European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 07, 2022

Original Research Article

Smarca4 Gene Polymorphism And The Breast Cancer: A Review

Usha Adiga[1*], Desy TM[2]

[1*] Professor, Nitte-DU, KS Hegde Medical Academy ,Department of Biochemistry, Mangalore, India

[2] Senior Research Fellow, ICMR, Dept of Biochemistry, KS Hegde Medical Academy, Nitte- Deemed to be University, Mangalore, India

***Corresponding Author :** Usha Adiga

[*]Professor, Nitte-DU, KS Hegde Medical Academy ,Department of Biochemistry, Mangalore, India
ushachidu@yahoo.com

Abstract

Cancer is simply due to the mutations at the genetic level, commonly known as genetic disorder. In this condition the cells suffer from uncontrolled growth of cell division. These mutations can be acquired or may occur in somatic cells. Somatic cell mutations cannot be inherited while germ line mutations are inherited. In general, cancer cells have more genetic changes than normal cells. But each person's cancer has a unique combination of genetic alterations. Some of these changes may be the result of cancer, rather than the cause. As the cancer continues to grow, additional changes will occur. Even within the same tumor, cancer cells may have different genetic changes.

The genes that contribute to cancer development are tumor suppressor genes, Oncogenes and DNA repair genes**.** Tumor suppressor genes are protective genes and they limit cell growth by monitoring how quickly cells divide into new cells, repairing mismatched DNA and controlling when a cell dies. These include BRCA1, BRCA2, and p53 or TP53. When a tumor suppressor gene mutates, cells grow uncontrollably. And they may eventually form a tumor. Oncogenes turn a healthy cell into a cancerous cell. Mutations in these genes are not known to be inherited. Common oncogenes are HER2 and the RAS family of genes.The role of SMARCA4 gene has been least explored in breast cancer.

Key Words: SMARCA4, Breast Cancer, single nucleotide polymorphism

Background

Breast cancer contributes to the second highest incidence of cancer-rated deaths among women worldwide [1]. Development of breast cancer is associated with multiple etiologic factors, including hormonal disorders, inheritance, ionizing radiation, and unhealthy eating habits [2]. Breast cancer is normally treated by a combination of surgery with radiotherapy, endocrine therapy, and/or chemotherapy. Despite improvements in diagnosis and treatment, the 5-year survival rate of patients with breast cancer was still viewed as unsatisfactory in recent decades, which highlights the ongoing need to understand the mechanisms by which it progresses and to explore new therapeutic targets [3].

Incidence and prevalence of breast cancer in India

Breast cancer is the most common site of malignancy in Indian women in urban areas and is the fastest growing cancer in the country [4]. National cancer registry programme (NCRP) reported annual percentage change (APC) of 0.68% for all site cancers over 3 years (2011– 2014). APC for

breast cancer over the same period was about 2.0%. Incidence of breast cancer has increased sharply over the past two decades. In Delhi, the APC increased from 0.91 to 5.31% over a period of 1988–2012 [5]. In Indian urban centres, most of breast cancer is detected in the age group of 40–49 years, while rural areas have highest incidence at age group 65–69 years. In urban centres, patients presented at mean age of 45 years [6,7]. Risk of breast cancer cases increases with number of affected first-degree relatives [8]. Family history of breast cancer is present in 15% of Indian women with breast cancer [9]

SMARCA4 and Cancer

SMARCA4 (SWI / SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4) encodes a protein involved in chromatin remodelling, which is important for regulating the binding of transcription factors to DNA. Loss of SMARCA4 characterizes several distinct neoplasms, including: small cell carcinoma of the ovary hypercalcemic type, SMARCA4 deficient undifferentiated uterine sarcoma and SMARCA4 deficient thoracic sarcoma [10-12].While SMARCA4 is considered a tumor suppressor gene, both loss of protein expression as well as protein upregulation have been associated with neoplasia [13,14]. It is frequently mutated in a variety of cancer cell lines [15]. A component of the SWI / SNF complex, which is involved in chromatin remodeling and thus the regulation of gene expression [16,17].SMARCA4 also plays a role in tumor suppression directly as well as through interaction with other key cancer related proteins (BRCA1, Rb, p53, beta-catenin, etc.) [18-21].It may also play roles in DNA repair or cell cycle control [22,13].

