Genetic Polymorphism and Possibility for Development of Breast Cancer: A Review

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Abstract **- Genetic polymorphism involves genetic variations. There are several types of genetic variations namely single nucleotide polymorphisms (SNPs), small-scale insertions/deletions, polymorphic, repetitive elements, and microsatellite variation. The most common type of genetic polymorphism/variation involves variation at a single base pair i.e., single nucleotide polymorphism. There are about ten million SNPs known in human genome itself. It can also be much larger and involve long stretches of DNA. Single nucleotide polymorphisms (SNPs) are playing an important role in various cancer progression types and are capable of serving as diagnostic tools. Variations in several oncogenes and tumor suppressor genes have been employed as having a role in human tumorigenesis. Likewise in breast cancer genes involved are interleukin-1, KRAS, ErbB2/HER2/neu, PIK3CA, c-myc and Cyclin D-1 (oncogenes) and p53, Rb1, PTEN, BRCA1/2, ATM and APC (tumor suppressor genes). This review describes several key oncogenes polymorphism that have been implicated in breast cancer progression. One of the most common cancers in women globally is breast cancer. The breast cancer influences over 1 million women yearly. Breast cancer is the second leading cause of cancer deaths worldwide. As far as functionality and biochemistry are involved, genes act at different levels and have different functions at the cellular level. Also, they are normal cellular genes, likely to have important functions in normal cell growth or differentiation. Moreover, in tumors, the function or regulation of the genes is altered, due to mutations.**

Index Terms **- Breast cancer, genetic polymorphism, oncogenes, SNPs, tumor suppressor genes.**

I.INTRODUCTION

Breast cancer is a type of malignant tumor that initiates from cells in the breast. The site of initiation of breast cancer emerges specifically form two sites namely: lobules or the ducts. Lobules are the milk-producing glands of the breast on the other hand ducts are the passages that help in draining out the milk form the lobules to the breast nipple. Rarely, breast cancer can begin via the stromal tissues (having structural or connective role) which includes the fatty and fibrous connective tissues of the breast. Once breast cancer initiation starts in the lobules or ducts, after a while, it starts metastasizing the nearby healthy tissues; followed by entering into the lymph nodes and once they make their way into the lymph node they then easily metastasize the entire parts of the body. Breast cancer is considered as the top 10 causes of death worldwide with a record of 110 000 cases of breast cancer per year according to the world health organization (WHO). It has been estimated that 252,710 new cases of invasive breast cancer will be diagnosed in 2021 among women in the US alone.

Breast cancer can be defined under different types and subtypes of a disease. The below table [a] shows types of breast cancer that can be explained by noninvasive and invasive types. Noninvasive breast cancers are within the milk ducts or lobules of the breast. They are not invaded or grown into, the normal breast tissue. Often referred to as carcinoma in situ and are sometimes referred to as pre-cancers. Secondly, invasive breast cancers initiate from the outside of the ducts or lobules of the breast into surrounding breast tissue. Thirdly, the subtypes of breast cancer are based on the genes by which cancer expresses

Table 1: Types and sub-types of breast cancer

Types		Sub-types
Non-invasive	Invasive	

Ductal carcinoma in situ	Invasive ductal carcinoma	Hormone receptor positive breast cancer
Lobular carcinoma in situ	Invasive lobular carcinoma	HER2 positive breast cancer
	Paget's disease of the nipple	Triple negative breast cancer
	Inflammatory breast cancer	
	Phyllodes tumours of the breast	
	Locally advanced breast cancer	
	Metastatic breast cancer	

Gene polymorphisms can occur in any place of the genome. The probability of polymorphisms that do not change the functionality or the expression of genes is relatively more in number than compared to the one that alters the functionality or the expression of the gene. Also, the interconnection between polymorphism and cancer possibility is increasing with an increase in the detection method techniques. Breast cancer is one of the most common diseases associated with western countries. It has been seen that 10-15% of breast cancer occurs due to a family history of the disease, out of which only 5% of them can be explained by rare, with highly penetrant mutations in genes.

