.0% of cases, which is significantly greater than in female patients with breast cancer[10]. This reflects the anatomical characteristics of male breast tissue, which lacks the complex glandular structure of female breasts, making tumors in the central breast region more easily palpable. Even though this anatomical advantage theoretically favors early detection, with 90.9% of patients presenting with early-stage disease (stages I-II), the overall prognosis of male breast cancer remains concerning compared with contemporary female patients with breast cancer[11].

Histological features further emphasize the unique characteristics of male patients with breast cancer. Invasive carcinoma of no special type (NST) predominated in 92.7% of cases, reflecting the limited histological diversity of male breast cancer. This predominant presentation starkly contrasts with female breast cancer, which more commonly presents as various special histological subtypes[12]. The uniformity seen in male breast cancer cases stems from the relatively simple structure of male breast tissue and the hormone-driven malignant transformation mechanisms of the ductal epithelium[2]. The absence of grade 1 tumors in this cohort, with 81.8% being grade 2 and 18.2% being grade 3, suggests that male breast cancer tends to present with intermediate- to high-grade features, which has important implications for prognostic assessment and treatment planning[13,14]. Lymphovascular invasion was detected in 36.4% of patients, and 27.3% of patients had axillary lymph node metastases, further emphasizing the biological aggressiveness of male breast cancer despite its relatively early clinical presentation[15–17].

These pathological features are directly related to molecular subtype distribution, revealing the remarkable characteristic of overwhelming hormonal dependence in male patients with breast cancer. In this study, luminal tumors accounted for 98.2% of all cases, with the luminal A subtype comprising 70.9% and the luminal B subtype comprising 27.3%. This distribution pattern shows a far greater proportion of hormone receptor-positive tumors than in female breast cancer, where luminal types typically account for approximately 70–80% of tumors[18,19]. The near-universal expression of hormone receptors reflects the unique hormonal environment and developmental patterns of breast tissue that are specific to males, providing a biological basis for the clinical observation that endocrine therapy remains highly effective in male patients with breast cancer.

The extremely low frequency of the HER2-overexpressing subtype (1.8%) and the complete absence of triple-negative breast cancer in this cohort highlight important therapeutic considerations[20–22]. This molecular profile suggests that male breast cancer patients are unlikely to benefit from anti-HER2 targeted therapy or treatments specifically developed for triple-negative breast cancer[23]. However, the predominance of hormone receptor-positive tumors indicates that endocrine therapy should remain the cornerstone of systemic treatment for male patients with breast cancer. The high proportion of the luminal A subtype also suggests that the prognosis of male breast cancer in patients may be favorable through the use of appropriate hormonal therapy[24], although this finding must be balanced against the inherent biological aggressiveness observed in pathological features.

To further understand the molecular basis of these clinical and pathological observations, a comprehensive genomic analysis was performed using the data of 32 patients in a 511-gene panel, and pathogenic genetic alterations were identified in 12 patients, providing important insights into the molecular pathogenesis of male breast cancer. PIK3CA somatic mutations were the most common pathogenic alterations and were detected in 6 patients[25]. PIK3CA encodes the catalytic subunit p110α of phosphatidylinositol 3-kinase, a key regulator of the PI3K/AKT/mTOR signaling pathway involved in tumor cell proliferation, survival, and metabolic reprogramming[26]. The importance of PIK3CA mutations

in clinical practice extends beyond biological understanding, as these alterations can serve as predictive biomarkers for PI3K inhibitor therapy[27]. The efficacy of alpelisib, a selective PI3Kα inhibitor, has been demonstrated in patients with hormone receptor-positive, HER2-negative breast cancer harboring PIK3CA mutations, providing a potential targeted therapeutic option for this subset of male patients with breast cancer[28].

