American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Moderate Spectrum Genes Associated With Breast Cancer

Ihtisham Ul Haq[1], Naqash Alam[1], Sadiq Ali[1], Shaker Khan[1], Farman Ali[2] and Haixia Lu[1]*

[1]*School of Basic Medical Sciences, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, China*

[2]*Department of Cell biology, Dalian Medical University, Liaoning, China*

***Corresponding author:** Haixia Lu, Department of Neurobiology, School of Basic Medical Sciences, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China, Email: hxl01@xjtu.edu.cn

To Cite This Article: *Ihtisham Ul Haq, Naqash Alam, Sadiq Ali, Shaker Khan, Farman Ali. Moderate Spectrum Genes Associated With Breast Cancer. Am J Biomed Sci & Res. 2022 - 15(4). AJBSR.MS.ID.002126.* DOI: 10.34297/AJBSR.2022.15.002126

Received: February 01, 2022; **Published:** February 22, 2022

Abstract

Worldwide, breast cancer is the most common form of malignancy among women. One out of every twelve women on the west side suffers breast cancer at some point in their lifetimes. According to one estimate, 5 % to 10% of all breast cancer cases in women are linked to genetic defencelessness caused to mutations in autosomal dominant genes. Genetic mutations of genes BRCA 1 and BRCA 2 are associated with an increased risk of breast cancer. Triple-negative breast cancer can potentially be caused by a mutation in the TP53 gene. However, most incidences of breast cancer are linked to moderate penetrance genes such as CTLA-4, Pik3ca, Kiss-1, TPD52, and PTEN which are likewise mutated in practically every group. In the present review, we will discuss the low spectrum of mutations related to breast cancer.

Keywords: Breast cancer, moderate, CTLA-4, TPD52, KISS-1, Malignancy; Autosomal; Spectrum; Morphological Traits; Proto-Oncogenes.

Introduction

The breast tumor is the second most common tumor globally counted as 9 percent of the cancer burden [1]. It is most common in women which is counted as 25 percent of all cancer [2]. In the developed countries the suffering ratio of breast cancer in women is from one to eight to one to twelve throughout their lifetime, and out of twenty-two one woman has likely to have disease in developing countries. Globally the prevalence rate of breast cancer ranges at least ten folds [1]. With a wide spectrum of morphological traits, clinical results, subgroups, and prevalence outcomes, breast cancer can manifest in a variety of ways [3]. One of the highest risk factors is associated with a positive family history of breast cancer and age factor [4]. According to estimates, autosomal dominant gene mutation susceptibility accounts for 5% to 10% of all breast cancer cases in women [5]. Two types of cancer-related genetic variants have been discovered in females. One is gain of function, which is caused by mutations in proto-oncogenes that drive cells to expand and divide; the other is loss of function, tumor suppressor genes which results in unrestrained cell growth, failure to repair DNA after damage, and a lack of cell cycle control points.

People who inherit loss of function mutations have a 70% chance of developing invasive breast cancer by the time they reach the age of 70 [5]. BRCA 1 and BRCA 2 mutations are the two primary players linked to an increased risk of breast cancer. Germline mutations in BRCA 1 and 2 are linked to 16% of all breast cancers [6]. A mutation in the TP53 gene causes triple-negative breast cancer. This is the most serious type of breast cancer, and treating it is a medical challenge. TP53, ATM, NBS1, STK11, and PTEN are all implicated in cancer syndromes such as Peutz-Jeghers (STK11/LKB1), Li-Fraumeni (TP53), Louis-Bar Syndrome (ATM), Cowden syndrome (PTEN), and Nijmegen Breakage Syndrome

(NBS1). Most occurrences of breast cancer are not connected to a high-penetrance mutant gene such as BRCA1, TP53, or BRCA2. Moderate penetrance genes, such as CTLA-4, Pik3ca, Kiss-1, TPD52, and PTEN mutated often in the general population and lead much to the development of breast cancer. The modest spectrum of mutations linked to breast cancer was explored in this review. We discuss each gene mutation individually before demonstrating how it relates to disease manifestation.

Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4)

The highly important antitumor response is made up of human cell immunity determined by T lymphocytes and Natural Killer (NK) cells. As a result, gene variations involved in controlling T-lymphocyte and NK cell production will be useful in predicting breast cancer risk. A gene on chromosome 2q33 codes for CTLA-4 a member of the immunoglobulin superfamily that transmits an inhibitory signal to T lymphocytes. CTLA-4 interacts with B-7 on antigen-presenting cells, and the CTLA-4 gene polymorphism suppresses B-7 surface activity and prevents T-lymphocyte activation [7, 8]. Furthermore, CTLA-4 inhibits immune response [9] as well as tumor-killing activities [10]. CTLA-4 is a four-exon gene that plays a key role in diseases involving T lymphocytes. There have been numerous studies linking polymorphisms in the CTLA-4 gene to autoimmune disorders such as diabetes mellitus type 1, Graves' disease, Hashimoto thyroiditis, and lupus [11-14], as well as the risk of developing cancer [15]. The link between multiple gene polymorphisms and polygenetic disorders such as diabetes, obesity, and various cancers is gaining traction [16] T cells and Natural Killer Cells (NK cells) play an important role in the fight against cancer [17]. T lymphocytes, particularly T killer cells, play a critical role in protecting cells against malignancies. The CTLA-4 molecule functions as an inhibitor on T-lymphocytes and has a variety of roles in T-cell function. This could hinder T cells from multiplying or potentially trigger apoptosis in activated T cells [18]. The inhibition of tumor immunity by CTLA-4 has been previously demonstrated [10]. A few examinations have shown the job of CTLA-4 bar in upgrading insusceptibility to tumors [19-21].