High risk factors associated with invasive female breast cancer include age, gender, race, family history, reproductive factors, pregnancy, radiation exposure, previous abnormal breast biopsy, diethylstilbestrol (DES), hormone replacement therapy, alcohol, and obesity. The below table (b) shows age-specific probabilities of developing invasive female breast cancer involve;

Table 2: Age-specific probabilities for development of invasive female breast cancer

Current age	The probability of develing breast cancer in next 10 years	Or 1 in:
20	0.06%	1,732
30	0.44%	228
40	1.45%	69
50	2.31%	43
60	3.49%	29
70	3.84%	26
Lifetime risk:	12.29%	8

Breast cancer genes further can be explained via oncogenes and tumor suppressor genes; wherein, around 40 oncogenes have been identified until now. When the normal control is disrupted by abnormality of the oncogene, this may contribute to tumor cell development. The disruption is due to 'mutations' in a wide context, either changing the protein coded from the gene or by changing the regulation of its expression. The two types of genes: Oncogenes have no crystal-clear definition; still several of these genes were shown to be evolutionarily conserved genes and to control important normal cell physiologic functions related to cell growth and differentiation. While on the other hand, we have Suppressor genes, or recessive oncogenes, that are cellular genes with unknown function. Suppressor genes encoding proteins; function to inhibit cell alteration and by which its inactivation is advantageous for tumor cell differentiation and cell survival. There are several mechanisms by which inactivation of tumor suppressor genes is very much possible, including intragenic mutations, chromosomal deletions, and loss of expression by methylation-mediated transcriptional silencing or increased proteolysis. Both alleles of such a gene have to be inactivated by mutations or lost by deletions in tumors where the genes play a role.

II. ROLE OF ONCOGENES IN HUMAN BREAST CANCER

Oncogenes are the sequences of DNA (deoxyribonucleic acid); alterations or amplifications of varied oncogenes have been observed primarily in human breast cancer and tumor cell lines. Importantly, such alterations can be sites of primary lesions for human breast cancer or the source of tumor progression or metastasis [1]. A number of oncogenes have been implicated in playing a role in breast cancer since they have been found in a mutated form in the cancer cells (truncation, amplification) [Table (c)]. Oncogenes are called proto-oncogenes, and they play role in the regulation of cell division. More than 40 different human oncogenes are known. Some of the oncogenes and their genetic polymorphism in human breast cancer explained below: interleukin-1, KRAS, ErbB2/HER2/neu, PIK3CA, C-MYC and Cyclin D-1

Table 3: Oncogene activation and dysregulation in tumors

Oncogene activation and dysregulation in tumors
• Increased expression/disregulation
• Controlled by viral promoter-enhancer
• Controlled by integrated viral enhancer
• Chromosome translocation: oncogene under influence of non-autologous promoter/enhancer
• Amplification
• Changed product with new function
• Point-mutation

A. Interleukin-1 gene polymorphisms and their associations with breast cancer

Interleukin-1 is among the 11 cytokines that plays a very important role in the regulation of immune and inflammatory responses to particular infections in the host. The morphology of IL-1 has been studied vigorously, to conclude that genetic polymorphism in such cytokine genes could affect the expressions or functions of the patients affected by breast cancer. Therefore, a recent study has been undertaken in a group showing IL-1 polymorphisms and IL-1 protein expression.

Interleukin-1 comprises of IL-1α, IL-1β, and IL-1 as receptor antagonist [2]. The human genes encoding IL1a, IL1b, and IL1rn are located within a 430 kb region on chromosome number 2q14.2 [3]. Genetic polymorphisms in IL1a, IL1b, and IL1rn correspond with alteration to IL-1α, IL-1β, and IL-1Ra protein expression in vitro and in vivo, respectively. IL-1α and IL-1β are the two important cytokines which initiates and propagates the inflammatory response [4].

Three tag SNPs of interleukin-1 (rs1143623, rs16944, and rs10490571) were taken in the recent study. For rs1143623, the homozygous mutant variant (G/G) (OR = 3.51, $p < 0.05$) and heterozygous mutant variant (G/C) (OR = 2.34, $p < 0.05$) was significantly associated with breast cancer patients, and not with the controls. Additionally, the association persisted when we combined the homozygous and heterozygous mutants (GG + GC), when compared with controls (OR = 2.29; $p < 0.05$). Similarly, the rs10490571 heterozygous mutant variant (T/C) and rs16944 heterozygous mutant variant (A/G) were significantly associated with breast cancer patients, and not with those in the control group. The homozygous mutant variants of rs10490571 (TT) and rs16944 (AA) were also significantly associated with breast cancer patients, and not with control individuals. Furthermore, the association for both alleles persisted when we combined the homozygous and heterozygous mutants (TC = TT and AA + AG).

The second single nucleotide polymorphism in other study, rs1143634 within Il-1β gene of interleukin-1 was analyzed using PCR-RFLP [5]. Three genotypes were detected: (i) homozygous genotype at 249 base pair (ii) homozygous genotype at 135 + 114 base pair and (iii) heterozygous allele presented both the base pairs (249 bp, 135 + 114 bp). It showed rs1143634 differs between breast cancer patients and healthy individuals. Hence, it proved that there is a significant association at the allelic level of rs1143634 with increased risk of breast cancer.

