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Multi-omics Investigation of BRCA1 Oncogenic Regulatory Performance in Breast Invasive Carcinoma

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ABSTRACT

Breast invasive carcinoma has poor prognosis in women malignances due to late diagnosis and lack of awareness. BRCA1 has a central role in growth suppression, cell-cycle arrest, and apoptosis in adverse carcinogenic situations. There is an inevitable need to re-analyze the regulatory behavior of BRCA1 in multiple breast malignancy parameters for advancing therapeutic regimen. Due to a huge bulk of molecular data regarding the role of BRCA1 in breast carcinoma, the current study designed rational *in silico* pipeline from data generation to analysis. Firstly, the study used GeneCards: The Human Gene Database of Gene Cards Suite for enrichment analysis, cBioPortal for Cancer Genomic platform for regulatory analysis, UALCAN database for expression analysis, REPAIRtoire database for determining the involvement of BRCA1 in repairing pathways, and finally Cancer Cell Lines Encyclopedia and the Genomics of Drug Sensitivity in Cancer projects (CCLE GDSC) toolkit for drug sensitivity analysis. The study revealed BRCA1's insufficient expression with huge number of mutations in Invasive Ductal Carcinoma (IDC), which leads towards non-functional protein synthesis. BRCA1 majority of mutations are presented in exon 8-11 that becomes unable to interact with RB1, RAD50, RAD51, MRE11, NBS1 and PALB1 damage sensing/repairing partners. BRCA1 promoter hyper methylation also reduces BRCA1 regulation, which is an alarming factor that may damage repairing apparatus. BRCA1-repairing pathways association also highlights its core significance in tumor protective system. BRCA1 regulation also plays an ideal supportive role in anti-cancer drug performance. On the basis of these *in silico* outcomes, in future, there might be an urgent need to design rational strategies for the activation of BRCA1 mutation reversal pathways, inhibition of methylation pathways towards BRCA1, construction of BRCA1-drug correlome map for ideal prognosis, and identification of alternative options other than

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BRCA1.

Keywords: BRCA1, Breast Invasive Carcinoma, cell-cycle arrest, DNA damage checkpoints, proliferation and drug sensitivity

1.INTRODUCTION

The mass of unwanted highly proliferating cells in breast milk glands with associated ducts and skin-bearing general symptoms, such as nipple discharge, thickening, swelling, and redness is known as 'breast carcinoma'. There are two staging systems, that is, American Joint Committee on Cancer (AJCC) and Surveillance, Epidemiology, and End Results (SEER) categorized breast carcinoma into various stages. These stages included existence of tumor cells in originated layer (in situ stage), invasive nature of tumor cells into other breast tissues (local stage), invasive dispersal of cancerous cells into nearby lymph nodes/tissues (regional stage), and trafficking of carcinoma cells into other organs (distant stage). Both staging systems address the prediction of disease outcomes (prognosis) based on receptors, such as estrogen, progesterone, and human epidermal growth factor receptor 2, as well as grading that reflects closeness of tumor cells with normal cells. The women with *in situ* ductal carcinoma (20%-53%) are more likely to develop breast invasive carcinoma which is the most prevalent (81%) breast cancer-type diagnosis mainly at premenopausal state. In breast invasive carcinoma, tumor cells shatter ductal walls and quickly spreading into neighboring tissues to organs [1–8].

Breast Cancer Susceptibility Gene 1 (BRCA1) encodes tumor suppressor protein for genome integrity and chromosome stability. The BRCA1 mutations have above 75% involvement in worse prognosis triple negative breast carcinoma that is a collection of somatic mutations [9]. BRCA1 gains highly influential attention due to participation in apoptosis, controlling cell cycle checkpoints, epigenetic remodeling of chromatin material, transcriptional regulation, and repairing of DNA damage sites [10–12]. BRCA1 performance depends on TP53 mediated signaling under genome aberration activities that trigger its export from cytoplasm to nucleus [13]. In cytoplasm, BRCA1 also has a key role in mitochondrial functions, such as autophagy that is an essential process for the regulation of nervous system, suppression of inflammatory pathways, and maintenance of normal cell growth patterns. BRCA1 mutations halt cardio-muscular activities by abnormal oxidative phosphorylation that leads to

