

ASSOCIATION OF POLYMORPHISMS IN GENES INVOLVED IN DNA REPAIR AND CELL CYCLE ARREST WITH BREAST CANCER IN A VIETNAMESE CASE-CONTROL COHORT

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Breast cancer (BC) is the most common cancer diagnosis in women worldwide. Among causative BC genes, MRE11, ERCC1, TNRC9 (TOX3), and CASC16 play an important role in DNA damage repair; FGFR2, CCNE1, ZMIZ1, and LSP1 involve in cell cycle checkpoint. A functional polymorphism of these genes may alter DNA repair capacity and genomic stability. Single Nucleotide Polymorphisms (SNPs) can modify the risk of cancer, and thus, SNPs may be considered as potential markers of carcinogenesis. Among them, eight SNPs (rs2981582, rs569550, rs3218035, rs704010, rs2155209, rs3212986, rs12443621 and rs4784227) are significantly associated with BC risk in various populations. This study was conducted to investigate the genetic susceptibility of these SNPs in the development of BC in Vietnamese women. MRE11 rs2155209 and CASC16 rs4784227 were found to be associated with BC risk (CC vs. CT + TT: OR = 0.57, 95% CI 0.34 to 0.97, P = 0.03 and CT vs. CC + TT: OR = 1.43, 95% CI 1.03 to 1.97, P = 0.03; respectively). These findings suggest that SNPs involved in DNA repair genes may affect the susceptibility of BC in Vietnamese women.

Key words: breast cancer, single nucleotide polymorphism, MRE11, rs2155209, CASC16, rs4784227

АСОЦІАЦІЯ МІЖ ПОЛІМОРФІЗМАМИ В ГЕНАХ, ЗАЛУЧЕНИХ ДО РЕПАРАЦІЇ ДНК І ТЕРМІНАЦІЇ КЛІТИННОГО ЦИКЛУ, ТА РАКОМ ГРУДЕЙ У КОГОРТНОМУ

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ДОСЛІДЖЕННЯ ТИПУ «ВИПАДОК-КОНТРОЛЬ» У В'ЄТНАМІ

Рак грудей (РГ) – це найпоширеніший діагноз ракового захворювання серед жінок у всьому світі. 3-поміж каузативних генів РГ, MRE11, ERCC1, TNRC9 (TOX3) і CASC16 відіграють важливу роль у репарації ДНК; FGFR2, CCNE1, ZMIZ1 і LSP1 беруть участь у контрольній точці клітинного циклу. Функціональний поліморфізм цих генів може змінювати здатність до репарації ДНК і стабільність геному. Однонуклеотидні поліморфізми (SNP) можуть модифікувати ризик появи раку, отже, SNP можна розглядати як потенційні маркери канцерогенезу. 3-поміж них, вісім SNP (rs2981582, rs569550, rs3218035, rs704010, rs2155209, rs3212986, rs12443621 і rs4784227) тісно асоційовані з ризиком появи РГ у різних популяціях. Це дослідження було проведене з метою вивчення генетичної схильності цих SNP у розвитку РГ серед в'єтнамських жінок. Було виявлено, що MRE11 rs2155209 і CASC16 rs4784227 пов'язані з ризиком виникнення РГ (CC vs. CT + TT: OR = 0,57, 95 % CI 0,34 до 0,97, P = 0,03 і CT vs. CC + TT: OR = 1,43, 95 % CI 1,03 до 1,97, P = 0,03; відповідно). Ці результати свідчать про те, що SNP, залучені до генів репарації ДНК, можуть впливати на схильність в'єтнамських жінок до РГ.

Ключові слова: рак грудей, однонуклеотидний поліморфізм, MRE11, rs2155209, CASC16, rs4784227.

REFERENCES

- Bretones G, Delgado M D, Leyn J. (2015) Myc and cell cycle control. *Biochimica et Biophysica Acta – Gene Regulatory Mechanisms* 1849(5):506–516
- Chen H, Qi X, Qiu P, Zhao J. (2015) Correlation between LSP1 polymorphisms and the susceptibility to breast cancer. *International journal of clinical and experimental pathology* 8(5):5798–5802
- Chen Y, Shi C, Guo Q. (2016) TNRC9 rs12443621 and FGFR2 rs2981582 polymorphisms and breast cancer risk. *World J Surg Oncol* 14(1):50–55. <https://doi.org/10.1186/s12957-016-0795-7>
- Couch FJ, Nathanson KL, Offit K. (2014) Two decades after BRCA: setting paradigms in personalized cancer care and prevention. *Science* 343(6178):1466–1470
- Cowper-Salari R, Zhang X, Wright JB, Bailey SD, Cole MD, Eekhoutte J, Moore JH, Lupien M. (2012) Breast cancer risk-associated SNPs modulate the affinity of chromatin for FOXA1 and alter gene expression. *Nature genetics*, 44(11):1191–1198. <https://doi.org/10.1038/ng.2416>
- Dorak MT. (2017) Genotyping Methods and Errors. In *Genetic association studies: background, conduct, analysis, interpretation*. Garland Science.

