MINI-REVIEW

The Spectrum of Genetic Mutations in Breast Cancer

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Abstract

Breast cancer is the most common malignancy in women around the world. About one in 12 women in the West develop breast cancer at some point in life. It is estimated that 5%-10% of all breast cancer cases in women are linked to hereditary susceptibility due to mutations in autosomal dominant genes. The two key players associated with high breast cancer risk are mutations in BRCA 1 and BRCA 2. Another highly important mutation can occur in TP53 resulting in a triple negative breast cancer. However, the great majority of breast cancer cases are not related to a mutated gene of high penetrance, but to genes of low penetrance such as CHEK2, CDH1, NBS1, RAD50, BRIP1 and PALB2, which are frequently mutated in the general population. In this review, we discuss the entire spectrum of mutations which are associated with breast cancer.

Keywords: Breast cancer - genetic mutations - BRCA1 - BRCA2

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Introduction

Breast cancer is the most prevalent malignancy in women around the world (Chauhan et al., 2011; Kanaga et al., 2011; Akhtari-Zavare et al., 2014; Erbil and Bolukbas, 2014; Bouguerra et al., 2014; Fallahzadeh et al., 2014; Karadag et al., 2014; Sathian et al., 2014; Sreedevi et al., 2014; Zhu et al., 2014). Breast cancer comprises 23% of all cancer cases diagnosed across the globe (Jemal et al., 2011). About one in 12 women in the West develop breast cancer at some point in their life (Antoniou et al., 2003). Breast cancer can have a varied presentation with vast diversities in its morphological characteristics, clinical outcomes, subtypes and prevalence trends (Al-Tamimi et al., 2011).

Among the major risk factors associated with breast cancer, the most important is age followed by a positive family history for breast cancer (Ravichandran et al., 2010; Rosmawati, 2010; Shallwani et al., 2010; Sreedharan et al., 2010; Badar et al., 2011; Serey et al., 2011; Norsa’adah et al., 2012; Wu et al., 2012; Norlaili et al., 2013; Radi, 2013). It is estimated that 5%-10% of all breast cancer cases in women are linked to hereditary susceptibility due to mutations in autosomal dominant genes (Loman et al., 1998). The genetic variations found in female breast cancer fall into two distinct categories. The first of which is gain-of-function mutations in the proto-oncogenes which provoke the cell to grow and divide; and the other is loss-of-function mutations in tumor suppressor genes which result in uncontrollable cell growth, inability to repair DNA after damage and lack of cell cycle checkpoint. Women who inherit loss-of-function mutations have a 70% chance of developing invasive breast cancer by the time they are 70 years old (Loman et al., 1998). The two key players associated with high breast cancer risk are mutations in BRCA 1 and BRCA 2. Sixteen percent of all hereditary breast cancers can be credited to germ-line mutations in BRCA 1 and 2 (van der Groep et al., 2011). Around three to five percent of breast cancer cases have been attributed to mutations in BRCA1 and BRCA2 in the United States and Canada (Donenberg et al., 2011). These are tumor suppressor genes because the wild type alleles of these genes are found to be absent in tumors from heterozygous carriers. BRCA proteins have a role in transcriptional regulation and DNA recombination.

Another highly important mutation can occur in TP53 resulting in a triple negative breast cancer, which is the most aggressive breast cancer sub-group whose management presents as a medical challenge. TP53, STK11, PTEN, ATM and NBS1 are involved in multiple cancer syndromes for instance Li-Fraumeni (TP53), Peutz Jeghers (STK11/LKB1), Cowden syndrome (PTEN), Louis-Bar Syndrome (ATM) and Nijmegan Breakage Syndrome (NBS1). The great majority of breast cancer cases are not related to a mutated gene of high penetrance like BRCA1, BRCA2 and TP53. Genes of low penetrance such as CHEK2, CDH1, NBS1, RAD50, BRIP1 and PALB2, which are frequently mutated in the general

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The Spectrum of Genetic Mutations in Breast Cancer Cases

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population, contribute most in breast cancer development. In this review, we discuss the entire spectrum of mutations which are associated with breast cancer. We talk about each gene mutation individually and then highlight how it leads to the manifestation of disease. We start with the more popular genes involved first and then move on to the rarer mutations.