reduced ATP synthesis [14–21]. Here, BRCA1 needs comprehensive study to investigate its part in breast invasive carcinoma progression based on copy number variation, mutation, expression, drug resistance, and association with repairing pathway members. The *in-silico* approach determines BRCA1 mechanistic view for advancement of therapeutic strategies in BRCA1 mediated breast malignancy. To address BRCA1 mediated participation in breast cancer primary initiation to invasive progression, the study selected TCGA project platform that offered a huge number of cancer genomic datasets with large sample numbers. The foremost objective was the exploration of therapeutic, diagnostic, and prognostic BRCA1 dependent biomarkers for early detection and prevention of tumorigenesis to carcinogenesis.

2.METHODOLOGY

2.1. BRCA1 Enrichment Analysis

The study performed BRCA1 gene enrichment analysis by GeneCards: The Human Gene Database of GeneCardsSuite (www.genecards.org) which is a user-friendly knowledgebase web resource for comprehensive enquiry regarding human genes. Firstly, the study queried 'BRCA1' as a human gene in search box and followed 'GO' option that displayed a variety of characteristics about the respective gene including aliases, functions, disorders, domains, pathways, orthologs, paralogs, localization, and several other biomedical features. Additionally, the study selected BRCA1 participation in pathways to determine its role in tissue microenvironment.

2.2. BRCA1 Regulation Analysis

The study performed BRCA1 genomic regulation analysis through cBioPortal for Cancer Genomic (www.cbioportal.org), which is an open access resource for multiple cancer type's genomic profiles. It has diverse molecular data types including copy number variation, mutations, methylations, phosphorylation, mRNA expression, and clinical data regarding prognosis. 'TCGA or ICGA' option was selected from the main page search box. Afterwards, the study chose 'Breast Invasive Carcinoma TCGA, PanCancer Atlas' that further followed submitting of 'BRCA1' as query gene in 'search box'. Finally, the 'submit' option was followed that displayed 'OncoPrint tab' alteration summary of BRCA1 gene in breast cancer dataset. Moreover, 'mutation tab' was used to determine the comprehensive mutational signatures in breast malignancy. The user-

friendly cBioPortal provided a unique coloring pattern for different molecular entities with various downloading options for export of molecular data.

2.3. BRCA1 Expression Analysis

The study used UALCAN database (www.ualcan.uab.edu) which is a human malignancies omics data analysis web resource. Initially, 'TCGA analysis' tab was followed that displayed the main analysis page. This consisted of listing human cancer omics datasets, search gene box, search cancer dataset bar, and 'explore' option. The study queried BRCA1 gene in search gene box, selected breast invasive carcinoma from dataset list, and followed the explore option that displayed box-whisker plots of BRCA1 with diverse attributes. Furthermore, the study selected expression and methylation profile of histologic subtypes that encompassed various breast cancer types. UALCAN database uses Transcript per Million (TPM) ratio and beta values for estimation of expression and methylation analysis. The *in silico* approach used TCGA-Assembler for level 3 RNA-seq data retrieval, which was processed into rsem.genes.results files of gene expression values by RSEM algorithm. The PERL program extracts TPM values for measurement of expression across diverse dataset samples. The PERL module algorithm is used to calculate minimum, 1st quartile, median, 3rd quartile, and maximum values. On the basis of clinicopathological aspects, the Welch's T-test is applied to estimate the significance of expression level differences among normal and BRIC subgroup samples. In cancer studies, relative expression levels among normal and tumor samples are determined by calculating TPM values.

2.4. Determination of BRCA1 Involvement in DNA Damage Signaling

The study used the REPAIRtoire database (www.repairtoire.genesilico.pl), which is an integrated resource of genome damage events, sensing and repairing molecular entities. It comprises molecular data of 3 model organisms, that is, *Homo sapiens*, *Saccharomyces* cerevisiae, and *Escherichia coli* regarding cytotoxic mutagenic elements for DNA damage, damage removal pathways, repairing enzymes, and damage mediated diseases. Firstly, 'Pathways' option list was selected at main page that displayed the above-mentioned 3 model organisms. Afterwards, the study selected '*Homo sapiens'* as specie with 'DNA Damage Signaling or Checkpoint pathway (DDS)'. As a result, it

displayed a comprehensive list of damage checkpoint sensors.

