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THE RISK OF BREAST CANCER ASSOCIATED WITH BRCA1 AND BRCA2 GENE GENETIC MUTATION: A REVIEW

S. Jawahar*

Dr. P. Sumathi**

Abstract

Breast cancer is a heterogeneous disease which is caused by the mutation in multiple genes. The discovery of mutations in BReast CAncer susceptibility gene (BRCA1/BRCA2) increases the risk of breast cancer in women. The various factors for breast cancer includes hereditary, environment, lack of breast-feeding and geographical location. Among these factors the early onset BRCA1/2 should be considered more with breast cancer history. The most important role is to detect the mutation carriers earlier in these genes for prevention, diagnosis and better treatment. The present study was aimed to review mutations in two predisposing genes (BRCA1/2). The mutation location and mutation type was summarized and classified for these two genes with some exons are having high mutation. By sequencing these high muted exons reduces the memory, run time, search time and has more accurate sequence data for predicting breast cancer. This study may be useful for selecting and screening the particular exon for patients with breast cancer.

Keywords: BRCA1 gene, BRCA2 gene, Mutation, Predisposing gene, exon, Breast Cancer

* Research Scholar, PG & Research Department of Computer Science, Government Arts College, Coimbatore-18, Tamilnadu. India

** Assistant Professor, PG & Research Department of Computer Science, Government Arts College, Coimbatore-18, Tamilnadu. India

Introduction

Cancer is the collection of various diseases which are related to each other. In human the uncontrolled growth of cells leads to cancer. The normal cells may become cancer cells. The specific function of normal cells is it mature into distinct cell for various functions. But cancer cells growths out of control and becomes interfering. There are various types of cancers namely 1) carcinoma 2) Sarcoma 3) Leukima 4) Lymphoma 5) Multiple Myeloma 6) Melanoma 7) Brain and Spinal cord tumors 8) Germ Cell Tumors and many more.

The genetic change may lead to cancer which affects three main types of genes namely 1) Proto-oncogenes 2) Tumor Suppressor Gene (TSG) and 3) DNA repair genes. The changes in these genes are called as drivers of cancer. Proto-oncogenes is responsible for normal cell growth and division. Tumor suppressor genes are also involved in controlling cell growth and division. DNA repair genes are involved in fixing damaged DNA.

The breast cancer is the most commonly occurring cancer among women [1] and is most common cancerous in women throughout the world. The BReast CAncer susceptibility gene (BRCA1*)* gene was discovered in 1994 and BReast CAncer susceptibility gene (BRCA2*)* in 1995 (Miki et al., 1994; Wooster et al., 1995). This paper will review the functions of BRCA1 and BRCA2 genes and their roles in breast cancer development in women.

SubGroups of Breast cancer

The subgroups of breast cancer can be used effectively to determine the treatments. In Figure1 the common subgroups of breast cancer are illustrated.

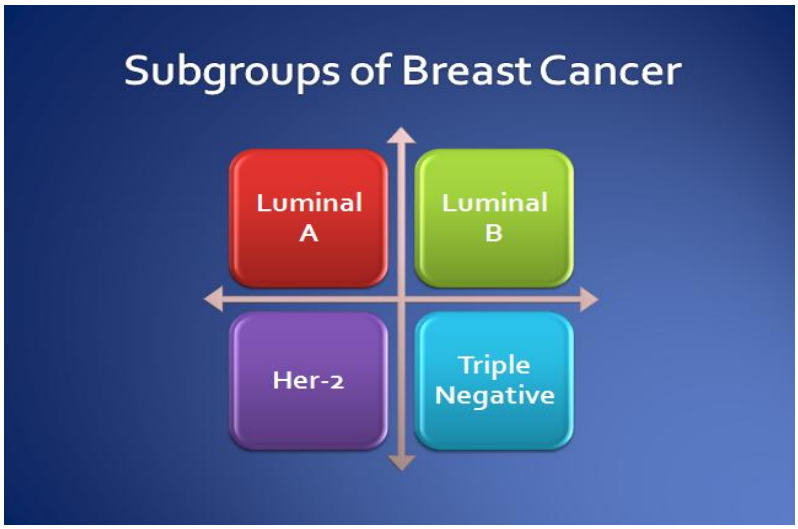

Figure1: SubGroups of Breast Cancer

Luminal A - These tumor cells are positive for estrogen receptor (ER+) and progestin receptor (PR+) but negative for HER-2. The survival rate is high with best prognosis.

Luminal B - These tumors can easily detect at younger age in women than Luminal A tumors. In this type either estrogen receptor (ER+) is positive or progestin receptor (PR+) is positive.

Her-2 - These tumors have poor prognosis. The estrogen receptor (ER-) and progestin receptor (PR-) are negative and has lower tumor grade.

Triple Negative or basal-type - These tumors are estrogen receptor negative (ER-), progestin receptor negative (PR-), and HER-2 negative and are called triple negative. These tumors basically occur in younger age and have a poor prognosis [2] [3].