Immuno-histochemical expression of SMARCA4 aids in the diagnosis of ovarian small cell carcinoma, hypercalcemic type (ovarian rhabdoid tumor), thoracic sarcoma, malignant rhabdoid tumor of the uterus etc. Concomitant loss of SMARCA4 and BRM in non small cell lung cancer is associated with worse prognosis [23].Loss of expression of SMARCA4 is associated with improved prognosis in clear cell renal cell carcinoma [24].Increased SMARCA4 expression is associated with worse prognosis in patients with breast invasive ductal carcinoma, hepatocellular carcinoma and clear cell renal cell carcinoma [25,13].

However role of SMARCA4 is not well established in breast cancer.

The mammalian switch/sucrose non-fermentable (mSWI/SNF or BAF) complex is an ATP-dependent chromatin remodeller. It uses the energy from ATP hydrolysis to slide, evict, deposit or alter the composition of nucleosomes, regulating the access of chromatin to other DNA-binding factors and transcriptional machinery [26, 27]. It plays critical roles in the development, differentiation and other important cellular processes like DNA replication and repair[28]. The BAF multimeric complex is formed by the combinatorial assembly of two mutually exclusive ATP-dependent helicases, SMARCA2 (BRM) and SMARCA4 (BRG1), with multiple accessory subunits that facilitate DNA-histone-binding, allowing for extensive complex diversity and tissue-specific functions [29].

Cancer genomic studies in primary human tumors and tumor-derived cell lines revealed more than 20% of human tumors have mutations in one or more BAF subunits, with certain subunits found mutated in unique tumor types [30-34]. Many of these mutations are loss-of-function, and a large body of work has demonstrated that these complexes are in fact bonafide tumor suppressors [35-38]. Alterations in the core catalytic subunit, SMARCA4, have been found in multiple tumor types [39-44]. Recent studies have demonstrated that SMARCA4 mutations in the ATP-binding pocket fail to evict polycomb repressive complex (PRC)-1 from chromatin and result in the loss of enhancer accessibility [32,33].

Strategies to therapeutically target BAF-mutant cancers have focused on identifying novel vulnerabilities due to the altered chromatin state caused by these mutations. Indeed, subsets of SMARCA4-deficient tumors were found to be sensitive to EZH2 inhibition, the catalytic subunit of PRC-2, with SMARCA2 expression potentially serving as a biomarker of insensitivity [45]. Synthetic lethal screens have also identified paralog dependence as an alternate vulnerability [46-50]. As BAF complexes have gained many paralogs that play distinct functions during development, somatic alterations in one paralog will result in a complete dependence on the remaining functional paralog for survival. Consequently, SMARCA2 has become an appealing therapeutic target in tumors that have mutation-driven loss of SMARCA4, and multiple efforts are ongoing to develop small molecule inhibitors of SMARCA2 activity or degraders [51-53].

Genomic studies thus far have described SMARCA4 alterations with limited patient data and have failed to assess differences in zygosity and co-occurrence with alterations in other BAF subunits and oncogenic drivers. However, to fully translate any potential SMARCA2-directed therapy into the clinic, it is imperative to understand the full spectrum of SMARCA4 mutations and their functional consequence.