There are a few reports on the connection between CTLA-4gene polymorphisms, what's more, breast malignancy, however, discoveries were clashing [22]. Single nucleotide polymorphisms (1661AG) in the CTLA 4 gene were studied in breast cancer patients and control participants, and their correlations with prognostic variables were analyzed. The goal of this case-control study was to see if there were any links between CTLA-4 polymorphisms AA, AG, and GG and breast cancer risk factors. Genetic differences in breast cancer patients and controls demonstrate that AA and GG genotypes are more frequent in cancer patients, whereas AG genotypes are more common in controls. These findings support the discovery of two more focuses on Iran and China, [23] GG genotype is more common among breast cancer patients, according to this study. In terms of AG genotype, Efrain et al. found no significant differences across their exploration groups. Another study in China discovered that the AG genotype is more common in breast cancer patients [24]. Furthermore, Sun et al., [20] reported that T cells with the AA genotype are less active than those with the GG genotype, and AG is associated with varying levels of malignant development in humans.

PIK3CA

PIK3CA is a gene of 34 kb comprising of 20 exons coding 1,068 amino acids and situated on the 3q26.3 chromosome [25]. The p110 a catalytic subunit of class IA Phosphatidylinositol-3 Kinase (PI3K) phosphorylates phosphatidylinositol-4,5-bisphosphate to produce the second courier Phosphatidylinositol-3,4,5-Trisphosphate (PIP3) at the plasma film encoded by PIK3CA (3q26.3) [26]. AKT, SGK, and PDK1, among other cell stability, expansion, motility, digesting, and angiogenesis-basic proteins, bind to PIP3 and operate on the plasma film. The PI3K/AKT pathway is the most frequently changed route in breast cancer, with PIK3CA alterations being the most well-known of these physical changes occurring at 20–40% recurrence rates [27,28]. When the PIK3CA mutation is expressed in human mammary epithelial cells, it causes constitutive activation of the PI3K/AKT pathway, which results in anchorage-independent proliferation, apoptosis defines, and drug resistance [29]. At two "areas of interest" in exon 9 and exon 20, which encode the helical (E542K and E545K) and kinase (H1047R), over 80% of these mutations happen [30].

Writing regarding the prognostic meaning of PIK3CA mutations is clashing. Gonzalez Angulo et al. discovered an affiliation between PIK3CA and poor prognostic highlights. Li et al., [28] negative discoveries additionally appeared in patients with tumors with PIK3CA changes [31]. Conversely, [32], PEREZ Tenorio et al., [33], and Kolinsky et al., [34] showed there was a link between PIK3CA mutations and better recurrence-free survival. [36] revealed that in patients with PIK3CA mutant tumors, there was an increase in relapse-free survival but no overall survival improvement. [35] and Dupont et al., [37] have shown a huge improvement in without metastasis endurance in PIK3CA mutant breast malignancy patients. In addition to inconsistent prognostic relevance, data on the interaction of PIK3CA mutations with oestrogen/progesterone receptor (ER/PR) expression or human epidermal growth factor receptor 2(HER2) overexpression were also diverse. Numerous bigger populace-based investigations demonstrate a solid relationship of PIK3CA changes with positive ER/PR, negative HER2 tumors [34,32,38].

[35] PIK3CA mutants who were PR positive or HER2 negative had a statistically significant improvement in metastatic-free survival, with a trend toward better survival in ER-positive tumors, compared to ER+ tumors with wild-type PIK3CA. Illogically, the presence of a PIK3CA mutation has been related to protection from anti-oestrogen treatment and proposes a job for mixed treatment with anti-oestrogens and PI3K inhibitors [39,40]. What's more, HER2-enhanced tumors that likewise harbor PIK3CA changes are less receptive to blends of HER2 inhibitors (trastuzumab/lapatinib and trastuzumab/epratuzumab), adding to the prognostic and helpful importance of PIK3CA mutation testing [35,41]. PIK3CA is the most as often as possible changed quality found in BC and plays a vital role in its turn of events, incorporating a solid relationship with Oestrogen Receptor (ER) articulation and an absence of a relationship with strong actuation of the classical style PI3 K pathway [42,43]. Following the underlying disclosure of PIK3CA mutations in BC, numerous gatherings explored mutational examination to advance the information on hereditary changes that corresponded with BC's clinic pathological qualities [42]. In breast tumors, PIK3CA changes were reliably connected with receptor-2 (HER2)-positive tumor status of ER-positive and human epidermal development factor [44,46,48]. The relationship between these changes and the anticipation of breast disease is less clear, with a few investigations revealing the relationship between PIK3CA mutations and lymph hub metastasis and more regrettable by and large and breast malignant growth explicit endurance [46,45], while different examinations showed a relationship with longer endurance, especially among patients with ER-positive, HER2-negative tumors [47-49].