2.5. BRCA1 Drug Sensitivity Analysis

Automatic rational pipeline Cancer Cell Lines Encyclopedia and the Genomics of Drug Sensitivity (CCLE GDSC) were used in the toolkit of cancer projects that offered easy to use web-based interface. This helped calculate and display genes expression effect on anticancer drug performance from the already randomly published data. The CCLE GDSC toolkit utilized spearman's correlation coefficient algorithm for estimation of gene expression impact on drug activity. The gene-drug association is expressed in a coloring pattern in which red color shows (positive correlation) and green color presents (negative correlation). Here, positive correlation defines gene expression resistance towards drug activity and negative correlation indicates supportive role in drug performance. The CCLE GDSC gene expression-drug sensitivity correlations toolkit integrates gene expression-drug effectiveness correlation data from cell lines experiments based on EC50 and IC50 values for 265 drugs against more than one thousand cancer cell lines. The toolkit calculated Spearman's rank correlation coefficients by using the R software and included only the correlations with $p < 0.05$.

3.RESULTS

Table 1. BRCA1 Involvement in KEGG Pathways

S.NO	Pathways
1	Breast cancer
2	Fanconi anemia pathway
3	Homologous recombination
4	MicroRNAs in cancer
5	PI3K-AKT signaling pathway
6	ATF-2 signaling pathway
7	ATM signaling pathway
8	BARD1 signaling pathway
9	Cell cycle transition and termination of DNA replication
10	DNA double strand break response

3.1. BRCA1 Enrichment Analysis

BRCA1 occurred at chromosome 17q21.31 of 125,951 bases that

encodes 1863 amino acids of 207721 Da molecular mass. BRCA1 activates various genes (CDKN1B, ATM, RBBPB and RNASEL) and inactivates (ESR1, AKT1, CTSD, FOXC2, HSPA5 and TFF1). BRCA1 is activated by (PALB2, RAD50, UIMC1, ABRAXAS1, AKT1, ASPM, ATM, ATR, AURKA, BARD1, BRIP1, CDK1, CDK2 and CHECK) and inactivated by (PPP1CA, CASP3, CDK4 and CTBP1). Here, BRCA1 showed influential significance due to involvement in cell cycle regulatory pathways, damage response and repairing pathways, growth arrest pathways, angiogenesis, and breast malignancy pathways (Table 1).

3.2. BRCA1 Regulation Analysis

The study analyzed BRCA1 genomic regulation in breast invasive carcinoma TCGA, PanCancer Atlas dataset of 996 samples, out of which 44 samples showed alteration in BRCA1 gene makeup. Here, 12 samples (amplification), 12 samples (truncating mutation), 11 samples (missense mutation with unknown significance), 5 samples (deep deletion), 2 samples (missense mutation putative driver), and 2 samples showed in-frame mutation putative driver. In this dataset, 32 samples showed BRCA1 deficiency in context of deletion and non-functional protein performance in diverse scenarios. This included post-translational modifications, protein-protein interaction, and transcriptional regulation (Figure 1).

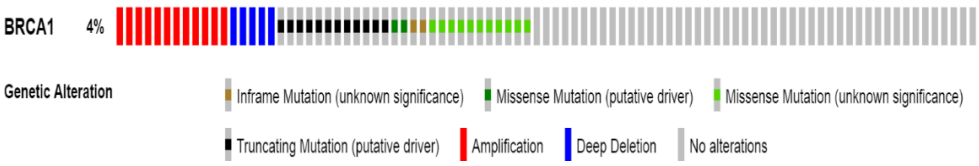

Figure 1. BRCA1 Genomic Regulatory View in Breast Invasive Carcinoma Dataset. Each Bar Represents Patient Sample with Relevant Coloring Pattern of Copy Number, Alteration, or Mutation. Here, 12 Red Bars Show Amplification of BRCA1 Copy Number Resulting in Overexpression of Protein Synthesis, 5 Blue Bars Show Deep Deletions of BRCA1 Gene Resulting into Abnormal mRNA Transcription, 12 Black Bars Show Truncating Mutations Leading to Premature Termination Codon Translation, 12 Dark/Light Green Bars Show Missense Mutations Indicating Non-Functional Protein Product, and Finally 2 In-frame Mutations also Result in BRCA1 Functionless Protein

