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Mutational signatures for breast cancer: therapeutic and prognostic insights

Pritisnigdha Pattnaik

Department of Biotechnology, Ravenshaw University, Cuttack, Odisha, India

ABSTRACT

Breast cancer, a complex and heterogeneous disease driven by genetic mutations in breast tissue cells, remains a leading cause of cancer-related mortality among women globally. A mutational signature can reveal the genomic landscape and history of breast cancer as it reflects the cumulative effect of various mutational processes that operate in cancer cells. This review provides an overview of the concept and classification of mutational signatures and discusses their clinical implications for breast cancer. We highlight how mutational signatures can provide insights into the therapeutic strategies, prognostic indicators, resistance mechanisms, and evolution of mutational signatures during treatment. Besides, we explore the potential applications of mutational signatures in personalized medicine for breast cancer, such as their integration with genomic profiling, prediction of treatment response, monitoring of treatment progression, and tailoring of therapeutic regimens based on signature analysis. We also address the challenges and limitations that need to be overcome before mutational signatures can be fully exploited for clinical benefit, such as the technical issues of data interpretation and standardization, the clinical translation of signature-based biomarkers, the exploration of emerging mutational signatures, and the longitudinal study of signature evolution. Future directions in mutational signature research encompass the exploration of emerging signatures, longitudinal studies to capture signature evolution, and the application of artificial intelligence to enhance signature detection and interpretation. While challenges remain, mutational signatures in breast cancer stand as a powerful tool that can revolutionize diagnosis and treatment, ultimately advancing our understanding and management of this complex disease.

KEYWORDS

Mutational signatures; Cancer diagnosis; Personalized medicine; Artificial intelligence; Prognosis; Therapeutics; Biomarkers

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Introduction

Breast cancer is a complex and heterogeneous disease characterized by uncontrolled cell division and change, resulting in a lump or mass in the breast tissue. It is the most common and the second deadliest cancer among women globally. As per the World Health Organization (WHO), breast cancer accounts for about 12% of all new cancer cases and 25% of all cancers in women [1]. Worldwide, there were 2.3 million breast cancer diagnoses in 2020 and 685,000 deaths resulting from the disease [1]. Breast cancer can affect women worldwide at any age following puberty, with the likelihood of occurrence rising as they advance in age [1]. However, advances in diagnosis, treatment, and personalized medicine have improved its management and prognosis.

The development and progression of cancer are underpinned by genetic alterations that accumulate within the DNA of affected cells. These mutations can disrupt the finely tuned cellular processes regulating growth, differentiation, and apoptosis. While some mutations are benign, others confer a selective advantage to the affected cells, leading to uncontrolled proliferation and the formation of tumors. In breast cancer, several genetic changes have been identified, including single nucleotide substitutions, insertions, deletions, copy number variations, and chromosomal rearrangements [2]. These genetic aberrations, collectively referred to as somatic mutations, contribute to the heterogeneity observed among breast tumors and influence their clinical behavior and response to therapy [3]. The emergence of high-throughput sequencing technologies has facilitated the identification and characterization of these somatic mutations, which have also revealed novel insights into the mutational processes underlying cancer development [3].

Mutational signatures are distinct patterns of mutational events within the genomes of cancer cells, reflecting the specific molecular mechanisms that generate them. These mechanisms can include endogenous factors, such as DNA replication errors or oxidative stress, or exogenous factors, such as exposure to carcinogens or radiation [4]. Mutational signatures are the footprints of these factors and processes on the cancer genome [5]. Mutational signatures can provide valuable information about the origin, progression, and prognosis of breast cancer, as well as the potential response to different therapeutic strategies. For instance, mutational signatures can be used to classify tumors into subtypes, predict the response to certain drugs, identify defects in DNA repair pathways, and suggest potential targets for therapy [6-8].