In terms of somatic alterations, BRCA2 germline pathogenic mutations were identified in 4 patients, representing a significantly higher frequency than that typically observed in female patients with breast cancer[29]. These findings provide important insights into the hereditary component of male breast cancer and partially explain the observed biological aggressiveness despite its relatively early clinical presentation. BRCA2 is involved in homologous recombination repair, and its functional loss leads to impaired DNA double-strand break repair capacity and increased genomic instability[29]. Beyond direct therapeutic implications, BRCA2 germline mutations carry important hereditary cancer risks, necessitating genetic counseling for patients and their families[30]. From a therapeutic perspective, BRCA2-deficient tumors exhibit synthetic lethal sensitivity to PARP inhibitors, providing important treatment opportunities for these patients[31]. The relatively high frequency of BRCA2 mutations in this male breast cancer cohort suggests that genetic testing should be strongly considered for all male breast cancer patients.

FGFR1 amplification was detected in 4 patients, further enriching the genetic landscape and representing another potentially actionable genetic alteration[32]. FGFR1 belongs to the receptor tyrosine kinase family and is involved in cell proliferation, differentiation, angiogenesis, and metabolic regulation. Gene amplification leads to protein overexpression and downstream signaling pathway activation, promoting the malignant behavior of tumor cells[32]. While FGFR-targeted therapy in breast cancer remains under investigation, the identification of FGFR1 amplification provides potential avenues for targeted therapeutic strategies in male breast cancer. Additionally, other detected amplifications, such as ERBB2 (2 cases, 6.25%), MYC (2 cases, 6.25%), and CCND1 (1 case, 3.13%), further demonstrated the genetic complexity of male breast cancer development.

In addition to the aforementioned key genetic alterations, pathogenic changes in genes such as CHEK2, ERBB2, MYC, and CCND1 were also detected, reflecting the complexity and heterogeneity of the genetic background in male breast cancer. Multigene testing not only identifies druggable targets to guide precision therapy but also reveals germline mutations, providing evidence for genetic counseling and family management[33].

The comprehensive genetic analysis conducted in this study demonstrated the clinical utility of multigene testing in male breast cancer patients, revealing complex interactions between genetic susceptibility, somatic alterations, and clinical phenotypes. The identification of actionable targets such as PIK3CA mutations and FGFR1 amplifications provides opportunities for precision therapy, whereas the detection of germline BRCA2 mutations has implications for both treatment selection and family

counseling. As our understanding of the genetic landscape of male breast cancer continues to evolve, these findings contribute to the development of more personalized and effective treatment strategies for this rare but clinically important malignancy. The integration of clinical, pathological, and molecular findings presented in this study provides a comprehensive framework for understanding male breast cancer biology and optimizing patient care.

Conclusions and Prospects

Through a systematic analysis of 55 male invasive breast cancer patients, this study comprehensively elucidated the clinicopathological characteristics and molecular genetic features of male breast cancer patients in a Chinese population, providing important scientific evidence for the precise diagnosis and treatment of this rare tumor. The results of this study revealed that invasive breast cancer in males primarily affects elderly populations, with clinical presentation characterized mainly by the presence of retroareolar masses. The histological type is predominantly invasive carcinoma of no special type, and the molecular subtyping demonstrates highly hormone receptor-dependent characteristics, with 98.18% of cases being luminal type. This proportion is significantly greater than that in female patients with breast cancer, suggesting that male patients with breast cancer have unique biological behavior patterns.

Furthermore, through high-depth sequencing analysis of genes, we revealed that PIK3CA somatic mutations, BRCA2 germline pathogenic mutations, and FGFR1 gene amplification constitute the most important pathogenic genetic alterations in male patients with breast cancer, providing patients with potential opportunities for targeted therapies, which include PI3K inhibitors, PARP inhibitors, and FGFR inhibitors. These findings not only increase our understanding of the molecular pathogenesis of male breast cancer but also establish a molecular foundation for formulating precision clinical treatment strategies.

Declarations

Ethics approval and consent to participate

This study protocol has been reviewed and approved by the Ethics Committee of Fudan University Shanghai Cancer Center (Approval No. 2602-ZZK-179) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). Owing to the retrospective design and anonymised data, the requirement for written informed consent was waived.

Acknowledgements

None declared.

Conflict of Interest

None declared.

Data Availability Statement

The datasets generated and/or analysed during the current study are available in the Genome Sequence Archive (GSA-Human) repository, https://ngdc.cncb.ac.cn/gsa-human/browse/HRA020116 (accession: HRA020116).

