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Short communication

Somatic Mutations as Possible Molecular Targets in Breast Cancer

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ABSTRACT

The breast cancer prevalence and associated mortality remains alarmingly high. Advances in personalized therapy have opened avenues for better management of breast cancer patients. Our study aims to explore somatic mutations associated with breast carcinoma which may play a pivotal target for possible precision therapy. This in-silico study was conducted by gene enrichment analysis and exploring COSMIC database. In our study, TP53 and PIK3CA were found to be the most commonly associated somatic mutations as per COSMIC cancer browser. The clinical phenotype on FunRich analysis showed significant association of breast cancer with TP53 and PIK3CA.We conclude that a combination of targeting PIK3CA pathway with TP53-*Myc* axis may help constitute a possible effective therapeutic target to improve breast cancer patient management. Further comprehensive molecular studies are warranted.

Keywords: In-silico, COSMIC database, Targeted therapy

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INTRODUCTION

Cancer remains a major cause of mortality worldwide.[1] Breast cancer has been reported to be the most frequent cancer among women and is significantly associated with cancer related mortality.[1,2] Breast cancer death rates are greater in underdeveloped countries.[3] Pakistan has a high burden of breast carcinoma related mortality, being highest among Asian population, which raises health concerns. Shaukat Khanum based registry of 2020 reports breast cancer to be the most commonly reported cancer among both gender and all ages. According to GLOBOCON 2020, worldwide, the incidence of breast carcinoma has surpassed lung carcinoma presenting with 2.3 million new reported cases in 2020. In this era of precision therapy, the world is moving towards mutation-based target therapy. Literature shows how breast cancer management has improved over the past decades owing to previous and ongoing research.[4] Furthermore, breast cancer management relies upon progress we make in screening, diagnostic and therapeutic strategies.[4] The current biomarkers and imaging techniques do not offer satisfactory monitoring of breast cancer treatment response.[5] There's a need to explore markers that can complement existing biomarkers to be used for identification of risk as well as progression of disease. The Catalogue of Somatic Mutations in Cancer (COSMIC) represents a database of somatic mutations in cancers and provides a platform for research to explore somatic mutations in various carcinomas.[6] We explored the database to identify somatic mutations that might play a vital role in breast cancer diagnosis, prognosis and therapeutic advances.

MATERIALS AND METHODS

This in-silico study was carried out by exploring COSMIC cancer browser to identify common somatic mutations in breast cancer. Further, the mutations in different classes of hormone receptor expression were explored. After identifying two most common somatic mutations, Gene enrichment analysis using FunRich_V3 was conducted to compare the clinical phenotypes associated with these genes.

RESULTS

On exploring Somatic mutations reported by COSMIC database PIk3CA were found to be in 29 % of the cases tested for possible PIK3CA mutations. The most common mutation in PIK3CA is mis-sense mutation (97%) with A>G transition as the most common substitution (47%). Out of the breast cancer tissues recruited for TP53 analysis, 27% TP53 mutations were found. Missense mutations were also found to dominate Tp53 with most common substitution as G>A (29%).

Upon researching frequency of PIK3CA and TP53 according to hormone receptor status, it was found that TP53 were predominant in case of triple negative breast cancers while the ER positive, ER PR positive and Triple positive tumors showed a relatively higher PIK3CA mutation frequency (Table 1). The gene enrichment analysis revealed significant association of both PIK3CA (p=<0.001) and TP53 (p=<0.001) with breast cancer (Figure 1)

Table 1: The Frequency of TP53 and PIK3CA in Breast Carcinoma hormone expressions as per COSMIC Database

Breast Cancer Hormones Receptor positivity	**TP53**	**PIK3CA**
ER positive	19%	39%
ER-PR positive	20%	32%
ER-PR- HER positive	36%	35%
Triple Negative	54%	15%

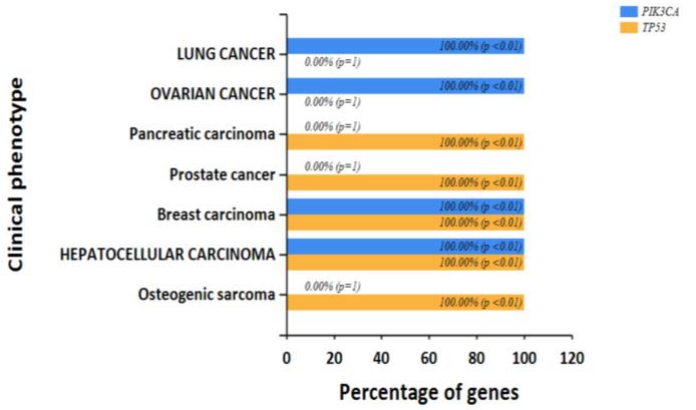

Figure 1: Percentage of TP53 and PIK3CA genes in various carcinomas as reported by Fun Rich analysis. Breast carcinoma and hepatocellular carcinoma showed significant association with PIK3CA and TP53 genes. The p-value of less than 0.05 is considered as significant

DISCUSSION

In this study, we explored COSMIC database to identify key somatic mutations which might serve as a marker of risk identification and as therapeutic targets as well. It has been documented that breast cancer relapse and metastasis have been associated with presence of cancer stem cells.[7] The epithelial mesenchymal transition paves way for cancer stem cells replication in breast cancer cells. Hence, metastasis and drug resistance occur.[7] The TP53 loss has been reported to activate mammary cancer stem cells (CSCs)through unchecked transcriptional activity of *Myc*.[8] The increased replicative potential of breast stem cells eventually results in uncontrolled aberrant growth leading to breast cancer.[8] In addition to TP53 mutation and resultant constitutive activation of *Myc*, many other signalling pathways are aberrant in cancer stem cells.[9] The PI3K/Akt/mTOR pathway is one of the main signaling pathways involved in the maintenance of stemness, proliferation, differentiation and epithelial to mesenchymal transition (EMT). Thus, suppressing the PI3K/Akt/mTOR pathway with inhibitors might be a promising strategy for targeted cancer therapy.[9] The association of PIK3CA with ER positive breast cancer has been reported by Nagy et al.[10] Moreover, Triple negative breast cancer (TNBC) which represents an aggressive type of cancer has been reported to be regulated by PI3K/Akt/mTOR pathway. A recent trial has also emphasized the importance of PIK3CA pathway inhibitors in improving the prognosis of TNBC.[11,12] The foundation of advancements in personalized therapy is identification of gene targets. Our study emphasizes upon the role of somatic mutations in development and progression of breast cancer. Moreover, the significance of these mutations in cancer therapeutics and precision medicine are highlighted. A limitation of our study is that our results are based upon information shared by one database and a more comprehensive in-silico study is warranted. In addition to genetic testing for hereditary genetic aberrations, vital somatic mutations should also be tested for timely identification of risk of breast cancer and its management.

CONCLUSION

Somatic mutations play an important role in breast cancer causation and progression. Targeted therapy is the need of time. Our study suggests that a combination of targeting PIK3CA pathway with TP53-Myc axis may help constitute a possible effective therapeutic target to improve breast cancer patient management.

Authors Contribution

1. SA: planned and designed the present work, to contributed to data search and manuscript Writing

2. SH: FunRich analysis and interpretation, manuscript Writing

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Institutional ethical board approval

Not required

Conflicts of Interest

The authors report no conflict of interest

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