BRCA1 has 5 main regions, that is, zinc finger (24-64 AA), serine-rich

domain associated with BRCT (344-507 AA), ethylene insensitive 3 (648-978 AA), BRCT domain (1662-1723 AA), and BRCT domain (1662-1723 AA). In mutatome map, 27 mutations are showed in which breast invasive ductal carcinoma has 23 mutations, breast invasive lobular carcinoma has 2 mutations, and breast invasive carcinoma mixed has 2 mutations. Here, 13 missense mutations are V83F, D1578H, G1788V, Q1811L, D1344H, E9Q, S1027I, D366N, D96H, E1419K, L1098I, D2E, and S915C. BRCA1 mutatome map has 12 truncating mutations, that is, X1559_Splice, X27_Splice, N1121Kfs12 (frameshift insertion), 3 frameshift deletions (E23Sfs8, T688Vfs12, C903Wfs97), Q934, Q1408, E720, E272, E1329, and Q139 non-sense truncating mutation. There are 2 in-frame mutations as well, that is, R1589_A1615del and C644del. The majority of mutations occur from 600-1811aa in ethylene insensitive 3 to BRCT domain tail that is highly involved in enzymatic activities (Figure 2).

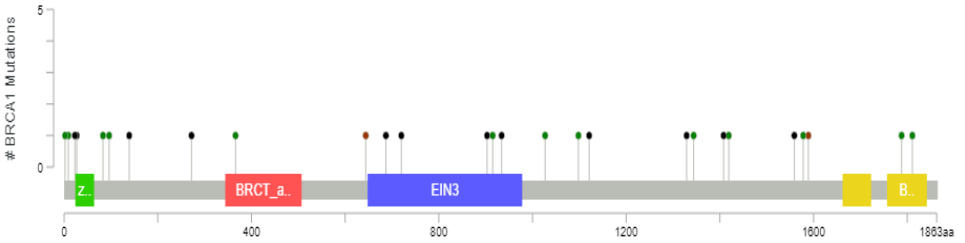

Figure 2. BRCA1 Mutatome Map in Breast Invasive Carcinoma Dataset Represents Significant Regions in BRCA1 gene. The Green Box Shows Zinc Finger from 24-64 AA, Red Box Shows Serine-Rich Domain Associated with BRCT from 344-507 AA, Blue Box Shows Ethylene Insensitive 3 from 648-978 AA, and 2 Yellow Boxes Show 2 BRCT Domain Repeats from 1662-1723 AA/ 1662-1723 AA. Here, Round-headed Lines Indicate Mutations, that is, Green-Circled Line Shows Missense Mutation and Black-circled Line Shows Truncating Mutation.

3.3. BRCA1 Expression and Methylation Analysis

In the *in silico* findings, BRCA1 showed overexpression in breast invasive carcinoma histological subtypes than normal tissue samples. The BRCA1 showed higher expression in IDC (25.11 TPM), Invasive Lobular Carcinoma (ILC) (18.24 TPM), mixed (18.51 TPM), others (20.16 TPM), mucinous (16.42 TPM), INOS (6.06 TPM), and medullary (15.20 TPM) as compared with normal tissues (6.73 TPM). Here, BRCA1 showed prominent upregulation in IDC, mucinous, and medullary type of carcinoma

derived from breast ductal branches harboring units of breast metastasis. BRCA1 epigenetic promoter methylation status in histological subtypes and normal tissue samples showed close affiliation towards hyper methylation. BRCA1 showed hyper methylation in all normal to medullary type of cancers. This reflects its significance for low level transcription. Here, 0 beta-values indicate unmethylated state, 1 beta-value fully methylated, 0.3-0.2 beta-value hypo-methylation, and 0.7-0.5 beta-value hyper-methylation (FigURE 3).

