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Genetic Study of Carcinoma Breast in Northwest Rajasthan

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ABSTRACT

We conducted a genetic study to investigate novel patterns in breast cancer within the population of Northwest Rajasthan. A total of 32 cases of modified radical mastectomy were randomly selected, with no exclusion based on age, occupation, or socioeconomic status. Genetic mapping was carried out to analyze mutations in P53, K-Ras, NAT2, and other genes associated with breast cancer susceptibility. We observed a consistent association of P53 and K-Ras mutations across all samples. Interestingly, NAT2 gene mutations were identified in 15 cases, and amplification of the KDMA6 gene was observed in one sample. Our findings underscore the significance of identifying NAT2 gene mutations in the Northwest Rajasthan population, especially given its more typical association with bladder cancer rather than breast cancer. This discovery provides new insights into the etiopathogenesis and potential genetic underpinnings of breast cancer in Rajasthan, India.

Key words: Breast Cancer, Northwest Rajasthan, Genetic Study

INTRODUCTION

Breast cancer remains a leading cause of morbidity and mortality among women worldwide, prompting extensive research into its intricate genetic basis. Breast cancer is by far the most frequent cancer among women, with an estimated 1.67 million new cases diagnosed in 2012 (about 25% of all cancers). It is now the most common cancer both in developed (794,000 cases) and in developing regions (883,000 cases). Incidence rate varies from 27 per 100,000 women in Eastern Africa to 98 per 100,000 women in Western Europe. The range of mortality rate is also similar, approximately 6-20 per lac, because of the more favorable survival of breast cancer cases in developed countries. As a result, breast cancer ranks as the fifth cause of death from cancer, but it is still the most frequent cause of cancer death in women in developing regions. In 2012 the worldwide burden of breast cancer accounted for 25.2% of total incidence and 14.7% of total cancer deaths. The five-year prevalence is 36.4% worldwide. It is about 240 cases/100,000 population worldwide[1].

In the Indian context, the incidence of breast cancer accounts for 27% (144,937 new cases) of all cancers. The mortality rate is 21.5% (70,218 cases) of all cancer deaths. The mortality rate is 12.7/lac population, ranking number one killer in women. The five-year prevalence is 35.3%. The proportion per one lakh population is 92.6%[1].

Advances in molecular genetics have revealed numerous genes associated with breast cancer susceptibility, with BRCA1 and BRCA2 being the most extensively studied due to their strong association with hereditary breast cancer. Additionally, the roles of genes such as P53 and K-ras in breast cancer pathogenesis are well established.

P53 – The Guardian of the Genome:

The P53 gene, located on chromosome 17p13, encodes a tumor suppressor protein crucial in maintaining genomic integrity. Known as the "guardian of the genome," P53 regulates essential cellular processes such as DNA repair, cell cycle arrest, and apoptosis. Upon activation in response to cellular stress, P53 facilitates DNA repair mechanisms or induces apoptosis in cells with irreversible damage. Loss or inactivation of P53 disrupts these regulatory pathways, often leading to uncontrolled cell growth and tumor development. Notably, P53 mutations are implicated in approximately 50% of human cancers, underscoring its pivotal role in cancer progression.

K-ras – A Proto-Oncogene in Cancer Development:

The K-ras gene, located on chromosome 12, encodes the P21GTPase protein, which regulates signaling pathways associated with cell growth and migration. Activating mutations in K-ras, particularly in codon 12, lead to constitutive activation of downstream signaling cascades, promoting uncontrolled proliferation and increased migratory capacity of cancer cells. This makes K-ras a significant contributor to tumorigenesis and cancer progression.

Expanding Genetic Investigations in Breast Cancer:

While BRCA1, BRCA2, P53, and K-ras have been widely studied, additional genetic factors influencing breast cancer susceptibility remain underexplored. In this study, we focused on the roles of the NAT2 and KDMA6 genes in breast cancer pathogenesis, specifically in the population of Northwest Rajasthan, India.

NAT2 – A Potential Contributor to Breast Cancer Susceptibility:

The NAT2 gene, located on chromosome 8, encodes the N-acetyltransferase 2 enzyme, which is responsible for metabolizing various drugs, environmental toxins, and carcinogens. NAT2 polymorphisms affect enzyme activity, altering the metabolism of carcinogenic compounds. While NAT2 has been predominantly associated with bladder cancer, emerging evidence suggests its involvement in breast cancer susceptibility, particularly in specific populations. This study investigates the role of NAT2 mutations in breast cancer within the Northwest Rajasthan cohort, offering new insights into its potential contribution.