**BRCA1**

BRCA1 gene carries utmost importance in the hereditary susceptibility associated with the development of breast cancer. Its association with breast cancer was established when a pedigree study of a large group of early onset breast cancer families was done (Hall et al., 1990).

BRCA1 gene is located on chromosome 17q and it comprises of 22 coding exons (Hall et al., 1990; Miki et al., 1994). It encodes for an extremely large protein molecule which consists of 1863 amino acids (Miki et al., 1994). The BRCA1 protein in humans has four main domains: The RING zinc finger domain, two BRCT domains and the serine domain (Bertwistle and Ashworth, 1998; Shuen and Foulkes, 2011). At the amino terminal of the protein, a RING zinc finger domain is present which interacts with another RING domain containing protein called BARD1 (Chen et al., 2002). The BRCA1/BARD1 complex carries E3 ligase activity which is responsible for ubiquitination (Chen et al., 2002).

At the carboxyl terminal, there are 2 BRCT repeats which are considered to activate transcription of reporter genes once they attach to a GAL 4 DNA binding domain and hence regulate transcriptional activation (Chapman and Verma, 1996). Moreover, the 2 BRCT repeats are not only thought to bind to phospho-peptides which participate in DNA repair and cell cycle check points but they also interact with other proteins like BACH1, CtIP, RAP80 and CCDC98 (Rodriguez and Songyang, 2008).

The serine domain has numerous phosphorylation sites which get phosphorylated by ATM kinases (Clark et al., 2012). The ATM kinases get activated when there is a DNA insult. Thereafter, the BRCA protein would attempt to localize the site of DNA damage (Clark et al., 2012). In addition, BRCA1 also gets fused to RAD51 and gets phosphorylated. This interaction between BRCA1 and RAD51 suggests a possible participation in the detection and recombination of double stranded breaks (DSBs) (van der Groep et al., 1998; Walsh et al., 2010).

Another location on the BRCA2 protein which serves as a binding site for Rad51 is the carboxyl terminal region of BRCA2 termed TR2 (Mizuta et al., 1997). This section of the protein is believed to play a significant role in recombination repair (Davies and Pellegrin, 2007). On the other hand, PALB2 interacts with the amino-terminal of the BRCA2 and leads to increased stability of BRCA2 in nuclear structures (Xia et al., 2006). This enables BRCA2 to undertake DNA repair at the S phase check point (Zhang et al., 2009). BRCA2 also has an involvement in the homologous recombination (HR) in meiosis via an interaction with RAD51 and DMC1 (van der Groep et al., 2011). BRCA2 fuses with the single strand DNA (ssDNA) and directly interacts with RAD51 to provoke strand invasion an essential step of homologous recombination. Strand invasion is a process in which the broken ssDNA and Rad51 complex recognizes a section of homology in intact duplex DNA. The broken single-strand DNA displaces one of the template strands, pairs its complement and hence produces a duplex.

Along with breast cancer, biallelic mutations in BRCA2 can cause a rare disorder called Fanconi Anemia (FA-D1) (Ripperger et al., 2009). Fanconi Anemia is characterized by congenital defects, bone marrow failure and chromosomal instability. The Breast Cancer Information Core (BIC) database has reported 1,853 unique mutations, polymorphisms and variants in the BRCA2 genes (van der Groep et al., 2011). The results of some studies have revealed that there is a link between loss of heterozygosity (LOH) of the wild type allele and breast cancer in 80% of cases (Collins et al., 1995). Hypermethylation in the BRCA2 promoter region is very uncommon and occurs only rarely in BRCA1 and BRCA2 related breast tumors (Esteller et al., 2001).

**CDH1**

The cellular adhesion molecule E-cadherin is encoded by the CDH1 gene which is located on chromosome 16q (Natt et al., 1989). It fulfills a critical role in the formation of normal cellular architecture, maintenance of tissue integrity and function of epithelial tissues. In addition, it is also considered a tumor suppressor of breast cancer.
mutations may also be linked to possible cases of sporadic breast cancer and hence may be useful in their diagnosis (Manie et al., 2009). In addition, a single nucleotide germ-line mutational change from CGC to CAC at exon 10 codon 337 of TP53 leads to an amino acid alteration from arginine to histidine (R337H). This missense mutation has been linked to early onset breast cancer. (Dick et al., 2011; Smith TR et al., 2011; Gomes et al., 2012; Masciari et al., 2012; Fostira et al., 2014; Silwal-Pandit et al., 2014).