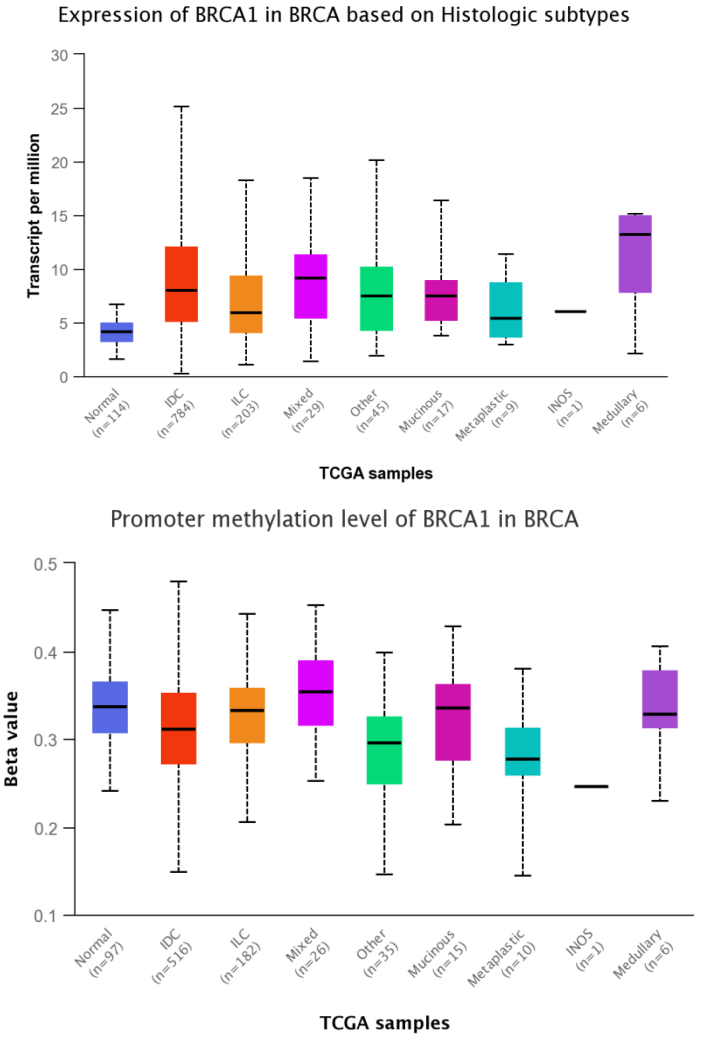

Figure 3. BRCA1 Expression/Methylation Profile in Breast Invasive

Carcinoma Dataset. Upper Plot Shows BRCA1 Expression Profile in Both Normal Tissues (114 samples) and Breast Carcinoma Histological Subtypes Including IDC (784 samples), ILC (203 samples), Mixed Types of Cancers (29 samples), Other Types of Cancers than Ductal Carcinoma (45 Samples), Mucinous Ductal Carcinoma (17 Samples), Metaplastic Ductal Carcinoma (9 Samples), INOS Ductal Carcinoma (1 Sample), And Medullary Ductal Type of Carcinoma (6 Samples). BRCA1 Expression Values are Defined by TPM Values that are Calculated from Quartile Ranges Data Analysis. Lower Plot Showed BRCA1 Promoter Methylation Profile in Both Normal Tissues (97 Samples) and Breast Carcinoma Histological Subtypes Including IDC (516 Samples), ILC (182 Samples), Mixed Types of Cancers (26 Samples), Other Types of Cancers than Ductal Carcinoma (35 Samples), Mucinous Ductal Carcinoma (15 Samples), Metaplastic Ductal Carcinoma (10 Samples), INOS Ductal Carcinoma (1 Sample), and Medullary Ductal Type of Carcinoma (6 Samples). BRCA1 Methylation Values are Estimated by Beta-values, that is, 0 (Unmethylated), 1 (Fully Methylated), 0.3-0.2 (Hypomethylation), and 0.7-0.5 (Hypermethylation).

