Focus on Candidate Genes in Molecular Genetics Analyses for Breast Cancer Treatment

Ebubekir Dirican*  
Marmara University, School of Medicine Department of Medical Biology, Istanbul, Turkey  
*Corresponding author: Marmara University, School of Medicine Department of Medical Biology, Istanbul, Turkey, Tel: 216 421 22 22/1575; E-mail: ebubekir.dirican@marmara.edu.tr

Received date: February 22, 2017; Accepted date: March 22, 2017; Published date: March 30, 2017

Abstract

Although a remarkable rise in the depth of our understanding and management of breast cancer (BCa) in the last decade, this matter is still a major public health problem the entire world. But, researchers investigate about reason of BCa. Especially, they detected some important genes (BRCA1/2, PIK3CA, MED12, CDH1, TP53, PTEN or SALL4) for BCa diagnosis or treatment. For this reason we reviewed about roles, functions or effects of these crucial genes in BCa. To determine candidate genes important in BCa processes need to be further analysis with a greater number of patients.

Keywords: Breast cancer; CDH1; PIK3CA; SALL4; PTEN; Candidate gene

Introduction

Breast cancer (BCa) is one of the most common women cancers and cause cancer death among women from cancer worldwide. 1.7 million women were diagnosed with BCa in 2012 [1]. For this reason scientists search for new prognostic and predictive factors to BCa. We know that important prognostic factors for patients with BCa are tumor size, histological type, degree of malignancy, and axillary lymph node status [2]. On the other hand, nowadays molecular biology and cancer genetic studies reveal new findings about BCa mechanism. The important of candidate genes studies has been implied. Cancer genetics research genetic and epigenetic mechanisms to tumor cell proliferation, control cell cycle genes expression; apoptosis regulates factors, and metastasis-related proteases levels [3]. In present review we summarized candidate genes roles or functions in BCa development.

Candidate Genes

Breast cancer (BCa) development includes numerous genetic events, which can activate dominant acting oncogenes and disrupt the function of specific tumor suppressor genes. Therefore, in BCa has been identified a lots of genes including in BRCA1 and BRCA2, PIK3CA, PTEN, SALL4. The ErbB2, PIK3CA, MYC, EGFR, RAS, ER, PR, NM23 and CCND1 (encodes cyclin D1) oncogenes are frequently deregulated in breast cancer. On the other hand, BRCA1/2, p53 or ATM are important tumor suppressors genes. Last studies implied that these genes may be useful prognostic marker in the management of patients with BCa.

Oncogenes and breast Cancer

PIK3CA: Phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) haves a crucial role in the initiation and progress of cancerous tumors through the overexpression of the PI3K pathway promoting uncontrollable levels of cell proliferation [4]. Furthermore, oncogenic mutations in the PI3K pathway generally involve the activation PIK3CA mutation which has been detected in numerous BCa subtypes [5]. PIK3CA mutations are related with favorable prognostic features such as high ER positivity and a relatively good clinical outcome with hormonal therapy [6]. But, in HER2+ BC, several reports show that PIK3CA mutations predict adverse outcomes after treatment with trastuzumab.

SALL4: SALL4 expression has been detected in various cancers, including a subset (30 %) of solid tumors, such as BCa, ovarian cancer, gastric cancer, Wilms tumor and germ cell tumors [7]. SALL4 improves cell migration in vivo [8]. Besides, SALL4 knockdown inhibits the growth of the drug resistant BCa due to cell cycle arrest and reverses tumor chemo-resistance through down-regulating the membrane transporter, BCPR. The researchers reported that SALL4 has potential as a novel target for the treatment of BCa [9].

TOP2A: Topoisomerase-II alpha (TopoIIA: TOP2A), a DNA gyrase isoforom that plays an important role in the cell cycle, is present in normal tissues and various human cancers, and can show altered expression in both. TOP2A gene amplifications forecast improved efficacy of epirubicin in patients with BCa. TOP2A which plays crucial roles in a number of fundamental nuclear processes including DNA replication, transcription, chromosome structure, condensation and segregation [10].