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Figures

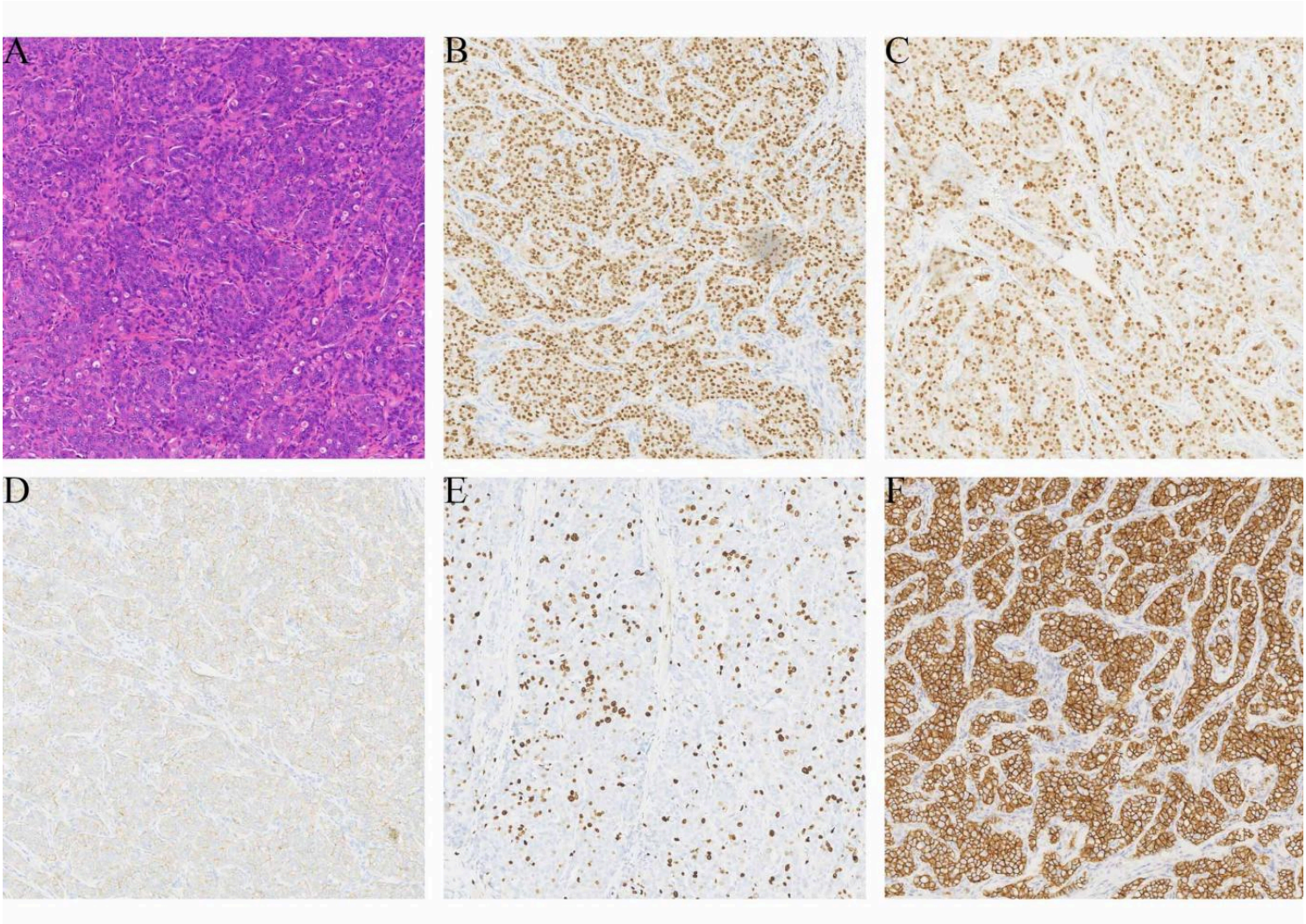


Figure 1

HE staining and immunohistochemistry of invasive carcinoma of no special type (NST) in male breast cancer. (A) invasive carcinoma of no special type (H&E, ×100). (B) ER (H&E, ×100). (C) PR(H&E, ×100). (D) HER2 (H&E, ×100) .(E) ki-67(H&E, ×100)and (F)E-cad(H&E, ×100).