KDMA6 – An Unexplored Gene in Breast Cancer Research:

Located on the X chromosome, KDMA6 is a gene with limited research regarding its role in cancer. Preliminary studies suggest its involvement in growth regulation and gene expression modulation, which are critical processes in tumor development. By examining KDMA6 mutations in breast cancer patients from Northwest Rajasthan, this study aims to elucidate its potential role as a genetic contributor and biomarker for cancer risk assessment.

Study Significance and Objectives:
This investigation aims to deepen the understanding of breast cancer genetics in the Northwest Rajasthan population by exploring the roles of NAT2 and KDMA6, alongside the established contributions of P53 and K-ras. Identifying novel genetic associations could provide valuable insights into breast cancer etiology, offering a foundation for personalized therapeutic strategies and risk assessment models tailored to this population.

MATERIALS AND METHODS

Study Population and Sample Collection:
This study involved a cohort of 32 female breast cancer patients. Informed consent was obtained from all participants, and strict measures were taken to ensure patient confidentiality. The participants were selected randomly, representing a diverse range of ages, castes, and cultural backgrounds. Tissue samples were collected during modified radical mastectomy procedures conducted in the Department of Surgery, Sardar Patel Medical College, Bikaner. Following surgical excision, the tissue specimens were processed into paraffin blocks in the Pathology Laboratory and subsequently transferred to the Multidisciplinary Research Unit for molecular analysis.

DNA Extraction and Quantification:
Genomic DNA was extracted from the processed tissue samples using Favorgen tissue isolation kits, adhering to the manufacturer's protocol. The purity and concentration of the extracted DNA were determined through spectrophotometric analysis at a wavelength ratio of 260/280 nm. The DNA was diluted to a final concentration of 25 ng/μL to ensure compatibility with downstream molecular analyses.

Polymerase Chain Reaction (PCR) Amplification:
PCR amplification was performed to target the NAT2, K-ras, P53, and KDMA6 genes. Each primer was used at a concentration of 10 pmol. Amplifications were carried out in a thermal cycler under the following cycling conditions: an initial denaturation step at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds (denaturation), 60°C for 30 seconds (annealing), and 72°C for 30 seconds (extension). A final extension step at 72°C for 10 minutes was included to ensure complete amplification.

Electrophoresis and Amplification Validation:
PCR products were analyzed using 1.2% agarose gel electrophoresis. The gels were run at 100V for one hour to separate amplified products based on molecular weight. A negative control, comprising the master mix without a DNA template, was included in each electrophoresis run to confirm the absence of contamination. Positive controls were not included in this study. Successful amplification was determined by the presence of distinct bands visible under UV illumination, with the absence of bands in the negative control confirming the validity of the results.

RESULTS

The study provided critical insights into the genetic landscape of breast cancer in the Northwest Rajasthan population. Among the 32 tissue samples analyzed, NAT2 gene amplification was observed in 15 cases (46.9%), indicating a potential role for NAT2 in breast cancer pathogenesis within this cohort. This finding is particularly significant given the traditional association of NAT2 with bladder cancer, suggesting a novel genetic link to breast cancer. (Figure 1)

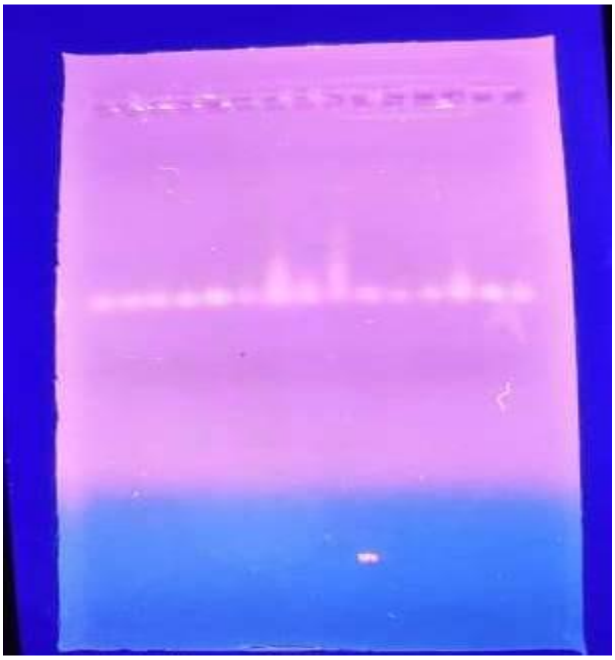

Figure 1 – Sample No. 1 to 15 were amplified with primer NAT2

In contrast, amplification of the KDMA6 gene was detected in only one sample (3.1%), implying a limited role for this gene in the breast cancer cases studied. While the precise involvement of KDMA6 in cancer remains unclear, its rare amplification in this cohort highlights the need for further investigation to elucidate its biological relevance.