KiSS-1

Kiss-1 is a gene that maps to the long arm of chromosome 1 (1q32-q41) and combines four exons, with only the last two partially translated [50]. The gene KiSS1 is made from four exons, the initial two untranslated. Exon 3 incorporates the translational beginning site followed by 103 translated bases, while exon 4 is the biggest with 335 translated bases and 121 non-translated bases [50]. At dibasic locales, for example, R66-R and K123-R, the encoded full-length 145-amino corrosive KiSS1 protein goes through post-translational cleavage bringing about dynamic 54-amino corrosive peptide metastas or then again kisspeptin-54 (KP54) [51,52]. A few more limited items, overall, called kisspeptins, result from proteolytic cleavage which happens normally. The kisspeptin which holds the last 10 carboxy-terminal amino acids can tie the receptor GPR54 to perform sKiSS1 activities [53]. At first, the Kiss-1 gene was distinguished as a competitor metastasis silencer in 1996, when its articulation was discovered to be differentially up-controlled in C8161 melanoma cells delivered nonmetastatic by the microcell-interceded move of an unblemished duplicate of human chromosome 6.

Even though the Kiss-1 gene has been recognized as a solid silencer of metastasis in an assortment of tumors, restricted and clashing information on the interlaced connections between the Kiss-1 framework and breast malignancy has been submitted, and its organic job in this specific disease stays to be explained [54,55]. Kiss-1 was first proposed as a breast cancer metastasis suppressor gene when it was discovered that Kiss-1-transfectant cells inoculated MDAMB-435 in sub-axillary mammary fads of female athymic nude mice suppressed regional lymph node and lung metastasis by at least 95% without affecting tumorigenicity [56]. Another examination directed by Martin et al., nonetheless, showed that the insertion of the Kiss-1 gene into the MDA-MB-231 breast malignancy cell line expanded motility and invasiveness and reduced matrix adhesion, hence giving more metastatic phenotypes [54]. Martin et al. also discovered that Kiss-1 levels in breast cancer tissues were greater than in background tissues and that node-positive tumors had much higher Kiss-1 levels than node-negative tumors. Kiss-1 expression was also higher in breast cancer patients than in healthy controls, and it increased with increasing grade and TNM status [54]. These outcomes are obviously in the clash with the initially proposed role of Kiss-1 as a metastasis inhibitor in breast disease. Marot et al., [55] also found that Era-positive tumors resected from postmenopausal women treated with TAM had a shorter backslide free endurance (RFS) in combination with higher tumor levels of Kiss-1 and GPR54 mRNA than tumors with lower levels of the two genes [55].

The scientists additionally showed that Kiss-1and GPR54 articulation in breast cancer cells has been contrarily controlled by oestrogen milieu, with ER-positive tumors showing lower levels of Kiss-1 contrasted with ER-negative tumors [55]. Rather than the above outcomes exhibiting Kiss-1as a facilitator of metastasis, Kotadiya et al. discovered that the Kiss-1 gene was silent in a vast majority (97%) of 272 resected stage II or III hubs positive breast adenocarcinomas [57]. Another examination likewise announced that KP-10 can restrain bone-coordinated movement of GPR54-positive MCF-7 breast malignancy cells [58]. In contrast to the high universal staining observed in normal tissue, Pentheroudakis et al. found that barely half of 48 malignancies (52%) were immunoassayed for kisspeptin (40 percent weakly and 12 percent moderately) [59]. In previous studies, increased Kiss1 expression has been linked to advanced tumor grade [54,55] and nodal positivity. Furthermore, lobular carcinomas have higher Kiss-1 expression than ductal carcinomas [54].

PTEN Gene

This novel tumor suppressor gene located on chromosomal band 10q23.3 is known as PTEN (MMAC1-mutated in multiple advanced cancers) [60]. It was recently reported that PTEN/MMAC1 encodes a dual-specificity phosphatase that dephosphorylates Focal Adhesion Kinase (FAK), inhibiting cell migration, spreading, and focal adhesion formation [61,62]. PTEN regulates the 1-phosphatidylinositol 3-Kinase Pathway (PI3K), which is crucial for cell proliferation and survival [63]. Cell line studies in breast cancer have shown that PTEN inhibits their growth by deregulating PI3K, with subsequent G1 arrests and cell death therefore [64,65]. The PTEN gene has been studied in embryonic stem cells and has shown an increased growth rate and early entry into S-phase cells with mutations of the gene [66]. In addition to a rapid G1/S transition, p27 expression was markedly down-regulated, which is indicative of an inhibitor of G1cyclin-dependent kinases. Finally, the findings indicated that PTEN regulates the progression of the cell cycle and cell survival. A genetic mutation in the PTEN gene is also associated with another rare, autosomal-dominant, hereditary disease known as Cowden disease, which increases a woman's risk of breast cancer by 25 to 50 % over their lifetime.