- Gao F, Ge R. (2019) LOC643714 Polymorphisms Contribute to an Elevated Susceptibility to Breast Cancer: A Meta-analysis of 231,191 Subjects. *Clin Breast Cancer* 19(5):596–610. <https://doi.org/10.1016/j.clbc.2019.04.016>
- Greenberg RA, Sobhian B, Pathania S, Cantor SB, Nakatani Y, Livingston DML. (2006) Multifactorial contributions to an acute DNA damage response by BRCA1/BARD1-containing complexes. *Genes and Development* 20(1):34–46
- Han JY, Wang H, Xie YT, Li Y, Zheng LY, Ruan Y, Song AP, Tian XX, Fang WG. (2012). Association of germline variation in CCNE1 and CDK2 with breast cancer risk, progression and survival among Chinese Han women. *PLoS One* 7(11):1–11 <https://doi.org/10.1371/journal.pone.0049296>
- Han MR, Deming-Halverson S, Cai Q, Wen W, Shrubsole MJ, Shu XO, Zheng W, Long J. (2015) Evaluating 17 breast cancer susceptibility loci in the Nashville breast health study. *Breast Cancer* 22(5):544–551. <https://doi.org/10.1007/s12282-014-0518-2>
- He X, Yao G, Li F, Li M, Yang X. (2014) Risk-association of five SNPs in TOX3/LOC643714 with breast cancer in southern China. *International journal of molecular sciences* 15(2):2130–2141. <https://doi.org/10.3390/ijms15022130>
- Heikkinen K, Rapakko K, Karppinen SM, Erkkö H, Knuutila S, Lundan T, Mannermaa A, Borresen-Dale AL, Borg A, Barkardottir RB, Petrini J, Winqvist R. (2006) RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. *Carcinogenesis* 27(8):1593–1599. <https://doi.org/10.1093/carcin/bgi360>
- Hue NT. (2012) Extraction of human genomic DNA from dried blood spots and hair roots. *International Journal of Bioscience* 2:21–26
- Jiang C, Yu S, Qian P, Guo R, Zhang R, Ao Z, Li Q, Wu G, Chen Y, Li J, Wang C, Yao W, Xu J, Qian G, Ji F. (2016) The breast cancer susceptibility-related polymorphisms at the TOX3/LOC643714 locus associated with lung cancer risk in a Han Chinese population. *Oncotarget* 7(37):59742–59753. <https://doi.org/10.18632/oncotarget.10874>
- Kim HC, Lee JY, Sung H, Choi JY, Park SK, Lee KM, Kang D. (2012) A genome-wide association study identifies a breast cancer risk variant in ERBB4 at 2q34: results from the Seoul Breast Cancer Study. *Breast Cancer Res* 14(2):1–12. <https://doi.org/10.1186/bcr3158>
- Li X, Zou W, Liu M, Cao W, Jiang Y, An G, Wang Y, Huang S, Zhao X. (2016) Association of multiple genetic variants with breast cancer susceptibility in the Han Chinese population. *Oncotarget* 7(51):85483–85491. <https://doi.org/10.18632/oncotarget.13402>
- Lin Y, Fu F, Chen M, Huang M, Wang C. (2014) Associations of two common genetic variants with breast cancer risk in a Chinese population: a stratified interaction analysis. *PLoS One* 9(12):1–12. <https://doi.org/10.1371/journal.pone.0115707>
- Meyer KB, Carroll JS. (2012) FOXA1 and breast cancer risk. *Nature genetics* 44(11):1176–1177.
- Naccarati A, Rosa F, Vymetalkova V, Barone E, Jiraskova K, Di Gaetano C, Novotny J, Levy M, Vodickova L, Gemignani F, Buchler T, Landi S, Vodicka P, Pardini B. (2016) Double-strand break repair and colorectal cancer: gene variants within 3' UTRs and microRNAs binding as modulators of cancer risk and clinical outcome. *Oncotarget* 7(17):23156–23169. <https://doi.org/10.18632/oncotarget.6804>
- O'Flaherty E, Kaye J. (2003) TOX defines a conserved subfamily of HMG-box proteins. *BMC genomics* 4(1):13–22
- Paull TT, Deshpande RA. (2014) The Mre11/Rad50/Nbs1 complex: recent insights into catalytic activities and ATP-driven conformational changes. *Exp Cell Res* 329(1):139–147. <https://doi.org/10.1016/j.yexcr.2014.07.007>
- Pei XH, Yang Z, Lv XQ, Li HX. (2014) Genetic variation in ERCC1 and XPF genes and breast cancer risk. *Genet Mol Res* 13(1):2259–2267. <https://doi.org/10.4238/2014.March.31.6>
- Rakowski LA, Garagiola DD, Li CM, Decker M, Caruso S, Jones M, Kuick R, Cierpicki T, Maillard I, Chiang MY. (2013) Convergence of the ZMIZ1 and NOTCH1 pathways at C-MYC in acute T lymphoblastic leukemias. *Cancer Res* 73(2):930–941. <https://doi.org/10.1158/0008-5472.CAN-12-1389>
- Shan J, DSouza SP, Bakhru S, Al-Azwani EK, Ascierio ML, Sastry KS, Bedri S, Kizhakayil D, Aigha II, Malek J. (2013) TNRC9 downregulates BRCA1 expression and promotes breast cancer aggressiveness. *Cancer research* 73(9):2840–2849
- Shaye A, Sahin A, Hao Q, Hunt K, Keyomarsi K, Bedrosian I. (2009) Cyclin E deregulation is an early event in the development of breast cancer. *Breast cancer research treatment* 115(3):651–659
- Shu J, Hui X, Zheng X, Zhao J, Xu Z, Chen Y, Lu C, Li J. (2019) Correlation of FGFR2 rs2981582 polymorphisms with susceptibility to breast cancer: a case-control study in a Chinese population. *J Int Med Res* 47(10):4753–4763. <https://doi.org/10.1177/0300060519869058>
- Tajbakhsh A, Farjami Z, Darroudi S, Ayati SH, Vakili F, Asghari M, Alimardani M, Abedini S, Kushyar MM, Pashar A. (2019) Association of rs4784227-CASC16 (LOC643714 locus) and rs4782447-ACSF3 polymorphisms and their association with breast cancer risk