3.4. Determination of BRCA1-repairing Pathway Association

A total of 34 members were obtained regarding DNA damage signaling or checkpoint that played essential role in cell cycle arrest. Here, RAD9-RAD1-HUS1 damage sensing complex with RAD17-RFC cascade regulates ATM-ATR-CHK1-CHK2 that further activates TP53-TP21-CDC25. As a result, deactivation of CDK family occurs, which is a signal of cell-cycle arrest. BRCA1 has key membership of damage checkpoint complex that is responsible for genome integrity and stability (Table 2).

Table 2. BRCA1 Involvement in DNA Damage Signaling Complex

ATM	ATR	ATRIP	BLM	BRCA1
CCNH	CDK7	CDKN1A	CHEK1	CHEK2
COPS5	DCLRE1A	DCLRE1B	FANCA	FANCC
GPS1	HUS1	MDC1	MNAT1	MRE11A
NBN	RAD1	RAD17	RAD18	RAD23A
RAD50	RAD9A	RFC1	RFC2	RFC3
RFC4	RFC5	TOPBP1	TP53	

3.5. BRCA1 Drug Sensitivity Analysis

In drug sensitivity analysis, BRCA1 expression showed an interesting

relationship towards anti-cancer drugs. Here, BRCA1 has regulatory association with 18 drugs and all functional correlations are negative, indicating its supportive role in drug efficiency. BRCA1 positive regulation enhances anti-cancer drug activity in breast cancer (Table 3).

Table 3. BRCA1 Drug Sensitivity Role in Breast Carcinoma

Drugs	Targets	Correlation
AG-014699	PARP1 and PARP2	Negative
BMS-754807	IGF1R	Negative
BX-912	PDK1	Negative
CAL-101	PIK3 Delta	Negative
Debrafenib	BRAF	Negative
GDC0449	SMO	Negative
GSK1070916	AURKB	Negative
KIN001-236	TIE2	Negative
LFM-A13	BTK	Negative
MLN4924	NEDD8-activity	Negative
NPK76-II-72-1	PLK3	Negative
PF-562271	FAK	Negative
Ruxolitinib	JAK1, JAK2 and TYK2	Negative
Salubrinal	GADD34 and PP1C	Negative
SGCO946	DOT1L	Negative
SNX-2112	HSP90	Negative
XMD14-99	EPHB3 and CAMK1	Negative
Obatoclax Mesylate	BCL2, BCL-XL and MCL-1	Negative

4. DISCUSSION

In various studies, BRCA1 is considered as a growth suppressor to inhibit error prone proliferation by mainlining genome repairing mechanism. BRCA1 alterations caused structural aberrations in a variety of proteins, leading towards over-growth of breast tissues. BRCA1-BRCA2 mutations carried 45-80% risk in developing breast cancer throughout the lifespan of females [22, 23]. BRCA protein's role in genome repairing proposed anti-oncogene components that offered resistance towards mutations. If BRCA1 gene carries deleterious mutations, then cellular machinery is unable to repair genomic lesions which harbor oncogenic mutations [24]. Above 30%, ovarian and breast malignancies cases carried BRCA gene mutations, and more than 10% breast carcinomas had BRCA1

deleterious mutations [25]. BRCA1 mutations varied in different ethnic zones, such as Jewish population had BRCA1 dominant gene mutations in breast cancer progression, while Italian population had lesser effect of BRCA1 mutations [26]. BRCA1 mutations in women breast carcinoma caused more than 80% elevated risk of ovarian and prostate carcinoma in women and men, respectively [27]. Several genome caretaker genes mutations including TP53, CHEK2, ATM, STK11, and CDH1 genes in breast cancer indicated that BRCA1 mutations influenced the whole genome repairing machinery [28]. BRCA1 gene mutations produced higher lymphatic penetrance and aggressive mitotic process, leading towards an invasive behavior of carcinoma [29].