**STK11/LKB1**

Breast cancer is strongly associated with mutations linked with Peutz-Jeghers Syndrome (PJS) (van Lier et al., 2011). STK11/LKB1 mutations have been found to be associated with estrogen-receptor positivity which henceforth may lead to breast cancer in susceptible individuals. Individuals with PJS were reported to be revolving around a lot of risk factors, of which the mutation of STK11/LKB1 may lead to breast, ovarian or lung cancer. Out of these, breast cancer is of pivotal importance in middle-aged women. Liver Kinase B protein (LKB1) is a tumor suppressor gene which is involved in a complex required for the activation of AMP-activated protein kinase (Luo et al., 2010).

LKB1 is actually a mammalian homolog of c elegans partitioning defective PAR4 which is encoded by the tumor-suppressor gene, STK11 (Launonen, 2005; Durgan et al., 2011). This gene, as mentioned above, is one of the key players involved in the mutations giving rise to Peutz-Jeghers Syndrome (PJS). Recent studies have further acted upon this research declaring that mutations on 19p encode the threonine-kinase which is responsible for the PJS. This syndrome has been reported to incur a high susceptibility of various different kinds of cancers, particularly when they age 60 or above. The LKB1 protein is a serine-threonine kinase protein which is responsible for the activation of AMPK. This has attracted attention previously deprived in regard of cancer susceptibility (Launonen, 2005). Though, LKB1 acts as a tumor-suppressor gene and may owe to suppress breast cancer in PJS, mutations of a single allele may result in an aggressive breast cancer leading to less survival chances. It is mainly due to the combination of the actual mutation which cause PJS and the loss of the homologous allele which may give rise to a weak battle against breast cancer. This is in fact apropos to the main concept of AMPK’s linkage with cancer. LKB1 if inactivated may lead to cancer of many types such as cervical, ovarian, breast, lung, colorectal cancer, prostate, pancreatic and biliary cancers (Sanchez-Cespedes et al., 2002). LKB1 may also be the only protein for which polarization has been reported to have an intimate relationship with energy metabolism (Williams and Brennan, 2008; Jansen et al., 2009).

Research studies have depicted convergence and conflict between the two leading factors which may lead to breast cancer in PJS. As also stated above, it is to be kept clear that LKB1 may only achieve mutations in individuals affected with PJS. There is no authentic proof or paper citing the factor as to how can AMPK be

**TP53**

P53 is a tumor-suppressor protein which due to mutated alleles holds the significance of eliciting breast cancer in middle-aged women in a ratio almost equal to that caused by the mutations in BRCA1. The gene is located on the short arm of chromosome 17 (17p13) (Kern et al., 1991). It has been reported to be linked with RB1 pathways and has also been in favor of phosphorylation techniques keenly embedded within its complex biochemical structure. TP53 is also associated with other syndromes such as Li-Fraumeni Syndrome which may be because of the presence of a single functional copy of the gene in the individual (Varley, 2003). TP53 in individuals associated with Li-Fraumeni Syndrome have been reported to be quite less, but in cases where they have been reported together resulted in early onset of severe breast cancer (Varley, 2003).

The TP53 gene is responsible for various factors; proficiently those which are involved in cell cycle, cell repair and apoptosis. TP53 mutations have been reported to play a massive role in the development of 20-40% of breast cancers. Breast cancer may be either stromal or epithelial. Mutations in TP53 promote mammary carcinogenesis particularly of the stromal type. TP53

(Berx and van Roy, 2001). E-cadherin is glycoprotein with three domains (Cleton-Jansen, 2002). There is an extracellular domain comprising of five cadherin repeats, a single transmembrane domain and a cytoplasmic domain that interacts with beta-catenin and p120-catenin. Beta-catenin can, in turn, bind to alpha catenin which helps to anchor E-cadherin to the actin cytoskeleton (Cleton-Jansen, 2002). Most of the mutations in infiltrating lobular carcinoma are either of the frameshift or nonsense type (Berx et al., 1995). These mutations result in the production of a non-functional E-cadherin molecule with decreased adhesion activity.