Moreover, showing heterozygous determinants was more frequently seen in healthy individuals, whereas homozygous determinants were more frequently seen in breast cancer patients.

B. KRAS gene polymorphisms and their associations with breast cancer

The KRAS gene belongs to the Ras family of oncogenes, also includes HRAS and NRAS genes. Mutations or polymorphisms in such genes cause a normal cell to become a cancerous cell. The function of the KRAS gene involves the making of protein that is involved in cell signaling pathways that control cell's growth, maturation, and death.

Lethal-7 (let-7) is the most common known miRNAs in human cancers. Wherein, miRNA are the small, noncoding, sequences of nucleotides that control gene expression through attaching to complementary sites in the 3'-untranslated region (3'UTRs) of target mRNAs [6]. KRAS is a recognized target for lethal 7 (let-7) family members, determined in the 3'-untranslated (3'UTR) region of the mRNA. In other words, let-7 acts as tumor suppressors, as they suppress oncogenes regulating in cell cycle or intracellular signaling cascades [7].

Single nucleotide polymorphism in the KRAS 3'UTR region (rs61764370) is associated with many cancers. Another single nucleotide polymorphism within the KRAS gene is in the rs712 region of the let-7 binding site [8], which is another miRNA target site that also shows its relation in many cancers excluding breast cancer but can be used as a new biomarker towards resistant tumor metastasis according to the study. It is confirmed through various studies that the rs61764370 region is associated with a higher risk of developing breast cancer, concerning the rs712 region was

associated with a reduced risk of breast cancer. Also, in the study, KRAS rs61764370 genetic polymorphism was closely associated with the risk of double primary breast cancer.

C. ErbB2/HER2/neu gene polymorphisms and their associations with breast cancer

ErbB2 is also referred to as HER2 gene. Whereas neu is the rodent homologue of the human c-erbB-2 (or HER-2, from human EGF-receptor 2). ErbB2 belongs to the epidermal growth factor receptor (EGFR) family. HER2 is the human epidermal growth factor receptor 2. It makes a protein that is placed over the breast cells. It is overexpressed approximately in 20% of invasive breast cancers. Also, the role of ERBB2/Her2 in cell growth, cell differentiation, and tissue development, as well as in carcinogenesis and metastasis have been well studied. Her2 plays a major role in the regulation of different pathways such as Raf/Ras/MAPK and PI3K/AKT pathways [9]. Trastuzumab a monoclonal antibody specifically binds to Her2 and disturbs the downstream pathways of Her2 and it is effectively used for the treatment of Her2 positive breast cancers [10] [11] [12]

Several studies in different populations have shown an association of Her2 variants with susceptibility to breast cancer, however, these results were inconsistent, inconclusive, and were controversial. One such single nucleotide transition mutation of Ile655Val [(Isoleucine (Ile) to Valine (Val)] showed susceptibility to breast cancer risk in African and Asian populations.

D. PIK3CA gene polymorphisms and their associations with breast cancer

Phosphatidylinositol-3-kinase (PI3K) is a group of enzymes that is involved in cell growth, cell maturation, cell motility and intracellular trafficking. It is an oncogene that plays a very important role in developing breast cancer. Whereas PIK3CA is a gene that encodes α catalytic subunit of enzyme (P13K).

Genetic polymorphism of PIK3CA, the CT genotype of rs17849079 region is seen associated with breast cancer risk. PIK3CA gene is located on chromosome number 3q26.32 and encodes the catalytic subunit of PI3K [13]. The principal role of SNP rs17849079 on PIK3CA expression may be due to the effect on the binding of hsamiR-4324 to the PK3CA mRNA, the hsa-miR-4324 regulate the PIK3CA expression and bind to the mRNA sequences at exon 20 of PIK3CA gene, which contains this single nucleotide polymorphism. This miRNA may bind only to the sequences containing the wild-type allele and not bind to the sequences containing the variant codon, and therefore this might affect the regulation of PIK3CA gene expression. Moreover, it can be also used as a molecular marker for early diagnosis of breast cancer susceptibility.