PTEN mutations in Cowden disease have been associated with breast tumorigenesis in a few studies, but by other investigators, this has not been confirmed [67-69]. Several studies have been conducted to examine the role of PTEN in sporadic breast cancer tumorigenesis. In such studies, PTEN gene mutations have been associated with a small number of cases [70]. In a recent study by Ghoshal al., it was revealed that PTEN functions as a transcriptional repressor, inhibits the cell-mediated survival signaling pathway, and negatively regulates human breast carcinoma cell growth [71]. In various malignancies, mutations at the PTEN locus have been observed, and recent studies indicate that PTEN regulates the growth of breast carcinoma cells [71]. Some studies failed to find the loss of PTEN heterozygosity in breast cancers, which suggests that PTEN may not play an important role in breast cancer development [72]. Researchers have found a significant down-regulation of PTEN expression (48%) in breast cancer. Several studies have found allelic loss of PTEN in 27 of 70 (39%) and 17 of 42 (40%) breast tumors, according to research published previously, another immunohistochemical analysis of 33%of breast cancers examined revealed a poor or negative tumor staining [73]. As a comparison, where the loss of heterozygosity is high (30 to 40%) and mutations predominate in a significant proportion of breast cancer cell lines, primary sporadic cancers are less likely to exhibit mutations [74,75]. On the other hand, PTEN mutations are an occasionally causative factor in familial breast cancer, with lifetime risks over 50% in patients with Cowden's disease [76,77]. A group of sporadic breast tumors previously analyzed using molecular techniques were also immunohistochemically analyzed to determine if PTEN loss occurred in these cancers [78].

TPD52

It was discovered nearly 20 years ago that the tumor protein D52 gene (TPD52) was over-expressed in human cancer, and a growing body of evidence strongly suggests it may be an amplification target at chromosome 8q21.13 [79]. There have been several investigations that suggest breast cancer is one of the specific cancer types expressing high levels of TPD52 [80,81,82]. Byrne et al. summarized several reports of focal chromosome 8q21.13 amplification involving the TPD52 locus which was specifically observed in breast cancer [83]. A wide genomic analysis demonstrated focal amplification of TPD52 and five adjacent genes on chromosome 8q21.13 associated with breast cancer [84]. TPD52 was identified as a possible driver gene by integrative analysis of the copy number and expression of breast cancers, and they are gradually categorized into a wide range of molecular subtypes, in addition to identifying subtypes associated with TPD52, research is also attempting to refine this molecular taxonomy. One of the most strongly amplified regions on chromosome 8q21.12-q21.13 is associated with the luminal B subtype [86].

The TPD52 gene showed the most significant association between copy number and expression in this amplicon, supported by neighboring locus MRPS28 [85]. Moreover, TPD52 was found to be substantially increased in copy number and expression in luminal B tumors, wherein it was also 1 of the 22 genes whose increased expression was associated with promoter demethylation [87]. A reproducible link between TPD52 expression and ERBB2 expression has been found in human breast cancer cell lines and tissues, as well as in mammary tissues from Erbb2-transgenic mice [88]. The analysis published recently revealed that TPD52 expression was significantly higher in ERBB2-positive diagnostic breast tumors compared with ERBB2-negative tumors, and that relative transcript levels of TPD52 were optimal in the hormone receptor- and ERBB2-positive subgroups [82]. TPD52 expression has been linked to poorer outcomes in breast cancer patients [80, 82], which is consistent with TPD52 expression being linked to both the luminal B subtype [80,81] and ERBB2 expression [82]. As shown in the study above, TPD52 levels across approximately 6% of the diagnostic test cohort were associated with a significantly decreased tumor-free survival [82]. In the TCGA cohort, TPD52-amplified breast cancers were found to be in a similar proportion to that of the breast cancers found to be amplified by TPD52 [84].

Conclusion

In this investigation, we tended to the low range gene changes and their job in breast disease inclination. Even though there are still a significant number of moderate-risk genes to be discovered, its functional implications may remain mysterious precisely because of the polygenic context in which each of them exists. It appears that the clinical relevance of genes associated with moderate-risk breast cancer will remain limited for quite some time. Even though some genes with moderate breast cancer risk carry a limited number of gene variants, others may carry multiple variations. Genes associated with moderate-risk breast cancer cause high disease penetrance only in polygenic settings and can thus not be recognized as gene-related breast cancer predispositions. Understanding these genes associated with tumor genesis and their pathways are basic in the improvement of preventive and restorative systems to battle breast disease.

Acknowledgment

I thank to Mr. Naqash Alam for valuable suggestions on this review article.

Conflict of Interest

None.