The SMARCA4 gene has not yet been characterized for any predisposing role in breast cancer. The evidence suggests that SMARCA4, along with other SWI/SNF complex genes, is significantly mutated in several cancers [54]. A study by Erica et al has reported that Low expression of SMARCA4/BRG1 is significantly associated with worse prognosis in non–small cell lung cancer [55]. Jin et al demonstrated that BRG1 plays an important role in human breast cancer pathogenesis. Increased BRG1 expression may facilitate tumor progression by enhancing cell growth, migration and invasion [56].Interestingly, a study by Gunjesh Kumar et al found a sequence change at codon 243 replaced glycine with serine in the SMARCA4 protein (p. Gly243Ser) in a breast cancer patient [57]. This particular variant has been reported in the literature in other malignancies with unknown significance, but not in breast carcinoma[58].Akihiko Yoshida et al suggested that SMARCA4 deficiency showed a protective role in thoracic carcinoma [59].They also mentioned comparative analysis supported the distinctiveness of SMARCA4-deficient thoracic sarcomas as they were distinguishable from 13 malignant rhabdoid tumors, 15 epithelioid sarcomas, and 12 SMARCA4-deficient lung carcinomas based on clinicopathological and immunohistochemical grounds.The study aims to assess the pattern of polymorphism of Gly243Ser of SMARCA4 in breast cancer.

FUTURE RESEARCH PERSPECTIVES

There is a scarcity of literature which explores the role of Gly243Ser of SMARCA4 Gene Polymorphism in the pathogenesis of breast cancer to the best of our knowledge. SMARCA4 gene is associated with DNA remodelling and damage repair mechanisms. Mutations of SMARCA4 may result in deranged DNA damage repair mechanisms and may contribute to the pathogenesis of breast cancer. A study may be planned to find out the association between Gly243Ser of SMARCA4 Gene Polymorphism, DNA damage and breast cancer.

CONCLUSION

Role of SMARCA4 gene has been least studied in breast cancer. If there is an association between the Gly243Ser of SMARCA4 gene polymorphism and breast cancer, detection of mutated allele could be a novel biomarker for the prediction of breast cancer. If the association between the gene polymorphism and clinical staging of the disease is established, probably mutated allele could be a predictor of invasiveness as well as a prognostic marker. Early prediction of cancer breast may help in personalizing the therapy which may lead to better prognosis. Early detection and treatment will

ISSN 2515-8260 Volume 09, Issue 07, 2022

definitely improve quality of life of breast cancer patients. This study may reveal the role of Gly243Ser of SMARCA4 in carcinoma of breast. SMARCA4 may also be a potential therapeutic target to treat hormone resistant breast cancers.

REFERENCES

1. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349: 1269–76.

2. Hunter DJ, Spiegelman D, Adami HO, Van Den Brandt PA, Folsom AR, Goldbohm RA et al. Non-dietary factors as risk factors for breast cancer, and as effect modifiers of the association of fat intake and risk of breast cancer. Cancer Causes & Control. 1997;8(1):49-56.

3. Ewertz M, Duffy SW, Adami HO, Kvåle G, Lund E, Meirik et al. Age at first birth, parity and risk of breast cancer: a meta- analysis of 8 studies from the Nordic countries. International journal of cancer. 1990;46(4):597-603.

4. Deng CX. SIRT1, is it a tumor promoter or tumor suppressor?. International journal of biological sciences. 2009;5(2):147.

5. Chen W, Bhatia R. Roles of SIRT1 in leukemogenesis. Current opinion in hematology. 2013;20(4):308-313.

6. Han L, Liang XH, Chen LX, Bao SM, Yan ZQ. SIRT1 is highly expressed in brain metastasis tissues of non-small cell lung cancer (NSCLC) and in positive regulation of NSCLC cell migration. International journal of clinical and experimental pathology. 2013;6(11):2357.

7. Riggio M, Polo ML, Blaustein M, Colman-Lerner A, Lüthy I, Lanari C et al. PI3K/AKT pathway regulates phosphorylation of steroid receptors, hormone independence and tumor differentiation in breast cancer. Carcinogenesis. 2012;33(3):509-18.

8. Lee MS, Jeong MH, Lee HW, Han HJ, Ko A, Hewitt SM et al. PI3K/AKT activation induces PTEN ubiquitination and destabilization accelerating tumourigenesis. Nature communications. 2015;6:7769.