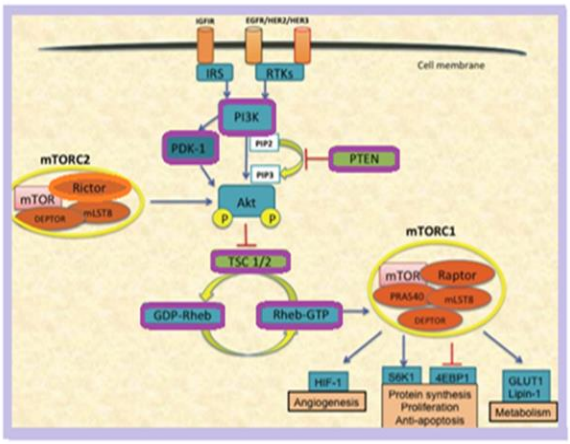

Fig 1: The PI3K/Akt/mTOR pathway is a major intracellular network that leads to cell proliferation

It has been seen that PIK3CA pathway aberrations are common in cancer of the breast. The above shown figure reflects P13K pathway is an important signaling pathway in cells that are involved in essential cellular functions and vice versa plays an important role in the development and progression of breast cancer. PIK3CA mutations are present in approximately 26% of breast cancer cases, especially in the estrogen-receptor-positive (ER+) and human epidermal growth factor receptor 2 (HER2) overexpressing (HER2+) subtypes [14][15].

E. c-myc gene polymorphisms and their associations with breast cancer

Myc gene codes for transcription factors. They belong to a family of regulator genes and proto-oncogenes. Three human genes related to the myc family include c-myc, l-myc, and n-myc. Wherein, C-myc is located on chromosome number 8 and functions in regulating expression of 15% of all genes through binding on enhancer box sequences. The unusual property of c-myc is that the antisense strand of the gene also yields transcripts. It is a multifaceted protein that regulates cell proliferation, cell maturation, and cell death.

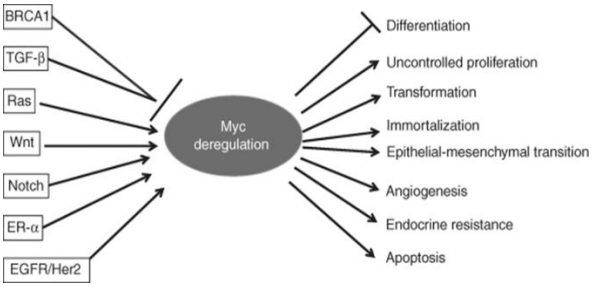

Fig 2: myc gene deregulation

This nuclear oncogene is amplified or overexpressed in about 22-32% of human breast cancer. The gene may be amplified during both the early and late stages of cancer progression [16]. The reported frequencies of overexpression of c-myc greatly vary. Also, only about 22% of the tumor cases show increased c-myc mRNA expression, and the overexpression was rarely due to the gene amplification [17]. There may be a correlation suggesting that the overexpressed mRNA might be related to gene amplification; which is because normal breast tissue is dominated by fat tissue; it differs greatly from tumor tissue in its epithelial cellularity and thus is not a rigorously normal counterpart for comparisons involving mRNA extraction.

Apart from the cellular location of c-Myc, it seems to show a higher percentage of breast cancer cases showing odd protein levels in c-myc than the percentage with the gene amplification [18][19]. This means that, in many cases, altered expression or altered stability of the mRNA or protein may be the mechanism for the increased levels of c-Myc.

In breast cancer, amplification in c-myc may correlate positively or negatively with alterations in other genes. Several reports have shown an association of c-myc gene amplification with a poor prognosis of breast cancer, whereas many other studies do not find such a correlation. Reports on the prognostic value of overexpression of c-myc mRNA or protein are not only inconsistent but also conflicting [20][21]. While many other studies do not find any association between c-myc expression and prognosis, several investigations find that a higher expression level correlates with a poorer outcome. However, a recent study shows that higher c-myc mRNA levels in breast cancer are correlated with better survival. Several studies show that benign breast lesions such as fibroadenomas and fibrocystic disease express c-Myc at levels as high as seen in breast cancer [22][23]. This property leads to a consideration that c-Myc may be involved in the early development of cancer and could be used as a marker for the pre-malignancy or the risk of cancer.

F. Cyclin D-1 gene polymorphisms and their associations with breast cancer

Normal cell cycle control assures a resting period during the cell cycle, allowing DNA damage in a cell to be repaired before the cell begins the process of growth, mitosis and division [24]. The transition through the G1 to the S period of the cell cycle is regulated by cyclin-dependent kinase (CDKs). CyclinD-1 (CCNDI) is one of the major cyclins related with cyclin-dependent kinases. CCND1 is a key administrative protein in this process, playing a basic job in the transition from the G1 to the S period of the cell cycle. The movement of CCNDI arrives at a maximum during the G1 stage and is associated with CDK4 and CDK6 in the mid to late G1 stage. Alterations in CCNDI are thought to be involved in carcinogenesis on the grounds that of activation of CCNDI and over-appearance of CCNDI has been found in many of tumors, including those of the breast cancer.