References

1. Brenda K Edwards, Anne Michelle Noone, Angela B Mariotto, Edgar P Simard, Francis P Boscoe, et al. (2004) Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. Cancer 101(1): 3-27.
2. Parkin DM, Bray F, Ferlay J, Pisani P (2001) Estimating the world cancer burden: Globocan. Int J Cancer 94(2): 153-156.
3. Dalal M Al Tamimi, Mohamed A Shawarby, Ayesha Ahmed, Ammar K Hassan, Amal A Alodaini (2010) Protein expression profile and prevalence pattern of the molecular classes of breast cancer: a Saudi population-based study. BMC Cancer 10(1): 223.
4. Sahar Mahmoud Radi (2013) Breast cancer awareness among Saudi females in Jeddah. Asian Pac J Cancer Prev 14(7): 4307-4312.
5. Loman N, Johannsson O, Bendahl PO, Borg A, M Fernö, et al. (1998) Steroid receptors in hereditary breast carcinomas associated with BRCA1 or BRCA2 mutations or unknown susceptibility genes. Cancer ACS 83(2): 310-319.
6. Petra Van Der Groep, Elsken Van Der Wall, Paul J Van Diest (2011) Pathology of hereditary breast cancer. Cell Oncol (Dordr) 34(2): 71-88.
7. Hurwitz AA, Kwon ED, Van Elsas A (2000) Costimulatory wars: the tumor menace. Curr Opin Immunol 12(5): 589-596.
8. Lieping Chen (2004) Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. Nat Rev Immunol 4(5): 336-347.
9. Leach DR, Krummel MF, Allison JP (1996) Enhancement of antitumor immunity by CTLA-4 blockade. Science 271(5256): 1734-1736.
10. Hurwitz AA, Foster BA, Kwon ED, Truong T, Choi EM, et al. (2000) Combination immunotherapy of primary prostate cancer in a transgenic mouse model using CTLA-4 blockade. Cancer Res 60(9): 2444-2448.
11. Hironori Ueda, Joanna Howson MM, Laura Esposito, Joanne Heward, Hywel Snook, et al. (2003) Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature 423(6939): 506-511.
12. Han Sz, Zhang Sh, Li R, Zhang Wy, Li Y (2006) The common -318C/T polymorphism in the promoter region of CTLA4 gene is associated with reduced risk of ophthalmopathy in Chinese Graves' patients. Int J Immuno genet 33(4): 281-287.
13. Suzana M Anjos, Constantin Polychronakos (2006) Functional evaluation of the autoimmunity-associated CTLA4 gene: The effect of the (AT) repeats in the 3'untranslated region (UTR). J Autoimmun 27(2): 105-109.
14. Marta Barreto, Eugénia Santos, Ricardo Ferreira, Constantin Fesel, Maria Francisca Fontes, et al. (2004) Evidence for CTLA4 as a susceptibility gene for systemic lupus erythematosus. Eur J Hum Genet 12(8): 620-626.
15. Mao H, Zhang L, Yang Y, Zuo W, Bi Y, et al. (2010) New insights of CTLA-4 into its biological function in breast cancer. Curr Cancer Drug Targets 10(7): 728-736.
16. Barkur S Shastry (2002) SNP alleles in human disease and evolution. J Hum Genet 47(11): 561-566.
17. Linsley PS, Ledbetter JA (1993) The role of the CD28 receptor during T cell responses to antigen. Annu Rev Immunol 11(1): 191-212.
18. Monika C Brunner Weinzierl, Holger Hoff, Gerd R Burmester (2004) Multiple functions for CD28 and cytotoxic T lymphocyte antigen-4 during different phases of T cell responses: Implications for arthritis and autoimmune diseases. Arthritis Res Ther 6(2): 1-10.
19. Ligers A, Teleshova N, Masterman T, Huang WX, Hillert J (2001) CTLA-4 gene expression is influenced by promoter and exon 1 polymorphisms. Genes Immun 2(3): 145-152.
20. Tong Sun, Yifeng Zhou, Ming Yang, Zhibin Hu, Wen Tan, et al. (2008) Functional genetic variations in cytotoxic T-lymphocyte antigen 4 and susceptibility to multiple types of cancer. Cancer Res 68(17): 7025-7034.
21. Lihong Wang, Dalin Li, Zhenkun Fu, Heng Li, Wei Jiang, et al. (2007) Association of CTLA-4 gene polymorphisms with sporadic breast cancer in Chinese Han population. BMC Cancer 7(1): 1-7.
22. Jian Zheng, Xiao Yu, Lan Jiang, Mang Xiao, Bing Bai, et al. (2010) Association between the Cytotoxic Tlymphocyte antigen 4+ 49G > A polymorphism and cancer risk: a meta-analysis. BMC Cancer 10: 522.
23. Dalin Li, Qiujin Zhang, Fengyan Xu, Zhenkun Fu, Weiguang Yuan, et al. (2012) Association of CTLA-4 gene polymorphisms with sporadic breast cancer risk and clinical features in Han women of northeast China. Mol Cell Biochem 364(1): 283-290.
24. Heng Li, Zhen Kun Fu, Li-Hong Wang, Da Lin Li, Na Wu, et al. (2008) Association of cytotoxic T lymphocyte antigen-4 gene polymorphisms with susceptibility to breast cancer. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 24(3): 282-284.
25. Volinia S, Hiles I, Ormondroyd E, Nizetic D, Antonacci R, et al. (1994) Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110α (PIK3CA) gene. Genomics 24(3): 472-477.
26. Dillon RL, White DE, Muller WJ (2007) the phosphatidyl inositol 3-kinase signaling network: implications for human breast cancer. Oncogene 26(9): 1338-1345.
27. Ian G Campbell, Sarah E Russell, David Y H Choong, Karen G Montgomery, Marianne L Ciavarella, et al. (2004) Mutation of the PIK3CA gene in ovarian and breast cancer. Cancer Res 64(21): 7678-7681.