It is also known that loss of heterozygosity (LOH) at the long arm of chromosome 16 leads to carcinomas of the breast (Cleton-Jansen et al., 2001). LOH is considered an important mutational event for the E-cadherin alleles of lobular breast cancers (Cleton-Jansen et al., 2001). However, for ductal carcinomas of the breast no E-cadherin mutations have been thus far recorded despite the fact these tumors show markedly decreased E-cadherin protein expression (Cleton-Jansen, 2002). This decreased protein expression can probably be attributed to hypermethylation, chromatin rearrangements and alterations in trans-factor binding (Hennig et al., 1996). Hypermethylation of the CDH1 promoter and the overlapping CpG island is believed to result in the decreased E-cadherin expression at the transcriptional level for ductal breast cancers (Hennig et al., 1996). The reduced E-cadherin function and expression have been associated with cancer metastasis. Due to the loss of the adhesion molecule, there is an increase in cellular motility which allows the cancer cells to cross the basement membrane and invade the nearby tissues (Chong et al., 2011; Schrader et al., 2011; Benusiglio et al., 2013; Heitzer et al., 2013)
activated in the presence of LBK1/STK11 mutation as the latter is necessarily required for its activation. Also, chromosomal deletions have been reported with the loss of LBK1 and AMPK which delineates the opinion regarding mitotic alterations.

AR

Androgen receptor (AR) is cytogenetically located on the long arm of X chromosome at position 12 (Xq12) (Lubahn et al., 1988). The normal function of AR gene is to help in the development of male sexual characteristics like regulating hair growth or sex drive. At a certain locus on the AR gene, there is a tri-nucleotide CAG repeat. Normally, the CAG repeats about 10 to 36 times in the AR gene. Several studies have tried to evaluate the relationship between the number of CAG repeats in the gene and the risk of developing breast cancer in women. However, their attempts have yielded conflicting results (Hao et al., 2010). Some studies suggest that an increased number of CAG repeat in the region augments breast cancer risk in women. (Rebbeck et al., 1999; Wu et al., 2008). Other studies have contradictory conclusions as they report that fewer CAG repeats are associated with an increased risk of aggressive breast cancer and benign disease (Yu et al., 2000, De Abreu et al., 2007).

ATM

Ataxia telangiectasia mutated gene, officially represented as ATM, is located on the long arm of chromosome X between positions 22 and 23(Xq22-Xq23) (Savitsky et al., 1995). The ATM gene provides instructions for making a protein that helps to control rate of cell division and growth (Shiloh, 2006). It is an important protein involved in regulation of several body systems, specifically nervous system and immune system. Moreover, it also provides assistance to cells to recognize their broken and damaged DNA strands (Shiloh, 2006). The ATM protein coordinates in repairing DNA by activating enzymes that easily fix the broken strands. After the damaged strands have been efficiently repaired, it helps to maintain the stability of the cells’ genetic information. The ATM protein works as a tumor suppressor. This protein is a tri-nucleotide CAG repeat. Normally, the CAG repeats about 10 to 36 times in the AR gene. Several studies have tried to evaluate the relationship between the number of CAG repeats in the gene and the risk of developing breast cancer in women. However, their attempts have yielded conflicting results (Hao et al., 2010). Some studies suggest that an increased number of CAG repeat in the region augments breast cancer risk in women. (Rebbeck et al., 1999; Wu et al., 2008). Other studies have contradictory conclusions as they report that fewer CAG repeats are associated with an increased risk of aggressive breast cancer and benign disease (Yu et al., 2000, De Abreu et al., 2007).