In this study, BRCA1 showed 27 mutations in which majority of mutations were missense mutations, followed by truncating mutations and frameshift alterations. The BRCA1 deep deletions, in-frame mutations, and splicing zone mutations encoded non-functional protein, which is unable to perform tumor suppression activity [30]. BRCA1 has several non-sense mutations which may lead towards truncated shortened protein product by mRNA premature termination [31]. In mutatome map, BRCA1 alterations indicated its abnormal protein synthesis via aberrant splicing and irregular modifications in protein structure, leading to functional failure in oncogenesis. BRCA1 showed key mutations (V83F, E9Q, D96H, D2E, E23Sfs8, and X27_Splice) in RING domains from exon 2-7, which are responsible for E3 ubiquitin activity mediated proteomic interactions. On the other hand, few mutations were also observed in BRCT domains (G1788V and Q1811L) from exon 16-24 which are very crucial for phosphoprotein, including ATM-ATR kinases binding. BRCA1 mutations in these domains clearly indicated its functionally de-active role in cell death regulation. BRCA1 has important D366N missense mutation in exon 11 which is vital for tumor suppressor Retinoblastoma (RB) protein interaction at ABC domain. BRCA1 exon 11 mutations caused inhibition of BRCA1-RB interaction that led towards cell cycle proliferation. Here, few mutations and in-frame deletions (D366N, E720, T688Vfs12, and C644del) in exon 11 prevent significant interactions with RAD50-MRE11-NBS1 genome repairing apparatus. These BRCA1 mutations deregulate both non-homologous ends joining (NHEJ) and homologous recombination (HR) repairing processes. The BRCA1 exon 11 mutations (S1027I, S915C, Q934 and C903Wfs97) inhibit essential association with RAD51 damage repairing protein. There is single non-sense E272 mutation in exon 8-11,

which is important for binding with c-MYC protein that promotes transcription of above 15% of whole genome, especially oncogenes. BRCA1 has 2 mutations in exon11-13 (E1419K and Q1408), which has gained attention for PALB2 binding that played vital role in HR. Here, serine cluster domain in exon11-13 has 2 mutations (D1344H and E1329) that halt BRCA1-ATM/ATR interaction, which are essential members of DNA damage response mechanism.

In the current study, BRCA1 showed majority of mutations in ductal invasive carcinoma which had above 95% cases in breast malignancy [32]. IDC is categorized into diverse types based on secretion location, type and amount, tissue cell type, and architectural pattern of proliferation [33]. Here, BRCA1 high frequency mutations in IDC indicate its sensitive significance in most prevalent and lethal forms of breast carcinoma. These findings proposed BRCA1 as diagnostic biomarker in IDC for estimation of functional efficacy of genome repairing pathways in worse prognosis malignancies. Here, BRCA1 overexpression in breast invasive carcinoma samples including IDC, ILC, and medullary type of carcinomas than normal tissue samples showed its successful dependence on transcriptional regulators. There is an urgent need to re-evaluate BRCA1 expression with association of its regulatory unit as regulome. BRCA1 upregulation in breast carcinoma is insufficient to carry out required damage response activities. Here, BRCA1 promoter hypermethylation also played a significant role in BRCA1 deregulation, leading towards reduced expression. In this study, BRCA1 showed key membership of DNA damage signaling or checkpoint complex, this indicated its functional correlation with protection of housekeeping regulatory genome. BRCA1 regulation had a supportive effect on anti-cancer drugs, proposing its powerful contribution against oncogenes. This study highlighted the novel role of BRCA1 in drug efficacy to block oncogenic transcriptional regulation. Here, BRCA1 has 2 core functions, that is, tumor suppressor activity by damage repairing/cell cycle arrest and increasing anti-oncogenic drug effect in breast carcinoma.

4.1. Conclusion

BRCA1 biology played a significant role in breast cancer therapeutics with the advent of omics era. Multiple research institutes conducted system biology-based laboratory and *in silico* experiments that generated a huge amount of molecular data regarding BRCA1 up/low-regulation in diverse stress scenarios. The *in silico* approach used in this study revealed the

regulatory behavior of BRCA1 towards a wide number of both normal and cancerous tissue samples with drug sensitivity patterns. Here, BRCA1 showed an influential relationship with the most prevalent invasive IDC in either the context of mutations or expression as diagnostic biomarker.

Author Contributions

Zafar Abbas Shah: methodology, writing-original draft, formal analysis, validation. **Shumaila Noreen:** writing-review & editing. **Faisal Nouroz:** project administration.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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Generative AI Disclosure Statement

The authors did not use any type of generative artificial intelligence software for this research.

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