28. Shao Ying Li, Minna Rong, Fabienne Grieu, Barry Iacopetta (2006) PIK3CA mutations in breast cancer are associated with poor outcome. Breast Cancer Res Treat 96(1): 91-95.

29. Steven J Isakoff, Jeffrey A Engelman, Hanna Y Irie, Ji Luo, Saskia M Brachmann, et al. (2005) Breast cancer-associated PIK3CA mutations are oncogenic in mammary epithelial cells. Cancer Res 65(23): 10992-11000.

30. Zhao L, Vogt PK (2008) Class I PI3K in oncogenic cellular transformation. Oncogene 27(41): 5486-5496.

31. Ana M Gonzalez-Angulo, Huiqin Chen, Meghan S Karuturi, Mariana Chavez-Macgregor, Spyrus Tsavachidis, et al. (2013) Frequency of mesenchymalepithelial transition factor gene (MET) and the catalytic subunit of phosphoinositide-3-kinase (PIK3CA) copy number elevation and correlation with outcome in patients with early stage breast cancer. Cancer 119(1): 7-15.

32. Naomi Maruyama, Yasuo Miyoshi, Tetsuya Taguchi, Yasuhiro Tamaki, Morito Monden, et al. (2007) Clinicopathologic analysis of breast cancers with PIK3CA mutations in Japanese women. Clin Cancer Res 13(2 Pt 1): 408-414.

33. Gizeh Pérez Tenorio, Liza Alkhori, Birgit Olsson, Marie Ahnström Waltersson, Bo Nordenskjöld, et al. (2007) PIK3CA mutations and PTEN loss correlate with similar prognostic factors and are not mutually exclusive in breast cancer. Clin Cancer Res 13(12): 3577-3584.

34. Kevin Kalinsky, Lindsay M Jacks, Adriana Heguy, Sujata Patil, Marija Drobnjak, et al. (2009) PIK3CA mutation associates with improved outcome in breast cancer. Clin Cancer Res 15(16): 5049-5059.

35. Magdalena Cizkova, Aurélie Susini, Sophie Vacher, Géraldine Cizeron Clairac, Catherine Andrieu, et al. (2012) PIK3CA mutation impact on survival in breast cancer patients and in ERalpha, PR and ERBB2-based subgroups. Breast Cancer Res 14(1): 1-9.

36. Sherene Loi, Stefan Michiels, Diether Lambrechts, Debora Fumagalli, Bart Claes, et al. (2013) Somatic mutation profiling and associations with prognosis and trastuzumab benefit in early breast cancer. J Natl Cancer Inst 105(13): 960-967.

37. Lao H Saal, Karolina Holm, Matthew Maurer, Lorenzo Memeo, Tao Su, et al. (2005) PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res 65(7): 2554-2559.

38. Todd W Miller, Justin M Balko, Carlos L Arteaga (2011) Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol 29(33): 4452-4461.

39. Campbell RA, P Bhat-Nakshatri, Patel NM, D Constantinidou, S Ali, et al. (2001) Phosphatidylinositol 3-kinase/AKTmediated activation of estrogen receptor alpha: a new model for anti-estrogen resistance. J Biol Chem 276(13): 9817-9824.

40. Katrien Berns, Hugo M Horlings, Bryan T Hennessy, Mandy Madiredjo, E Marielle Hijmans, et al. (2007) A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. Cancer Cell 12(4): 395-402.

41. Dimitrios Zardavas, Wayne A Phillips, Sherene Loi (2014) PIK3CA mutations in breast cancer: Reconciling findings from preclinical and clinical data. Breast Cancer Res 16(1): 1-10.

42. Ebubekir Dirican, Zehra Kaya, Gokce Gullu, Irem Peker, Tolga Ozmen, et al. (2014) Detection of PIK3CA gene mutations with HRM analysis and association with IGFBP-5 expression levels in breast cancer. Asian Pac J Cancer Prev 15(21): 9327-9333.

43. Lao H Saal, Karolina Holm, Matthew Maurer, Lorenzo Memeo, Tao Su, et al. (2005) PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res 65(7): 2554-2559.

44. Yuen Liang Lai, Bey Liing Mau, Wen Hsuan Cheng, Han Ming Chen, His Hsiung Chiu, et al. (2008) PIK3CA exon 20 mutation is independently associated with a poor prognosis in breast cancer patients. Ann Surg Oncol 15(4): 1064-1069.

45. Yuen Liang Lai, Bey Liing Mau, Wen Hsuan Cheng, Han Ming Chen, His Hsiung Chiu (2006) PIK3CA mutations in breast cancer are associated with poor outcome. Breast Cancer Res Treat 96(1): 91-95.