BARD1

BARD1 (BRCA1 associated RING domain 1) is located on the long arm of chromosome 2 between positions 34 and 35 (2q34-2q35) (Thai et al., 1998). The BARD1 gene provides instructions to make a protein for the cell growth and division. The BARD1 and BRCA1 protein work together to repair the damaged DNA (Westermark et al., 2003). Research studies show that the BARD1 protein binds to the BRCA1 protein. BARD1 stabilizes the BRCA1 protein and directs the BRCA1 protein to those sites where DNA strand is broken (Westermark et al., 2003). Both the proteins play a critical role in maintaining the stability of cells genetic information. The BARD1 protein also combines with another protein called TP53 to promote controlled cell death i.e. apoptosis or to regulate cell division (Feki et al., 2005).

BRIP1

The BRIP1 (BRCA1 interacting protein C-terminal helicase 1) gene is located on the long arm of chromosome 17 at position 22.2 (17q22.2) (Menichini and Linial, 2001). Normally BRIP1 helps in repairing damaged DNA. Inside the nucleus, the BRIP1 interacts with the BRCA1 and together they help in repairing DNA. If the DNA gets interrupted or broken, BRCA1 protein and BRIP1 protein act together to repair the damaged DNA. BRIP1 acts as a helicase by attaching to the particular region of the DNA and temporarily separating the two strands. It unwinds the DNA strands at the site where the DNA is damaged and allows BRCA1 to reach the damaged site and fix it (Cantor et al., 2001). BRIP1 plays a very important role in maintaining stability of the genetic information of the cell, which is why this protein is a tumor suppressor. Research studies show that the inherited mutation in the BRIP1 gene is associated with the increased risk of developing breast cancer (Seal et al., 2006; Papalan et al., 2013). Mutation occurring in one copy of the gene leads to the production of abnormally short and non-functional version of BRIP1 protein (Lewis et al., 2005). When this protein is defective or missing it cannot interact with BRCA1 protein and fails to repair the damaged DNA effectively (De Nicolo et al., 2008). Some studies have also found that a slight variation in a nucleotide in the BRIP1 gene is also associated with an increased risk of breast cancer (Song et al., 2007).

CHEK2

HEK2 (checkpoint kinase 2 gene) is cytogenetically located on the long arm of chromosome 22 at position 12.1(22q12.1) (Chaturvedi et al., 1999). This CHEK2 gene produces a protein called checkpoint kinase 2 protein that works as a tumor suppressor. This protein becomes activated when DNA gets interrupted or damaged. In response to the DNA damage, it works together with several other proteins including TP53
and stops the cell from dividing. The cell has two fates: either the cell lives following DNA repair or undergoes apoptosis if the damage is severe (Chehab et al., 2000). In addition, CHEK2 also interacts with BRCA1 (Lee et al., 2000). Inherited mutated CHEK2 genes have been identified in cases of breast cancer (CHEK2 Breast Cancer Case-Control Consortium, 2004). Abnormality is associated with a single DNA building block at nucleotide location 1100delC (CHEK2 Breast Cancer Case-Control Consortium, 2004). This particular mutation leads to an abnormally short and non-functional version of CHEK2 protein (CHEK2 Breast Cancer Case-Control Consortium, 2004).

**DIRAS3**

The DIRAS3 belongs to a large family of Ras gene that provides instructions to make proteins that control cell growth and maturation. It is cytogenetically located at the short arm of chromosome 1 at position 31 (1p31) (Yu et al., 2006). This gene differs from its other family members in a sense that it suppresses the cell to grow while its other family members encourage the cell to grow. The DIRAS3 codes instructions for a protein located within the cytoplasm and in the cell membrane of normal cells in breast and ovaries (Luo et al., 2003). It also interacts with many other proteins to help control the cell growth and division. In each cell, one copy of DIRAS3 gene is inherited from mother that remains inactive throughout life, the other copy is inherited from father that remains active. This is a process called 'genomic imprinting' (Luo et al., 2001). Due to genomic imprinting the cells usually have only one working copy of DIRAS3 gene. If this copy of gene is lost or becomes inactivated then the cells produce little or no functional DIRAS3 protein. This in turn increases the susceptibility to develop breast cancer. Research studies suggest that DIRAS3 is often down regulated in breast cancer cells (Hisatomi et al., 2002).