9. Pinton G, Zonca S, Manente AG, Cavaletto M, Borroni E, Daga A et al. SIRT1 at the crossroads of AKT1 and ERβ in malignant pleural mesothelioma cells. Oncotarget. 2016;7(12):14366-79.

10. Conlon N, Silva A, Guerra E, Jelinic P, Schlappe BA, Olvera N et al. Loss of SMARCA4 expression is both sensitive and specific for the diagnosis of small cell carcinoma of ovary, hypercalcemic type. The American journal of surgical pathology. 2016 Mar;40(3):395.

11. Kolin DL, Dong F, Baltay M, Lindeman N, MacConaill L, Nucci MR et al. SMARCA4-deficient undifferentiated uterine sarcoma (malignant rhabdoid tumor of the uterus): a clinicopathologic entity distinct from undifferentiated carcinoma. Modern Pathology. 2018 Sep;31(9):1442-56.

12. Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S, Firmin N et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nature genetics. 2015 Oct;47(10):1200-5.

13. Guerrero-Martínez JA, Reyes JC. High expression of SMARCA4 or SMARCA2 is frequently associated with an opposite prognosis in cancer. Scientific reports. 2018 Feb 1;8(1):1-7.

14. Reisman DN, Sciarrotta J, Wang W, Funkhouser WK, Weissman BE. Loss of BRG1/BRM in human lung cancer cell lines and primary lung cancers: correlation with poor prognosis. Cancer research. 2003 Feb 1;63(3):560-6.

15. Medina PP, Romero OA, Kohno T, Montuenga LM, Pio R, Yokota J et al. Frequent BRG1/SMARCA4–inactivating mutations in human lung cancer cell lines. Human mutation. 2008 May;29(5):617-22.

16. Khavari PA, Peterson CL, Tamkun JW, Mendel DB, Crabtree GR. BRG1 contains a conserved domain of the SWI2/SNF2 family necessary for normal mitotic growth and transcription. Nature. 1993 Nov;366(6451):170-4.

17. Hargreaves DC, Crabtree GR. ATP-dependent chromatin remodeling: genetics, genomics and mechanisms. Cell research. 2011 Mar;21(3):396-420.

18. Bochar DA, Wang L, Beniya H, Kinev A, Xue Y, Lane WS et al. BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer. Cell. 2000 Jul 21;102(2):257-65.

19. Dunaief JL, Strober BE, Guha S, Khavari PA, Ålin K, Luban J et al. The retinoblastoma protein and BRG1 form a complex and cooperate to induce cell cycle arrest. Cell. 1994 Oct 7;79(1):119-30.

20. Lee D, Kim JW, Seo T, Hwang SG, Choi EJ, Choe J. SWI/SNF complex interacts with tumor suppressor p53 and is necessary for the activation of p53-mediated transcription. Journal of Biological Chemistry. 2002 Jun 21;277(25):22330-7.

21. Barker N, Hurlstone A, Musisi H, Miles A, Bienz M, Clevers H. The chromatin remodelling factor Brg- 1 interacts with β- catenin to promote target gene activation. The EMBO journal. 2001 Sep 3;20(17):4935-43.

22. Lee HS, Park JH, Kim SJ, Kwon SJ, Kwon J. A cooperative activation loop among SWI/SNF, γ- H2AX and H3 acetylation for DNA double- strand break repair. The EMBO journal. 2010 Apr 21;29(8):1434-45.

23. Wang G, Fu Y, Hu F, Lan J, Xu F, Yang X et al. Loss of BRG1 induces CRC cell senescence by regulating p53/p21 pathway. Cell death & disease. 2017 Feb;8(2):e2607-.
24. Jiang W, Dulaimi E, Devarajan K, Parsons T, Wang Q, O'Neill R et al. Intratumoral heterogeneity analysis reveals hidden associations between protein expression losses and patient survival in clear cell renal cell carcinoma. Oncotarget. 2017 Jun 6;8(23):37423.