There are two factors which can cause breast cancer namely, genetic factor and non-genetic factor. Among these two genetic factors is the major cause for breast cancer [4, 5] and the hereditary factor is responsible for early-onset breast cancer. The non-genetic factors includes alcohol, tobacco, lack of breast feeding, geographical location, aging, obesity, less physical activity and many more [4, 6-16] .

BRCA1 and BRCA2 genes

The Breast cancer genes (BRCA1 and BRCA2) are predisposing genes and are the strongest susceptibility genes for breast cancer (Seong, Cho et al. 2009). The mutation in BRCA1 and BRCA2 has increased risk for early-onset breast cancer and ovarian cancer. These two genes are

most common genes for breast cancer and ovarian cancer [4]. The mutations in either BRCA1 or BRCA2 genes have risk of pancreatic, colon and gastric cancers [17].

The BRCA1 and BRCA2 genes produce Tumor Suppressor Gene (TSG) protein which is used to cell repair the damaged DNA. The TSG helps in preventing cells growing and dividing in uncontrolled way. BRCA1 gene is located in chromosome17q and BRCA2 gene is located in chromosome13q. Any mutation in these genes can lead to increased risk of breast cancer and ovarian cancer. The BRCA1 gene plays an essential role in embryonic development.

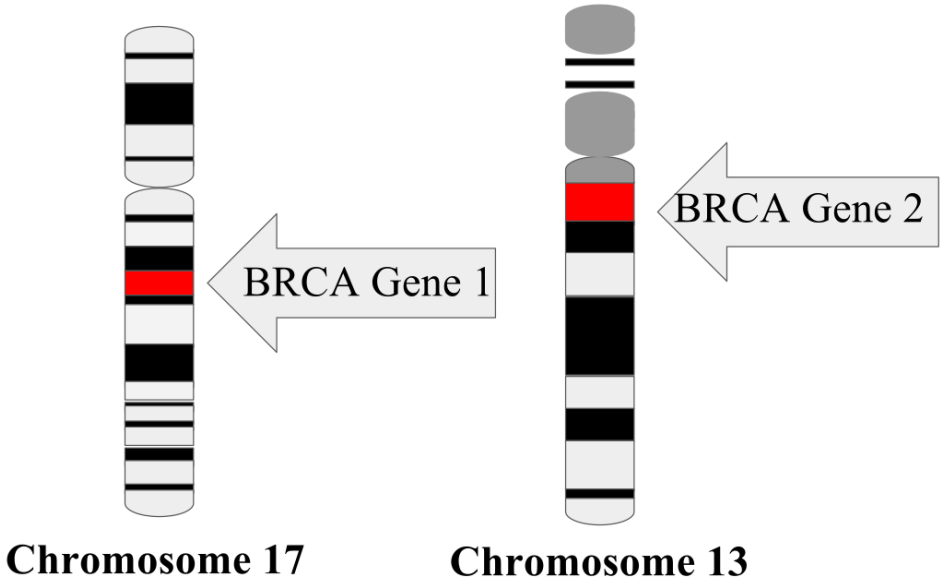

Figure 2: BRCA1 and BRCA2 gene locations on human chromosomes

S.No	Gene Name	No. of Amino Acids	Disease Causing Mutation
1	BRCA1	1863	1600
2	BRCA2	3418	800

The Loss of Heterozygosity (LOH) is an event that occurs in these two genes. The BRCA1 gene was discovered as first breast cancer predisposing gene and BRCA2 gene is the second predisposing gene. The possibility of breast cancer in BRCA1 mutation is 60 to 80 percent in women. Breast cancers in women with harmful BRCA1 mutation may lead tobe triple-negative cancers.

BRCA1 and BRCA2 genes mutations

Mutation is the process of changing the structure of one or more genes. The gene structure change can be caused by alternation of single base, insertion, deletion or rearrangements of genes. There are two types of mutations namely, 1. Germline Mutation and 2. Somatic Mutation. The germline mutation is also called as hereditary mutation. The germline mutations are passed on from parents. The somatic mutation alters any cells in the body except germ cells (sperm or egg). So these mutations are not passed on to the children.

BRCA1 and BRCA2 are well-known genes which are linked to breast cancer risk. Every human has these two genes, but some people have inherited mutation in one or both genes which leads to increased risk factor of breast cancer. The inherited mutation is also called as germline mutation or germinal mutation which can be passed through parent. The mutation in BRCA1/2 gene is also called as BRCA1/2 carrier. BRCA1/2 carrier risk estimates are [18, 19, 20]

1. BRCA1 carriers have a 55-65 percent chance of developing breast cancer by age 70, and
2. BRCA2 carriers have 45 percent chance of developing breast cancer by age 70.

Apart from BRCA1/2 , breast cancer susceptibility gene can be divided into two divisions,

1. High penetrance gene, and

2. Low penetrance gene.

The high penetrance gene includes p53, PTEN, ATM, NBS1 and LKB1 and low penetrance gene includes p450, CYP1A1, CYP2D6 and CYP19. Apart from breast cancer the mutation in BRCA1/2 have an increased risk for some other cancers like colon, gastric, prostate, pancreatic cancers (21, 22).