46. Sherene Loi, Benjamin Haibe Kains, Samira Majjaj, Francoise Lallemand, Virginie Durbecq, et al. (2010) PIK3CA mutations associated with gene signature of low mTORC1 signaling and better outcomes in estrogen receptor positive breast cancer. Proc Natl Acad Sci USA 107(22): 10208-10213.

47. Gizeh Pérez Tenorio, Liza Alkhori, Birgit Olsson, Marie Ahnström Waltersson, Bo Nordenskjöld, et al. (2007) PIK3CA mutations and PTEN loss correlate with similar prognostic factors and are not mutually exclusive in breast cancer. Clin Cancer Res 13(12): 3577-3584.

48. Kevin Kalinsky, Lindsay M Jacks, Adriana Heguy, Sujata Patil, Marija Drobnjak, et al. (2009) PIK3CA mutation associates with improved outcome in breast cancer. Clin Cancer Res 15(16): 5049-5059.

49. West A, Vojta PJ, Welch DR, Weissman BE (1998) Chromosome localization and genomic structure of the KiSS-1 metastasis suppressor gene (KISS1). Genomics 54(1): 145-148.

50. Ohtaki T, Shintani Y, Honda S, Matsumoto H, Hori A, et al. (2001) Metastasis suppressor gene KiSS1encodes peptide ligand of a G-protein coupled receptor. Nature 411(6837): 613-617.

51. Y Rouillé, Duguay SJ, Lund K, Furuta M, Gong Q, et al. (1995) Proteolytic processing mechanisms in the biosynthesis of neuroendocrine peptides: the subtilisin-like proprotein convertases. Front Neuro endocrinol 16(4): 322-361.

52. Yasuko Terao, Satoshi Kumano, Yoshihiro Takatsu, Masahiko Hattori, Atsushi Nishimura, et al. (2004) Expression of KiSS1, a metastasissuppressor gene, in trophoblast giant cells of the rat placenta. Biochim Biophys Acta1 1678(2-3): 102-110.

53. Lee JH, Welch DR (1997) Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KiSS-1. Cancer Res 57(12): 2384-2387.

54. Tracey A Martin, Gareth Watkins, Wen G Jiang (2005) KiSS-1 expression in human breast cancer. Clin Exp Metastasis 22(6): 503-511.

55. Didier Marot, Ivan Bieche, Chantal Aumas, Stéphanie Esselin, Céline Bouquet, et al. (2007) High tumoral levels of Kiss1 and G-protein-coupled receptor 54 expression are correlated with poor prognosis of estrogen receptor-positive breast tumors. Endocr Relat Cancer 14(3): 691-702.

56. Kostadima L, Pentheroudakis G, Pavlidis N (2007) the missing kiss of life: transcriptional activity of the metastasis suppressor gene KiSS1 in early breast cancer. Anticancer Res 27(4B): 2499-2504.

57. Teresa Olbrich, Elke Ziegler, Gregor Türk, Antje Schubert, Günter Emons, et al. (2010) Kisspeptin-10 inhibits bone-directed migration of GPR54-positive breast cancer cells: Evidence for a dose-window effect. Gynecol Oncol 119(3): 571-578.

58. Pentheroudakis G, Kostadima L, Dova L, Georgiou I, Tzavaras T, et al. (2010) A twisted kiss: in vitro and in vivo evidence of genetic variation

and suppressed transcription of the metastasissuppressor gene KiSS1 in early breast cancer. Neoplasma 57(1): 47-54.

59. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, et al. (1997) Identification of a candidate tumor suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 15(4): 356-362.

60. Marsh DJ, Coulon V, Lunetta KL, P Rocca Serra, Dahia PL, et al. (1998) Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 7(3): 507-515.

61. Tamura M, Gu J, Takino T, Yamada KM (1999) Tumor suppressor PTEN inhibition of cell invasion, migration, and growth: differential involvement of local adhesion kinase and p130cas. Cancer Res 59(2): 442-449.

62. Besson A, Robbins SM, Yong VW (1999) PTEN/MMAC1/TEP1 in signal transduction and tumorigenesis. Eur J Biochem 263(3): 605-611.

63. Weng LP, Smith WM, Dahia PL, Ziebold U, Gil E, et al. (1999) PTEN suppresses breast cancer cell growth by phosphatase activity-dependent G1 arrest followed by cell death. Cancer Res 59(22): 5808-5814.

64. Li J, Simpson L, Takahashi M, Miliaresis C, Myers MP, et al. (1998) The PTEN/MMAC1 tumor suppressor induces cell death that is rescued by the AKT/protein kinase B oncogene. Cancer Res 58(24): 5667-5672.

65. Sun H, Lesche R, Li D, Liliental J, Zhang H, et al. (1999) PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5-triphosphate and Akt/ protein kinase B signaling pathway. Proc Natl Acad Sci USA 96(11): 6199-6204.

66. Nelen MR, Kremer H, Konings IB, Schoute F, Van Essen AJ, et al. (1999) Novel PTEN mutations in Cowden disease: absence of clear genotype-phenotype correlations. Eur J Hum Genet 7(3): 267-273.

