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RESEARCH ARTICLE

# *IN SILICO* IDENTIFICATION OF TARGET PALINDROMIC GENES AS POTENTIAL DRUG TARGETS IN BREAST CANCER THERAPY

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## Abstract

**Objectives:** Breast cancer (BC) is the most common cancer worldwide prevalent among women with more than one million cases and is second only to lung cancer.
**Methods:** The identification of the sequences based on the unique tetramers GCAC, GTCA were selected from experimental work. The16 base pair DNA regulatory sequences of which the motifs area part of containing these motif in genes implicated in cancer CAGE1 (AAGCTGTCATTA), BRCA1(GACTGA GTCAA), ABCB1(CTCTAAGTCAT), ABCB5 (GATATGTTAAAGC) and ABI1 (CTTCTGGGAA) were then selected as novel putative targets in breast cancer therapy based on their selectivity on the BC oncogenes which are not found in the normal human genome 1-23 and the sex chromosomes X and Y were obtained via computational analysis.
**Results:** The single copy base pairs which will be potential drug targets as anticancer drugs were finally obtained as CTGTTATGACTGAGTCAA, CAGE1 with the 17 base pairs CATAAAAGCTGTCATTA and ABCB1TTGCCAACT CTAAGT CAT.
**Conclusion**: It is Possible that the *in silico* discovery of putative anti breast cancer targets of importance in the genome.
**Keywords:** ABCB, ABI!, Breast Cancer, BRCA, CAGE 1, Target genes.

## INTRODUCTION

Breast cancer is the most common malignancy in women accounting for about 18% of female cancers worldwide and over half a million diagnosed each year. Its incidence increases with age. It was the second most common cancer in the world with over 1million new cases. In Nigeria, cancer cases have increased by 21% out of which 10% are BC[1]. It originates in the cells of the breast and several genes bearing high-penetrance mutations have been implicated in inherited disposition to BC with BRCA1 and BRCA2 being the most important, BC susceptibility genes other than BRCA1 AND BRCA2 have been identified. These genes are in two categories:

1. Genes with rare-moderate penetrance (CHEK2, ATM and BRIP) (The CHECK2 Breast Cancer Case Control Consortium, 2004).
2. Genes with low penetrance allele[2].

ABCB1 MDR1 gene encodes a well characterized trans membrane transporter P-glycoprotein. It is expressed in cancer cells and involved in genomic instability of cancer cells, gene rearrangements and mutations. Permeability glycoprotein also known P-glycoprotein (P-gp; MDR1; ABCB1) is an efflux transporter which belongs to the ATP-binding cassette (ABC) super family of transporters, and actively transport a wide range of structurally and mechanistically diverse endogenous and xenobiotic chemical agents across the cell membrane at the energy expense of ATP hydrolysis[3]. P-glycoprotein has been implicated in the development of multidrug resistance to anticancer drugs when expressed in breast cancer cells[4] due to its ability to profoundly implicate the role of drug pharmacokinetics (PK) that can clinically alter the administrated drug efficacy or even lead to various adverse side-effects due to drug–drug interactions (DDIs) in the case of polypharmacy[3]. Presence of oestrogen have been found to downregulate P-glcoprotein expression in ER positive BC cell lines[5]. CAGE1 has been identified and characterized as a novel cancer antigene[6]. Total 5-10% of BC cases develop on a hereditary basis. Approximately 80% are accounted for by mutations in the BC susceptibility genes,BRCA1((40-45%) and BRCA2(35-40%).The remaining 20% of BCs may be due to mutations in other tumor suppressor genes as P53, PTEN and ATM in addition to other genes. Genetic events involved in BC tumor formation are as follows: tumor oncogene activation.