Breast cancer tumors can be identified by their mutational signatures, which provide information about their genomic history [9]. The main types of mutations in breast cancer include point mutations, insertions, deletions, and copy number alterations [9]. These mutations can arise from various sources, such as endogenous DNA damage, exogenous mutagens, and defects in DNA repair mechanisms. There are many challenges and opportunities associated with the study

***Correspondence:** Pritisnigdha Pattnaik, Department of Biotechnology, Ravenshaw University, Cuttack, 753003, Odisha, India, e-mail: priti.rosy007@gmail.com

of mutational signatures in breast cancer. One challenge is to develop robust methods for identifying mutational signatures from noisy sequencing data. This is because sequencing errors can be introduced during the process of sequencing, which can make it difficult to distinguish true mutations from errors [10,11]. Another challenge is to understand the biological mechanisms underlying the different mutational signatures and how they relate to clinical outcomes. For example, some mutational signatures may be associated with a better or worse prognosis than others [12,13].

Opportunities include the potential use of mutational signatures as biomarkers for diagnosis, prognosis, and treatment stratification. Mutational signatures can provide information about the underlying biological processes that have caused the mutations in a tumor. This information can be used to develop personalized patient treatment plans based on their genomic history. For example, if a patient has a mutational signature associated with defects in DNA repair mechanisms, they may benefit from treatment with PARP inhibitors [14]. PARP inhibitors are drugs that block the repair of DNA damage in cancer cells and make them more sensitive to other treatments.

In this review, we will discuss the existing knowledge and applications of mutational signatures for breast cancer diagnosis, therapy, and prediction of clinical outcomes. It will look at the different mutational signatures that have been identified in breast cancer and how they might affect the development and progression of cancer. The review will also discuss the role of mutational signatures in predicting response to therapy and prognosis, particularly in breast cancer. Furthermore, future directions of research in this field will be discussed in the review.

Mutational Signatures: Concept and Classification

A mutational signature refers to a combination of mutation types as a result of specific mutagenesis processes, including exogenous and endogenous genotoxin exposures, DNA replication infidelity, DNA enzymatic editing, and defective DNA repair pathways.

There are several types of mutational signatures, such as insertion/deletion (indel) signatures, base substitution signatures, and rearrangement signatures. Base substitution signatures are the most common type of mutational signature and are characterized by a specific pattern of nucleotide substitutions [15]. Indel signatures are characterized by insertions or deletions of nucleotides, while rearrangement signatures are characterized by structural changes in the genome [16,17].

Mutational signatures can provide new insights into cancer treatment and prognosis by identifying potential drug targets, predicting treatment response, detecting therapy-induced mutations, and monitoring tumor evolution [18]. Mutational signatures can also be used for breast cancer diagnosis using artificial intelligence models such as deep learning and support vector machines to classify breast cancer subtypes and predict survival outcomes based on breast cancer genetic profiles [19]. However, mutational signatures can vary depending on the breast cancer subtype, such as triple-negative breast cancer (TNBC) or BRCA1/2 mutation carriers [20,21], and may be influenced by factors such as ethnicity, age, and treatment [22]. Mutational signatures can be analyzed using various methods and tools such as whole-genome sequencing (WGS), whole-exome sequencing (WES), targeted sequencing, or mutational signature extraction algorithms [10,15,23].

Cancer research has become more important with mutational signature analysis as it provides insight into the biological mechanisms involved in the development of cancer [24]. It has also shown its applicability in cancer treatment and cancer prevention. Mutational signature analyses can be used to reveal the mutagenic processes that have contributed to cancer development. Researchers can gain insights into the underlying biology of cancer by identifying the specific mutational processes that occur during tumorigenesis [25]. For example, mutational signature analyses have been used to identify specific DNA repair pathways that are defective in certain types of breast cancer [6]. This information can be used to develop new targeted therapies that exploit these defects in DNA repair pathways [6].

The classification of mutational signatures is based on their underlying mechanisms. The following are the five major categories of mutational signatures:

1. **Age-Related Signatures:** These are caused by endogenous processes that occur during aging and are characterized by C>T transitions at CpG dinucleotides [26].

2. **Replicative Signatures:** These are caused by errors during DNA replication and are characterized by C>A transversions [27].