67. Carroll BT, Couch FJ, Rebbeck TR, Weber BL (1999) Polymorphisms in PTEN in breast cancer families. J Med Genet 36(2): 94-96.

68. Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, et al. (1997) Inherited mutations in PTEN that are associated with breast cancer, cowden disease, and juvenile polyposis. Am J Hum Genet 61(6): 1254-1260.

69. Rhei E, Kang L, Bogomolniy F, Federici MG, Borgen PI, et al. (1997) Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in primary breast carcinomas. Cancer Res 57(17): 3657-3659.

70. Ghosh AK, Grigorieva I, Steele R, Hoover RG, Ray RB (1999) PTEN transcriptionally modulates c-myc gene expression in human breast carcinoma cells and is involved in cell growth regulation. Gene 235(1-2): 85-91.

71. Chen ST, Yu SY, Tsai M, Yeh KT, Wang JC, et al. (1999) Mutation analysis of the putative tumor suppressor gene PTEN/MMAC1 in sporadic breast cancer. Breast Cancer Res Treat 55(1): 85-89.

72. Feilotter HE, V Coulon, Mcveigh JL, Boag AH, F Dorion Bonnet, et al. (1999) Analysis of the 10q23 chromosomal region and the PTEN gene in human sporadic breast carcinoma. Br J Cancer 79(5): 718-723.

73. Freihoff D, Kempe A, Beste B, Wappenschmidt B, Kreyer E, et al. (1999) Exclusion of a major role for the PTEN tumour-suppressor gene in breast carcinomas. Br J Cancer 79(5): 754-758.

74. Laugé A, Lefebvre C, Laurent-Puig P, Caux V, Gad S, et al. (1999) No evidence for germline PTEN mutations in families with breast and brain tumours. Int J Cancer 84(3): 216-219.

75. Marsh DJ, V Coulon, Lunetta KL, Rocca Serra P, Dahia PL, et al. (1998) Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. Hum Mol Genet 7(3): 507-515.

76. S Bose, Wang SI, Terry MB, Hibshoosh H, Parsons R (1998) Allelic loss of chromosome 10q23 is associated with tumor progression in breast carcinomas. Oncogene 17(1): 123-127.

77. Jennifer A Byrne, Sarah Frost, Yuyan Chen, Robert K Bright (2014) Tumor protein D52 (TPD52) and cancer-oncogene understudy or understudied oncogene?. Tumour Biol 35(8): 7369-7382.

78. Shehata M, Bièche I, Boutros R, Weidenhofer J, Fanayan S, et al. (2008) Nonredundant functions for tumor protein D52-like proteins support specific targeting of TPD52. Clin Cancer Res 14(16): 5050-5060.

79. Pierre Tennstedt, Charlotte Bölch, Gundula Strobel, Sarah Minner, Lia Burkhardt, et al. (2014) Patterns of TPD52 overexpression in multiple human solid tumor types analyzed by quantitative PCR. Int J Oncol 44(2): 609-615.

80. Nuruliza Roslan, Ivan Bièche, Robert K Bright, Rosette Lidereau, Yuyan Chen, et al. (2013) TPD52 represents a survival factor in ERBB2-amplified breast cancer cells. Mol. Carcinog 53(10): 807-819.

81. Jennifer A Byrne, Yuyan Chen, Nancy Martin La Rotta, Gregory B Peters (2012) Challenges in identifying candidate amplification targets in human cancers: chromosome 8q21 as a case study. Genes Cancer 3(2): 87-101.

82. Koboldt DCFR, Fulton R, McLellan M, Schmidt H, Kalicki Veizer J, et al. (2012). Comprehensive molecular portraits of human breast tumours. Nature 490(7418): 61-70.

83. Miriam Ragle Aure, Israel Steinfeld, Lars Oliver Baumbusch, Knut Liestøl, Doron Lipson, et al. (2013) Identifying intrans process associated genes in breast cancer by integrated analysis of copy number and expression data. PLoS ONE 8(1): e53014.

84. Guedj M, Marisa L, De Reynies A, Orsetti B, Schiappa R, et al. (2012) A refined molecular taxonomy of breast cancer. Oncogene 31(9): 1196-1206.

85. Stéphanie Cornen, Arnaud Guille, José Adélaïde, Lynda Addou-Klouche, Pascal Finetti, et al. (2014) Candidate luminal B breast cancer genes identified by genome, gene expression and DNA methylation profiling. PLOS One 9(1): e81843.

86. Wilson Ks, Roberts H, Leek R, Harris Al, Geradts J (2002) Differential gene expression patterns in HER2/neu-positive and -negative breast cancer cell lines and tissues. Am J Pathol 161(4): 1171-1185.

87. Kourtidis A, Jain R, Carkner RD, Eifert C, Brosnan MJ, et al. (2010) An RNA interference screen identifies metabolic regulators NR1D1 and PBP as novel survival factors for breast cancer cells with the ERBB2 signature. Cancer Res 70(5): 1783-1792.