Tumor suppressor gene inactivation, abnormal protein over expression and multiple gene alteration[7]. Systemic treatment options include cytotoxic, hormonal and immunotherapeutic agents[8]. In addition, surgery, radiotherapy, hormonal therapy, biological therapy as well as chemotherapy. The chemotherapeutic interventions are used in adjuvant, neoadjuvant, and metastatic settings. In general, systemic agents are active at the beginning of the therapy in 90% of primary BC cases and 50% of metastatic settings. Resistance to therapy occurs at this point. Most of the existing drugs are toxic, non specific and have severe side effects, many tumor develop resistance to majority of the chemotherapeutic agents[9]. Estrogen receptors ERs are dependent, inducible signal transducers which act through a non classical pathway in which liganded ERs are tethered to DNA via association with other transcription factor complexes including Fos/Jun [activator protein-1 (AP-1)–responsive elements] or SP-1[10]. They are capable of binding to palindromic DNA sequences 5′-TGAGTCA-3′ as well as similar sequences 5′-TTAGTCA-3′ and 5′-TGATTCA-3′[12,13]. A small number of genes containing an AP-1 site in their promoters have been shown to be regulated by ERs[14]. AP-1 can be induced by extracellular stimuli such as cytokines, UV radiation, growth factors, oxidative stress, and carcinogens can and promote AP-1 binding to the TRE of its target genes that are involved in cell growth, inflammatory responses, and repair processes. In cellular and viral genes, the AP-1 transcription factor is thus a major component of many signal transduction pathways. It is a complex dimer of homo- and heterodimer family members. The regulation of AP-1 target genes is regulated by AP-1 transcription factor via binding to the DNA regulatory sequence 12. The response TPA element sequence GCAC or GTCA are therefore bound by c-Jun homodimers and c-Jun/c-Fos heterodimers[15].

In this research work, DNA regulatory sequence motifs containing the unique tetramer GCAC, GTCA have been curated from experimental work and the post genomic era characterized by the completion of the human genome project, the start of both the proteomics and structural genomics revolutions and the development in information technology have resulted in the use of structure based drug design in the discovery of new drug targets. The human genome is the complete set of genetic information for humans (*Homo sapiens).* This information is encoded as DNA sequences within the 23 chromosome pairs (22 pairs being homologous) in cell nuclei and in a small DNA molecule found in the mitochondria. It includes both the protein-coding genes as well as the non-coding genes. The haploid human genome (contained in the spermatozoa and oocyte) consist of three billion DNA base pairs while the diploid genomes found in somatic cells have twice the c content[16]. There is an urgent need to identify novel putative targets into the breast cancer drug development pipeline as an early intervention method in breast cancer therapy. *In silico* intervention at various stages in the drug discovery cycle is equipped with the potentials to reduce both time and cost involved in the process. The interaction between small molecules and DNA is important due to its implication in the regulation of gene expression by activators and repressors *in vivo*. In view of the availability of such novel targets which to which selective chemotherapeutic agents against BC can be developed, 40% still die ultimately from the disease[9]. These warrant the need for the development of novel therapeutic agents in the treatment of BC via identification of potential drug targets[16].

## METHODS

The entire Human genome was downloaded via the file transfer protocol ftp from the database of the National Centre for Biotechnology Information (NCBI) ftp site. The download was done in the fasta format. The oncogenes BRCA, CAGE1, ABCB5 and ABI1 were also downloaded from the Online Mendelian Inheritance in Man was also downloaded from the website where OMIM is domiciled. The selectivity of the oncogenes as potential target agents was ascertained when the sequence frequency of occurrence in the human genome was determined.