3. **DNA Repair Deficiency Signatures:** These are caused by defects in DNA repair pathways and are characterized by C>T transitions [28].

4. **Environmental and Exposures Signatures:** These are caused by exposure to environmental factors such as UV radiation, tobacco smoke, and aflatoxin B1, among others [29].

5. **Unknown Signatures:** These are caused by unknown mechanisms and have not yet been classified [30].

Clinical Implications of Mutational Signatures in Breast Cancer

During tumorigenesis, mutational signatures are the imprints of DNA damage and repair processes. The mutations recorded during the development of the tumor are a record of the historical mutagenic activity [31]. In addition to providing insight into the underlying biology of cancer, mutational signatures can identify the mutational processes contributing to cancer development [31].

Therapeutic strategies

Targeted therapies based on signature-associated mutations are an effective therapeutic strategy for breast cancer. The use of these alterations for targeted therapies has emerged as a cornerstone of precision medicine. Table 1 represents some of the therapeutic strategies in breast cancer based on mutational signatures and specific genetic mutations:

BRCA1 and BRCA2 mutational signatures

Some breast cancers are marked by mutations in the BRCA1 and BRCA2 genes. These mutations disrupt the DNA repair mechanisms in cells, increasing the risk of tumorigenesis. PARP (Poly (ADP-ribose) polymerase) inhibitors, such as Olaparib and Talazoparib, have proven effective in treating breast cancers associated with BRCA1 or BRCA2 mutations

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[32-34]. These inhibitors exploit the defective DNA repair pathway in these cancers, leading to cell death.

Hormone receptor mutational signature

Hormone receptor mutations, particularly in the estrogen receptor (ER) and progesterone receptor (PR), can lead to resistance to hormone therapy in breast cancer [35]. In cases of hormone receptor mutations, treatment strategies may involve switching or combining hormone therapy drugs. CDK4/6 inhibitors may also be used in combination with hormone therapy to overcome resistance [36].

HER2-enriched mutational signature

A subset of breast cancers exhibits a high prevalence of HER2 (Human Epidermal Growth Factor Receptor 2) gene amplification or mutations, resulting in overactive signaling pathways promoting cancer growth [37]. Targeted therapies, including Trastuzumab and Pertuzumab, have been developed to treat HER2-positive breast cancers. These drugs specifically target HER2, inhibiting its activity and curbing cancer cell growth [37].

PIK3CA mutational signature

Mutations in the PIK3CA gene are prevalent in breast cancer and lead to increased activity of the PI3K pathway, which promotes cell growth and survival. Inhibitors of the PI3K pathway, such as Alpelisib, offer a targeted approach for breast cancers with PIK3CA mutations. By blocking this pathway, these drugs can slow down the growth of cancer cells [38].

Homologous recombination deficiency (HRD) mutational signature

Breast cancers with HRD mutational signatures, resulting from defects in DNA repair pathways, may respond to specific therapies. PARP inhibitors, such as Olaparib and Talazoparib, have demonstrated efficacy in treating breast cancers with HRD signatures. These inhibitors capitalize on the DNA repair defects in these cancers, leading to cell death [39].

Immune microenvironment mutational signature

Certain breast cancers, such as TNBC, exhibit mutational signatures linked to the immune microenvironment, often characterized by negative expression of estrogen (ER), progesterone (PR), and human epidermal growth factor receptor-2 (HER2), high mutational burdens that generate neoantigens. Immunotherapies, including checkpoint inhibitors like pembrolizumab and atezolizumab [40,41], can be effective in tumors with high mutational burdens. By blocking immune checkpoints, these drugs enhance the immune system's ability to recognize and attack cancer cells [42,43]. While immunotherapy's success varies among subtypes, mutational signatures can guide patient selection for these treatments, enhancing the likelihood of positive outcomes. These approaches exploit specific characteristics of breast cancer cells to develop more effective and personalized treatments.

Table 1. . Therapeutic strategies for breast cancer based on mutational signatures and specific genetic mutations.