- among Iranian population. *EXCLI J* 18:429–438. <https://doi.org/10.17179/excli2019-1374>
- Tsai CW, Chang WS, Shen TC, Su CH, Wang HC, Liu LC, Bau DT. (2018) Contribution of excision repair cross-complementing group 1 genotypes to triple negative breast cancer risk. *PLoS One* 13(8):1–11. <https://doi.org/10.1371/journal.pone.0202112>
- Wu Z, Wang P, Song C, Wang K, Yan R, Li J, Dai L. (2015) Evaluation of miRNA-binding-site SNPs of MRE11A, NBS1, RAD51 and RAD52 involved in HRR pathway genes and risk of breast cancer in China. *Molecular Genetics and Genomics* 290(3):1141–1153. <https://doi.org/10.1007/s00438-014-0983-5>
- Yang, Z., Fang, X., Pei, X., & Li, H. (2013). Polymorphisms in the ERCC1 and XPF Genes and Risk of Breast Cancer in a Chinese Population. *Genetic Testing and Molecular Biomarkers* 17(9):700–706. <https://doi.org/10.1089/gtmb.2013.0122>
- Zhang H, Wang Y, Liu Z, Yao B, Dou C, Xu M, Li Q, Jia Y, Wu S, Tu K. (2016) Lymphocyte-specific protein 1 inhibits the growth of hepatocellular carcinoma by suppressing ERK 1/2 phosphorylation. *FEBS Open Bio* 6(12):1227–1237
- Zhang L, Long X. (2015) Association of three SNPs in TOX3 and breast cancer risk: Evidence from 97275 cases and 128686 controls. *Scientific reports* 5:12773–12773. <https://doi.org/10.1038/srep12773>
- Zhang Y, Zeng X, Liu P, Hong R, Lu H, Ji H, Lu L, Li Y. (2017) Association between FGFR2 (rs2981582, rs2420946 and rs2981578) polymorphism and breast cancer susceptibility: a meta-analysis. *Oncotarget* 8(2):3454–3470. <https://doi.org/10.18632/oncotarget.13839>
- Zhao R, Ying MF. (2016) Association between ERCC1 and ERCC2 polymorphisms and breast cancer risk in a Chinese population. *Genet Mol Res* 15(1):1–6. <https://doi.org/10.4238/gmr.15017263>
- Zuo X, Wang H, Mi Y, Zhang Y, Wang X, Yang Y, Zhai S. (2020) The association of CASC16 variants with breast cancer risk in a northwest Chinese female population. *Mol Med* 26(1):1–10. <https://doi.org/10.1186/s10020-020-0137-7>

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