## RESULTS AND DISCUSSION

The selected genes have been ABCB1, CAGE1 and BRCA1 have been implicated in the proliferation and development of cancer cells. The base pairs numbers of these genes are as follows 11 base pairs for BRCA1 and ABCB1 while CAGE1 has 12 base pairs Table 1. The sequences contain GCAC and GTCA which are unique tetramers however the frequency of occurrence of the sequences 615 for BRCA1 Table 2 ABCB1 11 base pair CTCTAAGTCAT occurs at a frequency of 810 in the human genome while CAGE1 with 12 base pairs AAGCTGTCATTA occurs 328 times. The criteria for an ideal target is that it must occur in a frequency of 1 for it to be non toxic that is it must be a single copy gene. Therefore to obtain a single copy gene from these oncogenes, the start and stop positions were identified such that the the sequences to the right and left of the core sequences were determined Table 2, Table 3 and Table 4.

**Table 1: Summary of selected oncogenes, start/stop positions on the specific chromosome, gene sequence and the base pair number.**

| Gene Name | Length | Transcription Factor | Chromosome Number | Binding Position | Base pairs | BP no |
|---|---|---|---|---|---|---|
| BRCA1 | 26 | AP-1 | Chr7 | 41267898-41267908- | GACTGAGTCAA | 11 |
| CAGE 1 | 3 | TGIF | Chr6 | 7405451-7405462 | AAGCTGTCATTA | 12 |
| ABCB1 | | AP-1 | Chr7 | 87336139-87336149 | CTCTAAGTCAT | 11 |

**Table 2: 16 base pair sequences as potential drug targets from 11bp BRCA1.**

| Gene Name | Base pairs | BP no | Length |
|---|---|---|---|
| BRCA1 | GACTGAGTCAA | 11 | 615 |
| | TGACTGAGTCAA | 12 | 197 |
| | ATGACTGAGTCAA | 13 | 75 |
| | TATGACTGAGTCAA | 14 | 14 |
| | TTATGACTGAGTCAA | 15 | 4 |
| | GTTATGACTGAGTCAA | 16 | 2 |
| | TGTTATGACTGAGTCAA | 17 | 2 |
| | CTGTTATGACTGAGTCAA | 18 | 1 |

**Table 3: 16 base pair sequences as potential drug targets from 11base pair sequence of CAGE1.**

| Gene Name | Base pairs | BP no | Length |
|---|---|---|---|
| CAGE1 | AAGCTGTCATTA | 12 | 328 |
| | AAAGCTGTCATTA | 13 | 122 |
| | AAAAGCTGTCATTA | 14 | 37 |
| | TAAAAGCTGTCATTA | 15 | 9 |
| | ATAAAAGCTGTCATTA | 16 | 5 |
| | CATAAAAGCTGTCATTA | 17 | 1 |

The single copy base pairs which will be potential drug targets as anticancer drugs were finally obtained as CTGTTATGACTGAGTCAA, CAGE1 with the 17 base pairs CATAAAAGC TGTCATTA and ABCB1 TTGCCAA CTCTAAGT CAT.

**Table 4: 16 base pair sequences as potential drug targets from 11base pair of ABCB1 oncogene.**

| Gene Name | Base pairs | BP no | Length |
|---|---|---|---|
| ABCB1 | CTCTAA**GTCA**T | 11 | 810 |
| | ACTCTAAGTCAT | 12 | 199 |
| | AACTCTAAGTCAT | 13 | 63 |
| | CAACTCTAAGTCAT | 14 | 13 |
| | CCAACTCTAAGTCAT | 15 | 6 |
| | GCCAACTCTAAGTCAT | 16 | 3 |
| | TGCCAACTCTAAGTCAT | 17 | 2 |
| | TTGCCAACTCTAAGTCAT | 18 | 1 |

## CONCLUSION

Potential anti breast cancer targets which will go a long way when drugs are developed against them include CTGTTATGACTGAGTCAA, CAGE1 with the 17 base pairs CATAAAAGCTGTCATTA and ABCB1 TTGCCAACTCTAAGTCAT. Further research work based on drug design techniques can be developed.

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## AUTHOR'S CONTRIBUTION

**Awofisayo O:** Writing original draft, review, literature survey, editing, methodology, data curation.

## CONFLICT OF INTEREST

None to declare.

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