25. Do SI, Yoon G, Kim HS, Kim K, Lee H, Do IG et al. Increased brahma-related gene 1 expression predicts distant metastasis and shorter survival in patients with invasive ductal carcinoma of the breast. Anticancer research. 2016 Sep 1;36(9):4873-82.

26. Hodges C, Kirkland JG, Crabtree GR. The many roles of BAF (mSWI/SNF) and PBAF complexes in cancer. Cold Spring Harbor perspectives in medicine. 2016 Aug 1;6(8):a026930.

27. Valencia AM, Kadoch C. Chromatin regulatory mechanisms and therapeutic opportunities in cancer. Nature cell biology. 2019 Feb;21(2):152-61.

28. Alfert A, Moreno N, Kerl K. The BAF complex in development and disease. Epigenetics Chromatin 12 (1): 19.

29. Mashtalir N, D'Avino AR, Michel BC, Luo J, Pan J, Otto JE et al. Modular organization and assembly of SWI/SNF family chromatin remodeling complexes. Cell. 2018 Nov 15;175(5):1272-88.

30. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PloS one. 2013 Jan 23;8(1):e55119.

31. Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, Ranish J et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. Nature genetics. 2013 Jun;45(6):592-601.

32. Stanton BZ, Hodges C, Calarco JP, Braun SM, Ku WL, Kadoch C et al. Smarca4 ATPase mutations disrupt direct eviction of PRC1 from chromatin. Nature genetics. 2017 Feb;49(2):282-8.

33. Hodges HC, Stanton BZ, Cermakova K, Chang CY, Miller EL, Kirkland JG et al. Dominant-negative SMARCA4 mutants alter the accessibility landscape of tissue-unrestricted enhancers. Nature structural & molecular biology. 2018 Jan;25(1):61-72.

34. Wong AK, Shanahan F, Chen Y, Lian L, Ha P, Hendricks K et al. BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. Cancer research. 2000 Nov 1;60(21):6171-7.

35. Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. Nature Reviews Cancer. 2011 Jul;11(7):481-92.

36. Roberts CW, Galusha SA, McMenamin ME, Fletcher CD, Orkin SH. Haploinsufficiency of Snf5 (integrase interactor 1) predisposes to malignant rhabdoid tumors in mice. Proceedings of the National Academy of Sciences. 2000 Dec 5;97(25):13796-800.

37. Roberts CW, Leroux MM, Fleming MD, Orkin SH. Highly penetrant, rapid tumorigenesis through conditional inversion of the tumor suppressor gene Snf5. Cancer cell. 2002 Nov 1;2(5):415-25.

38. Deribe YL, Sun Y, Terranova C, Khan F, Martinez-Ledesma J, Gay J et al. Mutations in the SWI/SNF complex induce a targetable dependence on oxidative phosphorylation in lung cancer. Nature medicine. 2018 Jul;24(7):1047-57.

39. Reisman DN, Strobeck MW, Betz BL, Sciariotta J, Funkhouser Jr W, Murchardt C et al. Concomitant down-regulation of BRM and BRG1 in human tumor cell lines: differential effects on RB-mediated growth arrest vs CD44 expression. Oncogene. 2002 Feb;21(8):1196-207.

40. Medina PP, Romero OA, Kohno T, Montuenga LM, Pio R, Yokota J et al. Frequent BRG1/SMARCA4–inactivating mutations in human lung cancer cell lines. Human mutation. 2008 May;29(5):617-22.

41. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul;511(7511):543.

42. Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N, Tomiak E et al. Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nature genetics. 2014 May;46(5):438-43.

43. Jelinic P, Mueller JJ, Olvera N, Dao F, Scott SN, Shah R et al. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. Nature genetics. 2014 May;46(5):424-6.

44. Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S, Firmin N et al. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nature genetics. 2015 Oct;47(10):1200-5.

45. Januario T, Ye X, Bainer R, Alicke B, Smith T, Haley B et al. PRC2-mediated repression of SMARCA2 predicts EZH2 inhibitor activity in SWI/SNF mutant tumors. Proceedings of the National Academy of Sciences. 2017 Nov 14;114(46):12249-54.