Mutational Signature	Targeted Therapy	Mechanism of Action	References
BRCA1 and BRCA2	PARP Inhibitors (e.g., Olaparib, Talazoparib)	Exploit defective DNA repair pathways, leading to cell death	[32-34]
Hormone Receptor	Hormone Therapy Switch/Combination, CDK4/6 Inhibitors	Overcome resistance to hormone therapy	[35, 36]
HER2-Enriched	HER2-Targeted Therapies (e.g., Trastuzumab, Pertuzumab)	Inhibit HER2 signaling, curbing cancer cell growth	[37]
PIK3CA	PI3K Pathway Inhibitors (e.g., Alpelisib)	Block PI3K pathway, slowing down cancer cell growth	[38]
Homologous Recombination Deficiency	PARP Inhibitors (e.g., Olaparib, Talazoparib)	Exploit DNA repair defects, leading to cell death	[39]
Immune Microenvironment	Checkpoint Inhibitors (e.g., pembrolizumab, atezolizumab)	Enhance immune response, attacking cancer cells	[40-43]

Prognostic indicators

Mutational signature analyses have emerged as a powerful tool in understanding the genomic landscape of breast cancer, and their utility extends beyond elucidating the molecular mechanisms driving the disease. These analyses can also provide valuable prognostic indicators for breast cancer patients. By identifying distinct mutational patterns and signatures within a patient's tumor DNA, researchers and clinicians can gain insights into the tumor's aggressiveness, likely response to treatment, and overall prognosis.

Several published studies have demonstrated the prognostic potential of mutational signatures in breast cancer. Through an analysis of 100 tumor genomes, the researchers observed variations in the number of somatic mutations, with

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strong correlations between mutation number, age at cancer diagnosis, and cancer histological grade. The study identified multiple mutational signatures, including one characterized by numerous mutations of cytosine at TpC dinucleotides in approximately ten percent of tumors. Importantly, the study identified driver mutations in several new cancer genes, such as AKT2, ARID1B, CASP8, CDKN1B, MAP3K1, MAP3K13, NCOR1, SMARCD1, and TBX3, emphasizing the genetic diversity within breast cancer. These findings provide insights into the prognostic potential of mutational signatures and highlight the complex genetic landscape of this common disease [38].

Another study that described the status of several mutational signatures in cancer genomes found that breast cancer patients with a high prevalence of a specific mutational signature had a worse prognosis than those with a low prevalence [24]. The study mentioned several mutational signatures, including base substitution signatures, COSMIC signatures, Mutation in BRCA1, BRCA2, PALB2, MLH1, RAD51C genes, and CS-6, CS-15, CS-10, CS-20, and CS-26 genes, indel signatures, rearrangement signatures, geographically localized mutational phenomena, or other signatures characterized by copy-number variations. This information can be used to develop personalized treatment plans for breast cancer patients based on their mutational signatures. Mutational signatures can also reveal the mechanisms of resistance and evolution of breast cancer during treatment. Therefore, mutational signatures can serve as potential prognostic indicators for breast cancer patients and guide personalized treatment decisions.

Resistance mechanisms and evolution of mutational signatures during treatment

Mutational signatures represent valuable tools for gaining insights into resistance mechanisms, enabling clinicians to tailor treatment strategies accordingly [44]. A study conducted by researchers at Memorial Sloan Kettering Cancer Center identified two groups of mutations in the FOXA1 gene that cause breast cancer cells to grow and resist aromatase inhibitors in distinct ways [44]

The study revealed that mutations in the FOXA1 gene, specifically grouped as Wing2 and SY242CS mutations, play a critical role in driving resistance to aromatase inhibitors in estrogen receptor-positive breast cancer. These mutations use distinct resistance mechanisms, with SY242CS altering the FOXA1 protein shape to modulate chromatin and gene expression, enabling cancer cell growth in the presence of estrogen deprivation, while Wing2 mutations enhance cell response to limited estrogen levels. This discovery suggests that personalized treatment strategies can be employed for patients with FOXA1 mutations, potentially benefiting from alternative hormone therapies like fulvestrant. However, further validation and research with a larger patient cohort are essential to confirm the efficacy of tailored treatments, emphasizing the significance of institutions committed to translational science in advancing personalized breast cancer therapy [44].