In the breast, cyclin D1 protein plays a role in both normal mammary development and malignant transformation. Cyclin D1 is one of the most commonly overexpressed oncogenes in breast cancer, with 45-50% of primary ductal carcinomas overexpressing this oncoprotein [25]. In particular, alterations in the CCND1 gene may be a fundamental and early step in breast cancer progression [26] [27] [28]. The G870A polymorphism has been examined in association with breast cancer risk and progression in many epidemiological studies. It has been proposed that the 870-A variant leads to the alternative splice variant b, which misses exon 5 and has a longer half-life than the common transcript a [29] [30]. Contrary to this, Howe and Lynas have reported that GG homozygous individuals produce more transcript b, while AA homozygous ones have more transcript a [31].

III. ROLE OF SUPPRESSOR GENES IN BREAST CANCER

Tumor suppressor genes slow down the cell division, helps in repairing DNA mismatches, and gives information to the cell when to go for apoptosis. In

cancer, tumor suppressor genes are either lost or deleted, facilitating the initiation and progression of cancer through several biological events, including cell proliferation, cell death, cell migration, and cell invasion. In other words, when TSG does not work properly or when they do not function, this eventually leads to abnormal and uncontrolled growth of cells followed by cancer development. Usually, death due to cancer occurs due to metastasization rather than the mass effect of the primary tumor, and several tumor suppressors regulate metastasis. Genetic polymorphism through allelic loss is one of the important factors for the dysregulation of tumor suppressor genes. Importantly, promoter hypermethylation of several tumor suppressor genes has been associated with tumor progression. Besides, several signaling mechanisms are dysregulated in breast cancer as a result of mutations in the tumor suppressor genes. The molecular and genetic basis of inherited breast cancer risk started to increase after the discovery of BRCA1 and BRCA2 genes in the year the '90s. Currently, BRCA1 and BRCA2 are considered to be the most important genes in human breast cancer. Among the tumor suppressors, BRCA1 and BRCA2, p53, PTEN, ATM, Rb, LKB, Nm23, and p16 are some of the examples.

Table 4: Several suppressor genes involved in breast cancer

Gene	Location	Function	Mechanism
TP53 (p53)	17p13	DNA repair, cell cycle, apoptosis and angiogenesis regulator	Intragenic mutation, deletion
Rb1	13q14	Cell cycle inhibitor	Intragenic mutation, deletion
PTEN	10q23	Dual-specific phosphatase	Intragenic mutation, deletion
BRCA1	17q21	DNA repair	
BRCA2	13q12	DNA repair	Intragenic mutation, deletion
ATM	11q22	DNA repair	Intragenic mutation, deletion
STK11 (LKB1)	19p13	Serine-threonine kinase	Deletion
CDKN1B (p27kip1)	12p13	Cell cycle inhibitor	Proteolytic degradation, relocalization
CDKN2A (p16INK4)	9p21	Cell cycle inhibitor	Deletion, methylation
SERPINB5 (maspin)	18q21	Serine protease inhibitor	Decreased expression
IGFII-R	6q26	Growth factor receptor	Deletion
CDH1 (E-cadherin)	16q22	Cell adhesion molecule	Methylation
RARβ2	3p24	Retinoic acid receptor	Intragenic mutation, deletion, methylation
MLH1	3p21	Mismatch repair	Methylation
MSH2	2p22	Mismatch repair	Inactivating mutation
APC	5q21	Inhibitor of β-catenin transcription	Deletion, methylation

IV. CONCLUSION

The relationship between genetic polymorphism and cancer risk has not been evaluated efficiently yet, because the results of studies on this issue has been questionable. However, several critical pathways to breast cancer have been identified and effective pharmacological advancements, like the targeting of steroid hormone receptors and PI3K/Akt/mTOR pathways, are now available. Although various polymorphisms in cancer-causing agent using proteins or metabolizing enzymes has been recognized, their detailed commitment to malignancy susceptibility stays moderate. Most information emphatically recommend that age, sex, identity, environmental exposure, and gene-gene interactions should be considered for exact assessment of the relationship between hereditary/genetic polymorphism and breast malignancy risk. Breast cancer is known for their diversity in character and content, that is seen in the expression of cancer stem cell surface markers. The possible capacity of metabolic polymorphisms to regulate the phenotype and malignancy risk related with heritable cancer syndrome is generally charming. Meanwhile, technological and other related advances in understanding of breast cancer tumor suppressor genes and oncogenes will continue to provide understanding for the development and progression of breast cancer.

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Conflict of interest

The authors declare that there is no conflict of interest.

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