Tumor suppressor genes and breast cancer

BRCA1 and BRCA2: Inherited mutations in BRCA1 and this gene, BRCA2, confer increased lifetime risk of developing BCa. Particularly, both BRCA1 and BRCA2 are involved in maintenance of genome stability, specifically the homologous recombination pathway for double-strand DNA repair [11]. Germline pathogenic variants in BRCA1/2 are inherited in an autosomal dominant manner. According to a study, the proportion of BRCA1 mutations among triple negative (TN) cases ranged from 9–100% (mean 35%), while the proportion of BRCA2 mutations among TN cases ranged from 2–12% (mean 8%) [12].
PTEN and TP53: Phosphatase and tensin homolog (PTEN) and TP53 are associated with various subtypes of BCa. PTEN is a lipid phosphatase whose action targets phosphatidylinositol 3,4,5-trisphosphate (PIP3), a component of the lipid cellular membrane and has role as a tumor suppressor [13]. PTEN is reported as one of the most frequently mutated or mutated in many human cancers. Moreover, many findings have exhibited that PTEN as well as TP53 plays a critical role in DNA damage response. Nakanishi et al. [14] reported that the role of PTEN signaling through its interaction with p53 and MDM2 pathways for the potential implications in hereditary cancer prevention and therapeutic intervention. Bertheau et al. [15] reported that in ER negative (ER(-)) TP53 mutated BCa, accumulation of genetic abnormalities would lead to mitotic catastrophe and subsequent better response. However, PTEN mutations are more extensively seen in ER (+) BCa.

CDH1: E-cadherin (CDH1) is a glycoprotein that interferes adhesion between epithelial cells. Moreover, CDH1 suppresses cancer invasion and mutation/deletion of the CDH1 gene has been detected in 30-60% cases of invasive lobular carcinoma (ILC). But, little is known about genomic differences between ILC with and without a CDH1 alteration [16]. E-cadherin is an important switch in EMT [17]. Moreover, we know there are many EMT-associated genes; VIM, SNAI1, SNAI2, TWIST1, TWIST2, ZEB1, ZEB2, CLDN3 (claudin 3), CLDN4 (claudin 4), CLDN7 (claudin 7).

Other important genes in breast cancer

Mutations in the ESR1 gene, encoding ERα, found in about 20% of recurrent and metastatic BCa patients treated with endocrine therapies [18], whereas ESR1 mutations are extremely rare in primary BCa [18]. Moreover, ESR1 mutations are currently considered as novel mechanisms of resistance to endocrine therapies [19].

AKT1 is related with altered cell migration and invasion in several mammalian systems. Thus, AKT1 is considered a valuable therapeutic target for several cancer types [20]. AKT1 gene amplification only accounts for 1% of estrogen receptor (ER)-positive breast carcinomas [21].

Conclusion

Single gene analysis to anticipate whether cancers reply to specific targeted therapies is performed progressively often. Developments in molecular genetic technology collectively referred to as high resolution melting analysis (HRM) or next generation sequencing (NGS) mean the entire cancer genome [22].

BCa is the most common cancer among women worldwide and the second most common cancer overall. Many studies suggest that BRCA1/2, PIK3CA, MED12, CDH1, TP53, PTEN or SALL4 genes abnormalities may be related with increased risk of BCa development. A lot of inhibitors and drugs has been development for BCa (examples: everolimus or caffeine for PIK3CA; VO-OHpic for PTEN; C2826 for TP53). Pentraxin-3 as a newly identified PI3K-regulated biomarker and a potential therapeutic target in basal-like breast cancers [23]. WEE1 inhibitors and PARP inhibitors are all in advanced phases of clinical trials for BRCA1/2 mutated tumors. Therefore, these candidate genes could be considered as one possible risk factor of BCa according to new studies. So, the genes may be a biomarker for BCa prognosis or treatment. Targeted of candidate genes has potential clinical utility to detect biomarkers from BCa-targeted therapies.