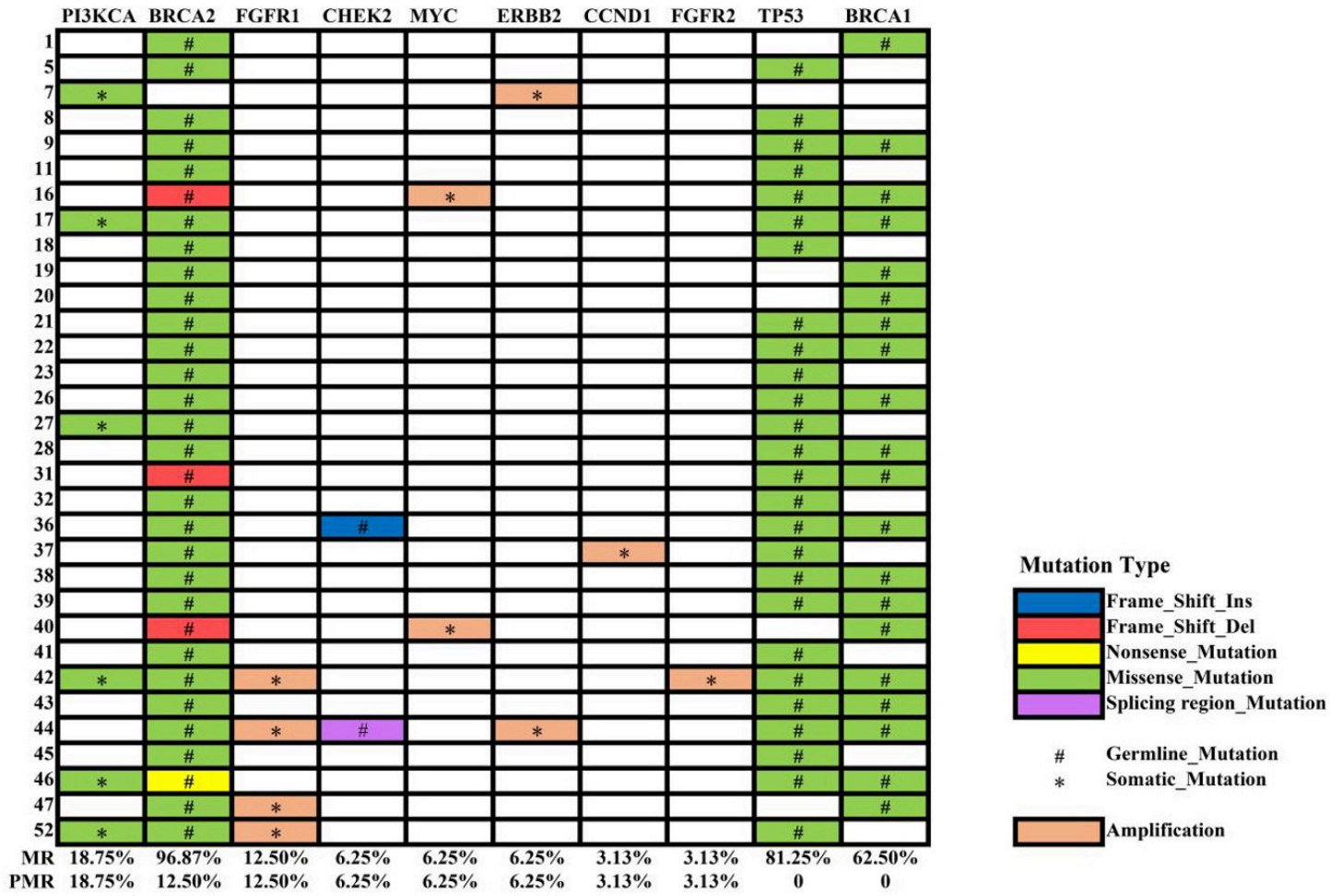


Figure 2

Genetic abnormalities in 32 male breast cancer patients analyzed by next-generation sequencing