**EGFR and ERBB2**

EGFR gene locus is present on chromosome 7, whilst, ERBB2 gene, more commonly known as Her-2/neu, (v-erb-b2 avian erythroblast leukemia viral oncogene homolog 2) is located on the long arm of chromosome 17 at position 12 (17q12) (Coussens et al., 1985). These are members of the family of epidermal growth factor receptors. Studies done in the Western world have highlighted that EGFR protein expression is present in about 7-36% of breast cancer patients (Lynch et al., 2004). But gene amplification has been detected in only about 6% of breast cancer patients (Lynch et al., 2004). On the other hand, studies done in Saudi Arabia have reported that the incidence of EGFR protein associated breast cancer can be as low as 1.3%, suggesting an ethnic pre-disposition for EGFR associated breast cancer cases (Shawarby et al., 2011).

A Saudi study demonstrated by immunohistochemistry that the frequency of HER2+ breast cancer cases can be as high as 28% (Al-Tamimi et al., 2009). In 25-30% of the breast cancer cases, the ERBB2 gene is amplified (Tan and Yu, 2007). This gene provides instructions for making ErbB2 growth factor receptor protein which is located on the surface of the cells, where it associates with similar kind of receptors to form a complex. ErbB2 plays a very important role in cell adhesion, cell specialization and cell mobility (Olayioye, 2001). Extra copies of this gene overexpress the ErbB2 receptor protein on the cell. Excess amount of ErbB2 receptor protein can result in the growth of cancerous tumors by providing continuous signals to the cell to divide and to grow rapidly. Over-expression of ErbB2 gene is associated with increased risk of breast tumors that are most likely to metastasize (Emens, 2005).

**NBN**

NBN gene is cytogenetically located on the long arm of chromosome 8 at position 21 (8q21) (Carney et al., 1998). The gene NBN provides instructions to make protein called nibrin that performs several functions including the repair of damaged DNA (Kobayashi, 2004). Nibrin interacts with other proteins like MRE11A and RAD50 genes to make a protein complex (Carney et al., 1998). It regulates the activity of this protein complex by carrying itself and the other two proteins into the nucleus, and helps to repair the damaged DNA site. Nibrin is a tumor suppressor and mutations in NBN gene prevent it from responding to DNA damage effectively. Many recent studies reveal that the inherited NBN gene change is associated with an increased risk of developing breast cancer (Bogdanova et al., 2008). People with Nijmegen breakage syndrome have a mutated gene c.657_661del5. Individuals suffering from this syndrome are also at a three times higher risk of developing cancer (Steffen et al., 2006).

**PALB2**

PALB2 gene gives instructions for making a protein called partner and localizer of BRCA2. It is located at short arm of chromosome 16 at position 12.2 (16p12.2) (Xia et al., 2006). PALB2 works along with BRCA2 and prevents the cells from accumulating mutations by repairing broken strands of DNA. Gene mutation in PALB2 results in around two-fold increased risk of developing breast cancer (Rahman et al., 2007). These mutations occur in a single copy of gene in each cell and results in abnormally short version of PALB2 protein (Rahman et al., 2007). The defective PALB2 protein cannot work effectively with BRCA2 protein to repair the damaged DNA.

**RAD50 and RAD51**

RAD50 homolog is cytogenetically located on the long arm of chromosome 5 at position 31 (5q31) (Kinoshita et al., 2009). The RAD50 protein holds the broken strand of DNA together during the repairing process. To make a larger protein complex, it interacts with two other proteins that are produced from MRE11A and NBN
genes (Kinosita et al., 2009). When mutation occurs in RAD50 gene it leads to the formation of an abnormally small, non-functional version of RAD50 protein. RAD51 homolog is cyogenetically located on the long arm of chromosome 15 at position 15.1 (15q15.1) (Conway et al., 2004). RAD51 protein interacts with many other proteins like BRCA1, BRCA2 and PALB2 to repair the damaged DNA (Buisson et al., 2010). BRCA2 protein transports the RAD51 protein to the damage sites of DNA inside the nucleus. Many mutations in RAD51 have been associated with an increased risk of developing breast cancer.

Conclusion

In this review, we have discussed the mutations in genes of high, moderate and low penetrance and their role in predisposition to breast cancer. Understanding such genes involved in tumorigenesis and their pathways is of crucial importance in development of preventative and therapeutic targets to fight breast cancer.

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