References

1. (2012) International Agency for Research on Cancer. Press Release 223.
2. Matsyiak M, Kapka-Skrypczak L, Jodlowa-Jedrzych B, Kruzewski M (2017) EMT promoting transcription factors as prognostic markers in human breast cancer. Arch Gynecol Obstet 295: 817-825.
3. Kumar P, Aggarwal R2 (2016) An overview of triple-negative breast cancer. Arch Gynecol Obstet 293: 247-269.
4. Kolinjivadi AM, Sannino V, de Antoni A, Techer H, Baldi G, et al. (2017) Moonlighting at replication forks - a new life for homologous recombination proteins BRCA1, BRCA2 and RAD51. FEBS Lett.
5. Wang W, Lv J, Wang L, Wang X, Ye L (2016) The impact of heterogeneity in phosphoinositide 3-kinase pathway in human cancer and possible therapeutic treatments. Semin Cell Dev Biol.
6. Dirican E, Akkiprik M, Özer A (2016) Mutation distributions and clinical correlations of PIK3CA gene mutations in breast cancer. Tumor Biol 37: 7033-7045.
7. Worby CA, Dixon JE (2014) PTEN. Annu Rev Biochem 83: 641-669.
8. Nakanishi A, Kitagishi Y, Ogura Y, Matsuda S (2014) The tumor suppressor PTEN interacts with p53 in hereditary cancer (Review). Int J Oncol 44: 1813-1819.
9. Dirican E, Akkiprik M (2016) Functional and clinical significance of SALL4 in breast cancer. Tumor Biol 37: 11701-11709.
10. Itou I, Tanaka S, Li W, Iida A, Sehara-Fujisawa A, et al. (2017) The Sal-like 4 - integrin a6β1 network promotes cell migration for metastasis via activation of focal adhesion dynamics in basal-like breast cancer cells. Biochim Biophys Acta 1864: 76-88.
11. Shen YY, Li ZZ, Ye YY, Xu F, Niu RJ, et al. (2016) Knockdown of SALL4 inhibits the proliferation and reverses the resistance of MCF-7/ADR cells to doxorubicin hydrochloride. BMC Mol Biol 17: 6-9.
12. Ping Z, Siegal GP, Harada S, Eltoum IE, Youssef M, et al. (2016) ERBB2 mutation is associated with a worse prognosis in patients with CDH1 altered invasive lobular breast cancer. Oncotarget 7: 80655-80663.
13. Hamblin A, Wordsworth S, Fermont JM, Page S, Kaur K, et al. (2017) Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. PLoS Med 14: e1002230.
14. Nakanishi A, Kitagishi Y, Ogura Y, Matsuda S (2014) The tumor suppressor PTEN interacts with p53 in hereditary cancer (Review). Int J Oncol 44: 1813-1819.
15. Bertheau P, Lehmann-Ché J, Varna M, Dumay A, Poirot B, et al. (2013) p53 in breast cancer subtypes and new insights into response to chemotherapy. Breast 22: S27-29.
16. Ping Z, Siegal GP, Harada S, Eltoum IE, Youssef M, et al. (2016) ERBB2 mutation is associated with a worse prognosis in patients with CDH1 altered invasive lobular cancer of the breast. Oncotarget 7: 80655-80663.
17. Polyak K, Weinberg RA (2009) Transitions between epithelial and mesenchymal states: Acquisition of malignant and stem cell traits. Nat Rev Cancer 9: 265-273.
18. Segal CV, Dowsett M (2014) Estrogen receptor mutations in breast cancer--new focus on an old target. Clin Cancer Res 20: 1724-1726.
19. Yanagawa T, Kagara N, Miyake T, Tanai T, Naot Y, et al. (2017) Detection of ESR1 mutations in plasma and tumors from metastatic breast cancer patients using next-generation sequencing. Breast Cancer Res Treat.
20. Kim D, Kim S, Koh H, Yoon SO, Chung AS, et al. (2001) Aki/PKB promotes cancer cell invasion via increased motility and metalloproteinase production. FASEB J 15: 1953-1962.
21. Hamblin A, Wordsworth S, Fermont JM, Page S, Kaur K, et al. (2017) Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. PLoS Med 14: e1002230.
22. Kirkegaard T, Witton CJ, Edwards J, Nielsen KV, Jensen LB, et al. (2010) Molecular alterations in AKT1, AKT2 and AKT3 detected in breast and prostatic cancer by FISH. Histopathology 56: 203-211.
23. Thomas C, Henry W, Cuiffo BG, Collmann AY, Marangoni E, et al. (2017) Pentraxin-3 is a PI3K signaling target that promotes stem cell-like traits in basal-like breast cancers. Sci Signal 10: 4674.