Hence, the clinical implications of mutational signatures in breast cancer are extensive, encompassing their role in guiding treatment choices, prognosticating patient responses, and enhancing our understanding of resistance development throughout therapy.

Applications of Mutational Signatures in Personalized Medicine

In personalized medicine, mutational signatures can be used to predict treatment response, monitor treatment progression, and tailor therapeutic regimens based on signature analysis [7,45].

Here are the applications of mutational signatures in personalized medicine:

Integration with genomic profiling

Mutational signatures can be integrated with genomic profiling to identify the underlying biological mechanisms that drive cancer development and progression. This can help in the identification of potential therapeutic targets and the development of personalized treatment regimens. A study has used a computational approach to identify the mutational signatures associated with APOBEC-dependent mutations in breast cancer. They have found that a germline copies number polymorphism of APOBEC3A and APOBEC3B is associated with an increased burden of putative APOBEC-dependent mutations in breast cancer [46].

Prediction of treatment response

It is possible to predict cancer treatment response by using mutational signatures. For instance, a study by Sammut et al., used multi-omic data from 168 breast cancer patients to predict treatment response. They discovered that pre-treatment features, including mutational signatures, played a significant role in determining therapy outcomes [47].

Monitoring treatment efficacy

In breast cancer, mutational signatures can be used to monitor treatment efficacy and resistance. Mutational signatures can be used to identify the genomic alterations that occur during treatment progression. By analyzing the genomic alterations, researchers can identify the specific mutational processes that are responsible for treatment resistance. This information can be used to develop new treatment strategies that target the specific mutational processes responsible for treatment resistance.

In a study, targeted next-generation sequencing (NGS) of 416 cancer-relevant genes was performed on 41 plasma biopsy samples of 19 HER2+ and 12 HER2- BC patients [48]. Longitudinal ctDNA (circulating tumor DNA) samples were analyzed in three BC patients over the treatment course for detecting acquired mutations. It was found that ctDNA monitoring provides valuable insights into the assessment of targeted therapy efficacy and gene alterations underlying trastuzumab resistance and chemotherapy resistance in HER2+ and HER2- BC patients, respectively [48].

Tailoring therapeutic regimens based on signature analysis

Mutational signatures can be used to tailor therapeutic regimens based on signature analysis [18]. For example, a study revealed that Signature Multivariate Analysis (SigMA) effectively detects a mutational signature associated with HR deficiency (SBS3) from WGS, WES, and targeted gene panels, linked to HRD in cancer cells, allowing for the identification of patients who could benefit from PARP inhibitors, irrespective of BRCA1/2 mutations, leading to improved outcomes [49].

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Future Directions and Challenges

As the field of mutational signatures in breast cancer continues to evolve, several challenges and promising avenues for future research have emerged. Addressing these challenges and capitalizing on emerging opportunities will be essential in fully harnessing the potential of mutational signature analysis for clinical benefit.

Technical limitations and data interpretation

One of the primary technical challenges is the identification and validation of the mutational mechanisms responsible for each unique signature. While certain signatures have established connections to recognized factors like DNA repair defects, oxidative stress, or environmental exposures, some still elude explanation. Furthermore, the interactions and dynamics of multiple mutational processes within a tumor or across different tumor subtypes are not well understood. Therefore, more comprehensive and integrative analyses of genomic, epigenomic, transcriptomic, and proteomic data are needed to elucidate the causes and consequences of mutational signatures in breast cancer [31].

Another technical challenge is the data interpretation and standardization of mutational signatures. Different methods and models have been used to infer mutational signatures from genomic data, which may lead to inconsistent or incompatible results. Furthermore, the optimal methods and platforms for detecting and interpreting mutational signatures in clinical samples are not standardized or validated. Therefore, more robust and reliable methods and criteria are needed to compare and harmonize mutational signatures across different studies and settings [31].