Interestingly, both the P53 and K-ras genes exhibited consistent amplification across all 32 samples (100%), reinforcing their well-established roles in breast cancer pathogenesis. P53, a pivotal tumor suppressor gene, and K-ras, a key proto-oncogene, are known to drive tumorigenesis through dysregulation of cell proliferation, apoptosis, and growth signaling pathways. (Figure 2)

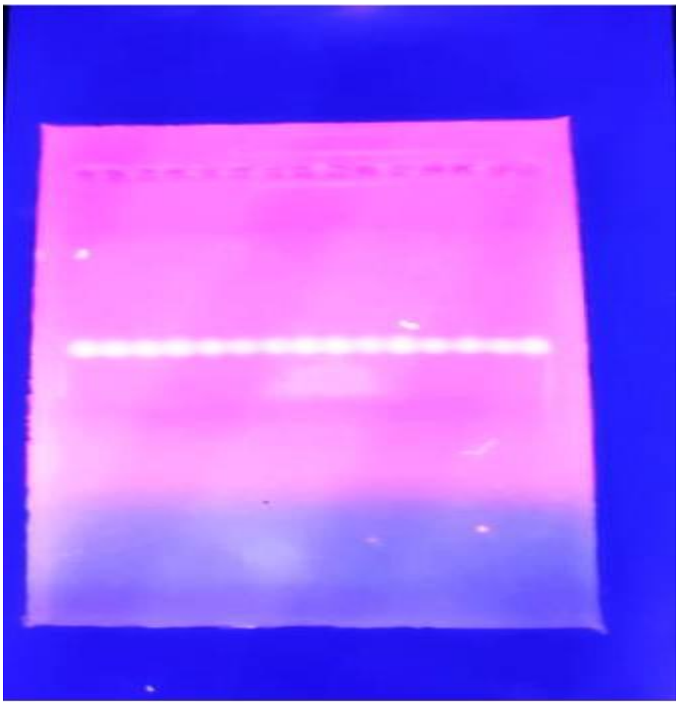

Figure 2 – All samples were amplified with Kras Primer

These findings collectively suggest that, in addition to the established significance of P53 and K-ras, NAT2 may play a previously underexplored role in the genetic framework of breast cancer in this population. The association of NAT2 with breast cancer highlights a potential genetic susceptibility specific to the Northwest Rajasthan cohort, warranting further in-depth studies. This discovery opens new avenues for understanding breast cancer etiopathogenesis and may contribute to the identification of novel biomarkers or therapeutic targets for managing the disease. (Table 1)

Table 1 – Gene Amplification Observation

Gene	Amplification Observed	Percentage	Comments
NAT2	15/32	46.9%	Suggests a potential involvement in breast cancer genetics in the studied population.
KDMA6	1/32	3.1%	Indicates a less common role in breast cancer within this cohort.
P53	32/32	100%	Highlights its established importance in breast cancer pathogenesis.
K-ras	32/32	100%	Reaffirms its critical role in breast cancer pathogenesis.

NAT2 amplification is significant in the Northwest Rajasthan population and may play a novel role in breast cancer genetics, alongside the established importance of P53 and K-ras. KDMA6 shows limited involvement in this cohort.

DISCUSSION

Investigation into the genetic studies of breast cancer identified the Putative Breast Cancer 3 (BRCA3) locus, shedding light on its potential role in familial breast cancer. Linkage analysis involving 237 families affected by breast and ovarian cancer revealed significant linkage rates of 52% to BRCA1 and 32% to BRCA2. However, further evaluation suggested a more complex contribution of these genes, necessitating a reassessment of their roles in hereditary breast cancer[2].

Genetic analysis of Finnish breast cancer families uncovered unique mutation patterns. Among families with three or more breast cancer cases, mutations in BRCA1 were detected in only 10%, while BRCA2 mutations were present in 11%. These findings highlight the diverse genetic predisposition among populations and underscore the heterogeneity of hereditary breast cancer[2].