The DNA sequence of a human gene can be altered or mutated in a number of ways. These gene alterations have various effects on health depending on the mutation in specific function for essential proteins. The various types of mutations are [23]:

1. Insertion
2. Deletion
3. Missense Mutation

4. Non-Sense Mutation
5. Frame Shift Mutation
6. Duplication
7. Repeat Expansion

Insertion

In insertion the DNA bases in a gene are altered by adding a piece of DNA. Due to this process the protein made by the gene may not function properly

Deletion

In deletion the DNA bases in a gene are altered by removing a piece of DNA. A small deletion removes one or few base pairs within a gene and a large deletions removes entire gene. Due to this process the DNA may alter the function of resulting proteins.

Missense Mutation

In missense mutation one DNA base pair in a gene is altered resulting in the substitution of one amino acid for another amino acid in the protein made by a gene.

Non-Sense Mutation

A non-sense mutation is similar to missense mutation, one DNA base pair in a gene is altered. Also the altered DNA sequence prematurely signals the cell to stop building a protein. Due to this process normal proteins are shortened which may function improperly or not function at all.

Frameshift Mutation

In frameshift mutation the bases in the group are shifted which changes the code for amino acids. A reading frame generally contains group of 3 bases which code for one amino acid. The protein generated is nonfunctional. The insertion, deletion and duplication can be frameshift mutation.

Duplication

In duplication process a piece of DNA is abnormally copied one or more times in a gene. Due to this mutation protein function is altered and produces improper protein.

Repeat Expansion

In repeat expansion mutation the number of times the short DNA sequence repetition is increased. This process results in improper function of the protein. Generally the nucleotide repeats are short DNA sequences that are repeated a number of times in a row.

The mutation in splicing spot leads to produce a non-functional protein [24, 25].

Table1: BRCA1 Mutation

S.No	Mutation Location	Mutation Type
1	Exon11	Deletion
2	Exon11	Missense
3	Exon4	Deletion
4	Exon11	Deletion
5	Exon24	Deletion
6	Exon11	Duplication
7	Exon11	Deletion
8	Exon11	Deletion
9	Exon2	ND
10	Exon25	ND

ND: Not Determined

Table1 represents the various classifications of BRCA1 mutation based on mutation location and mutation type. In the above table 10 mutations in BRCA1 gene is related to breast cancer in women which are reported with mutation location. Mostly these mutations led to producing truncated protein or improper protein. These proteins may affect the DNA bases or nucleotides. The study reveals that most of the mutations are located in BRCA1 gene exon11.

Among the 10 mutations in BRCA1 gene, 6 mutations are located in exon11. So about 60% of the mutations in the gene BRCA1 is present in exon11. The size of the exon11 in BRCA1 gene is 89bps (base pair). The length of the exon is smaller but larger number of mutation occurs

in this exon. The mutation types in this exon are deletion, duplication and missense. The mutation type deletion occurs 4 times in the table which means 40% of the type is deletion.

Table2: BRCA2 Mutation

S.No	Mutation Location	Mutation Type
1	Exon12	Missense
2	Exon11	Missense
3	Exon11	Deletion
4	Exon11	Deletion
5	Exon11	Deletion
6	Exon11	ND
7	Exon21	Deletion
8	Exon11	Deletion
9	Exon11	ND
10	Exon24	ND
11	Exon11	Insertion
12	Exon16	ND
13	Exon11	Insertion
14	Exon11	Deletion
15	Exon2	Splicing

ND: Not Determined

Table2 represents the various classifications of BRCA2 mutation based on mutation location and mutation type. In the above table 15 mutations in BRCA2 gene is related to breast cancer in women which are reported with mutation location. Mostly these mutations led to producing truncated protein or improper protein. These proteins may affect the DNA bases or nucleotides. The study reveals that most of the mutations are located in BRCA2 gene exon11.

Among the 15 mutations in BRCA2 gene, 10 mutations are located in exon11. So about 67% of the mutations in the gene BRCA2 is present in exon11. The size of the exon11 in BRCA1 gene is 89bps (base pair). The length of the exon is smaller but larger number of mutation occurs

in this exon. The mutation types in this exon are Insertion, deletion, duplication and missense. The mutation type deletion occurs 5 times in the table which means 33% of the type is deletion.

Conclusion

The breast cancer review has provided a clear insight about BRCA1/2 mutation which can be used for prevention and treatment for the disease. The BRCA mutation carrier can be diagnosed at the early stage to detect and prevent the disease. The BRCA1 and BRCA2 genes are analyzed for finding the mutation location and mutation type. The mutation in these two genes led to production of truncated or malfunction protein. Our study shows that exon11 is the most mutated exon in BRCA1 and BRCA2 genes. So exon11 can be considered more important for sequencing than other exons in the genes. The runtime is greatly reduced because only particular exons are used for the process.

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