46. Hoffman GR, Rahal R, Buxton F, Xiang K, McAllister G, Frias E et al. Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. Proceedings of the National Academy of Sciences. 2014 Feb 25;111(8):3128-33.

47. Helming KC, Wang X, Wilson BG, Vazquez F, Haswell JR, Manchester HE et al. ARID1B is a specific vulnerability in ARID1A-mutant cancers. Nature medicine. 2014 Mar;20(3):251-4.

48. Wilson BG, Helming KC, Wang X, Kim Y, Vazquez F, Jagani Z et al. Residual complexes containing SMARCA2 (BRM) underlie the oncogenic drive of SMARCA4 (BRG1) mutation. Molecular and cellular biology. 2014 Mar;34(6):1136.

49. Ehrenhöfer-Wölfer K, Puchner T, Schwarz C, Rippka J, Blaha-Ostermann S, Strobl U et al. SMARCA2-deficiency confers sensitivity to targeted inhibition of SMARCA4 in esophageal squamous cell carcinoma cell lines. Scientific reports. 2019 Aug 12;9(1):1-2.

50. Vangamudi B, Paul TA, Shah PK, Kost-Alimova M, Nottebaum L, Shi X et al. The SMARCA2/4 ATPase domain surpasses the bromodomain as a drug target in SWI/SNF-mutant cancers: insights from cDNA rescue and PFI-3 inhibitor studies. Cancer research. 2015 Sep 15;75(18):3865-78.

51. Farnaby W, Koegl M, Roy MJ, Whitworth C, Diers E, Trainor N et al. BAF complex vulnerabilities in cancer demonstrated via structure-based PROTAC design. Nature chemical biology. 2019 Jul;15(7):672-80.

52. Papillon JP, Nakajima K, Adair CD, Hempel J, Jouk AO, Karki RG et al. Discovery of orally active inhibitors of brahma homolog (BRM)/SMARCA2 ATPase activity for the treatment of brahma related gene 1 (BRG1)/SMARCA4-mutant cancers. Journal of medicinal chemistry. 2018 Oct 19;61(22):10155-72.

53. Rago F, DiMare MT, Elliott G, Ruddy DA, Sovath S, Kerr G et al. Degron mediated BRM/SMARCA2 depletion uncovers novel combination partners for treatment of BRG1/SMARCA4-mutant cancers. Biochemical and biophysical research communications. 2019 Jan 1;508(1):109-16.

54. Shain AH, Pollack JR. The spectrum of SWI/SNF mutations, ubiquitous in human cancers. PLoS One 2013;8:e55119.

55. Moes – Sosnowska J, SzafronL, Nowakowska D, Dansonka‐ Mieszkowska A, Budzilowska A, Konopka B, *et al*. Germline SMARCA4 mutations in patients with ovarian small cell carcinoma of hypercalcemic type. Orphanet J Rare Dis 2015;10:32.

56. Bai J, Mei P, Zhang C, Chen F, Li C, Pan Z et al. BRG1 is a prognostic marker and potential therapeutic target in human breast cancer. PloS one. 2013 Mar 22;8(3):e59772.

57. Singh GK, Bajpai J, Chougule A, Chandrani P. Rare mutations in breast cancer and implications in the clinic: Oscillation between sharp horns of dilemmas!. Cancer Research, Statistics, and Treatment. 2020 Jul 1;3(2):302.

58. National Center for Biotechnology Information. ClinVar. Available from: https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000408659.3.[Last accessed 2020 Apr 20].

59. Yoshida A, Kobayashi E, Kubo T, Kodaira M, Motoi T, Motoi N, Yonemori K, Ohe Y, Watanabe SI, Kawai A, Kohno T. Clinicopathological and molecular characterization of SMARCA4-deficient thoracic sarcomas with comparison to potentially related entities. Modern Pathology. 2017 Jun;30(6):797-809.