Further exploration into the genetic landscape of breast cancer led to an investigation of the 13q21 locus, which has been implicated as a potential susceptibility region. Findings suggest that its role is confined to a small subset of non-BRCA1/BRCA2 families with multiple cases of early-onset breast cancer. This highlights the multifactorial nature of breast cancer etiology and the need for further investigation into this complex region[3].

A novel association between breast cancer and genes involved in the glutamate and pyruvate transaminase (GPT) pathways[4] was identified. This discovery establishes a potential link between metabolic processes and breast cancer development, offering new avenues for research into metabolic regulation in cancer.

Analysis of the P53 gene revealed its widespread expression in invasive breast cancer. Immunohistochemical staining demonstrated significant P53 expression in 22% (11/49) of breast cancer cases[5], underscoring its potential as a biomarker and its complex role in tumor pathogenesis.

A groundbreaking finding in 2004 identified five novel alternative transcripts of the ARHGEP5 gene[6]. These transcripts, uniquely expressed in breast tumors, expand the understanding of breast cancer genetics and may provide new molecular targets for research and therapy.

In 2006, 189 genes exhibiting high mutation frequencies in two distinct types of human cancer were identified. Among these, 15 mutations were determined to be critical for

tumor initiation, progression, or maintenance[7]. This mapping effort provides a comprehensive view of the genetic mutations driving tumorigenesis, laying a foundation for diagnostic and therapeutic advancements.
Research had uncovered the combined oncogenic influence of LSM1, BAG4, and C80RF4 in transforming human mammary epithelial cells[8]. This discovery highlights the intricate interplay between these genes in promoting tumor development, offering insights into the molecular mechanisms of cancer transformation.
An in-depth analysis of triple-negative breast cancer revealed distinct tumor clonal subtypes, emphasizing the complexity of this aggressive breast cancer subtype. These findings provide valuable insights into the biological foundations and therapeutic responses associated with triple-negative breast cancer[9].
In 2012, the Cancer Genome Network identified two novel protein expression-defined subgroups of breast cancer. This finding challenged the notion of uniformity among biological subtypes, emphasizing the clinical plasticity and heterogeneity within individual subtypes[10].
The integration of molecular cytogenetics with histopathology, pioneered in 1987 by Lundberg et al., marked a significant advancement in breast cancer diagnostics[11]. This approach highlighted the complementary nature of molecular and traditional methods, paving the way for more precise diagnostic techniques.
Investigation into the XM gene pathway revealed significant genetic associations with breast cancer, particularly among current and former smokers. Variations in genes such as NAT2, CYP2C18, and CYP2 underscore the complex interplay between genetic predisposition and environmental factors in breast cancer development[12].
This comprehensive exploration of the genetic architecture of breast cancer highlights the multifaceted nature of its etiology and offers promising directions for future research into diagnostics, therapeutics, and personalized medicine.

CONCLUSION

The results of our study provided valuable insights into the genetic landscape of breast cancer in the Northwest Rajasthan population. Of the 32 samples analyzed, 15 showed amplifications of the NAT2 gene (46.9%), indicating a potential role for NAT2 in breast cancer pathogenesis within this cohort. This finding is particularly significant given the traditional association of NAT2 with bladder cancer, suggesting a novel genetic link to breast cancer.
In contrast, amplification of the KDMA6 gene was detected in only one sample (3.1%), implying a limited role for this gene in the breast cancer cases studied. While the precise involvement of KDMA6 in cancer remains unclear, its rare amplification in this cohort highlights the need for further investigation to elucidate its biological relevance.
Interestingly, both the P53 and K-ras genes exhibited consistent amplification across all 32 samples (100%), reinforcing their well-established roles in breast cancer pathogenesis. P53, a pivotal tumor suppressor gene, and K-ras, a key proto-oncogene, are known to drive tumorigenesis through dysregulation of cell proliferation, apoptosis, and growth signaling pathways.
These findings collectively suggest that, in addition to the established significance of P53 and K-ras, NAT2 may play a previously underexplored role in the genetic framework of breast cancer in this population. The association of NAT2 with breast cancer highlights a potential genetic susceptibility specific to the Northwest Rajasthan cohort, warranting further in-depth studies. This discovery opens new avenues for understanding breast cancer etiopathogenesis and may contribute to the identification of novel biomarkers or therapeutic targets for managing the disease.

Declaration by Authors

Ethical Approval and Consent to Participate:
We have taken ethical approval from ethics committee of Sadar Patel Medical College, Bikaner, Rajasthan.
We have taken consent from the patient / patient's relative to participate in study.

Consent for Publication: Not Applicable

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Conflict of Interest: The authors declare no conflict of interest.

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