Incorporating signatures into clinical practice

A further challenge is the clinical translation of mutational signatures for diagnosis, prognosis, and treatment. Although some signatures have been related to clinical outcomes or drug responses in breast cancer, the predictive value and utility of these signatures in routine practice are still uncertain. For instance, the signature related to BRCA deficiency has been shown to predict sensitivity to PARP inhibitors, but not all BRCA-deficient tumors have this signature, and not all tumors with this signature are BRCA-deficient [7]. Furthermore, the clinical relevance and applicability of some signatures may vary depending on the tumor subtype, stage, or treatment history [9]. Therefore, more robust and reliable biomarkers based on mutational signatures are needed to guide personalized medicine for breast cancer patients.

Exploration of emerging mutational signatures

A promising direction for future research is the exploration of emerging mutational signatures that have not been fully characterized or understood yet. For example, some signatures may reflect epigenetic alterations that affect DNA methylation or chromatin structure [50]. These epigenetic signatures may provide novel insights into the regulation and dysregulation of gene expression and genome stability in breast cancer. Moreover, some signatures may involve structural rearrangements such as deletions, duplications, inversions, or translocations [31]. These rearrangement signatures may reveal novel mechanisms of genomic instability and oncogene activation in breast cancer.

Longitudinal studies and evolution of signatures

Another focus for future research is the longitudinal study of mutational signatures and their evolution over time and space. Mutational signatures are not static but dynamic features that may change during tumor development, progression, and treatment [51]. Therefore, longitudinal sampling and sequencing of tumors from different sites or time points may provide a more comprehensive and accurate picture of the mutational landscape and history of breast cancer. Moreover, longitudinal studies may help identify temporal or spatial patterns of mutational signatures that may reflect tumor heterogeneity, clonal evolution, or therapy resistance [52].

A promising direction for future research is the application of artificial intelligence (AI) tools to decipher mutational signatures in breast cancer. AI techniques such as machine learning and deep learning can help overcome some of the limitations of conventional methods, such as statistical inference or clustering. For example, AI can help discover novel or complex signatures that are not captured by existing models or infer causal relationships between signatures and mutational processes [53]. AI can also help integrate mutational signatures with other types of data to provide a more comprehensive and accurate picture of breast cancer biology and behavior [54]. However, the use of AI for mutational signatures also poses new challenges, such as data quality, interpretability, reproducibility, and ethical issues that need to be carefully addressed [55].

Conclusions

Mutational signatures are a powerful tool for deciphering the genomic landscape and history of breast cancer, as well as for identifying new targets and strategies for prevention and therapy. They reflect the cumulative effects of various mutational processes that operate in breast cancer cells, such as DNA repair defects, oxidative stress, environmental exposures, or epigenetic alterations. Mutational signatures have important clinical implications for breast cancer, as they can provide insights into the therapeutic strategies, prognostic indicators, resistance mechanisms, and evolution of mutational signatures during treatment. The applications of mutational signatures in personalized medicine emerged as a pivotal theme in our exploration. We discussed their integration with genomic profiling, demonstrating how these signatures can enhance our ability to decipher the genomic complexity of breast cancer. Moreover, we outlined how mutational signatures can aid in predicting treatment responses, monitoring treatment progression, and tailoring therapeutic regimens to maximize their effectiveness, ultimately steering us toward more individualized and targeted treatment approaches. However, many challenges and limitations remain to be addressed before mutational signatures can be fully exploited for clinical benefit. Future research should focus on improving the understanding, detection, and interpretation of mutational signatures in breast cancer using advanced technologies such as AI. Moreover, future research should explore emerging mutational signatures that have not been fully characterized or understood yet, such as those involving structural rearrangements or epigenetic modifications. Furthermore, future research should conduct longitudinal studies of mutational signatures and their evolution over time and space to capture the dynamic and

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heterogeneous nature of breast cancer. In conclusion, mutational signatures in breast cancer represent a promising avenue for unraveling the molecular mechanisms, prognostic factors, and therapeutic targets of this heterogeneous disease.

Disclosure statement

No potential conflict of interest was reported by the author.

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