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CHEK2 gene in breast cancer

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ABSTRACT

Checkpoint kinases (Chks) are serine/threonine kinases that are involved in the control of the cell cycle. Two subtypes have so far been identified, Chk1 and Chk2. They are essential components to delay cell cycle progression in all cells and act at all three cell cycle checkpoints. Here we provide more information regarding the CHEK2 gene and its role in breast cancer as well as known mutations that present a higher cancer risk.

Keywords: CHEK2, CHk2, breast cancer, Checkpoint kinase 2, 1100delC

INTRODUCTION

Initially, suspicion was raised about the pathological potential of this gene in 2005.

The CHEK2 gene plays an important role in the encoding of CHk2 kinase (Checkpoint kinase 2). The mode of action of the gene is by inhibiting the entry of the cell into mitosis by stopping it in stage (G1), in response to DNA damage. The role of the gene is to alter the intercellular signal in cases of DNA damage, inducing a prompt phosphorylation response. Specifically, in situations where the action of this gene is inactivated, various types of cancer will occur, including breast cancer [1,2].

ASSESSMENT

Variant I157T involves the substitution of isoleucine for threonine, and this affects several interactions such as the kinase domain of the protein, leading to problems in homodimerization of CHEK2 which is necessary for its activation [3].

The gene is activated by the phosphorylation of Thr68 by ATM, which produces the dimerization of the gene, giving it the ability to function as a kinase. Subsequently, the gene reacts with phosphatase CDC25, protein kinase Ser / THr NEK6, transcription factor FOXM1, protein p53 and BRCA1 or BRCA2. Mutations of CHEK2 or TP53 have been associated with resistance to anthracycline-based chemotherapy in patients with breast cancer. Another study in Chinese women with breast cancer demonstrated that H371Y carriers may have better response to neoadjuvant chemotherapy [4,5].

The cytogenetic region where this gene is located is 22q12.1. The types of cancer that can result from gene mutations are both sporadic and hereditary. Mutations found include R117G, I160M, G167R, G167A and others. Especially the 2 variants associated with oncological pathology 1100delC and I157T. The most common variant in northern Europe is 1100delC. In Poland, another common variant has been discovered that has been associated with lobular carcinoma, I157T [3,6,7,8].

The 1100delC mutation variant was observed in Cowden syndrome and Li Fraumeni syndrome. According to Schmidt et al. the chance of oncological pathology at an older age is lower [6].

Further studies regarding the 1100delC mutation revealed that the absolute risk after a 10 year span, regarding breast cancer in CHEK2*1100delC heterozygotes, summed up to 24%, in women older than 60 years undergoing hormone replacement therapy. The variant CHEK2*1100delC in a heterozygous form is associated with a 3 times higher risk of breast can-

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cer, compared to women in the general population [9,10].

Although mutations in this gene can cause several cancers in various organs, in patients with 1 family member of 1st or 2nd degree confirmed with breast cancer, the chances of developing a type of breast cancer in a lifetime are 28 -37%, but does not increase the risk of developing ovarian cancer.

Mutations in CHEK2 and ATM genes are known to be associated with moderate risk of breast cancer, although an agreement has been reached for reporting truncated variants, in addition to the c.7217T> G ATM mutation [p.Val2424Gly), which is already known for a high risk of breast cancer [1,5].

Comparing the effects of CHEK2 gene mutations to TP53 mutations underlines the importance of the role of CHEK2 in chemoresistance. The findings of Chrisanthar et al. revealed that roughly 50% of the patients with tumours presenting TP53 L2/L3 mutations to be non-responders to primary therapy. They hypothesized that therapy response in tumours presenting TP53 L2/L3 mutations could be caused by pathways acting synchronously. Although no definite conclusion can be drawn from a limited number of cases observed, the fact that CHEK2 not only phosphorylates p53, but also phosphorylates other substrates such as Cdc25A, Cdc25C and E2F1 in response to etoposide-induced DNA damage. It may indicate that inactivation of redundant pathways could take place in parallel. So far attempts to identify single markers and gene expression arrays predicting chemoresistance have not been proven successful [11-13].

PARP (poly adenosine diphosphate-ribose polymerase) is an enzyme that helps repair DNA damage in cells. PARP inhibitors are a type of targeted therapy that works by blocking the protein that repairs DNA damage in cancerous cells, ultimately facilitating their death. Research and clinical trials have widened the use of PARP inhibitors. People with a CHEK2 mutation who have been diagnosed with cancer should ask their physician about PARP inhibitor therapy.

As a sidenote regarding the development of PARP inhibitors, Lynparza (olaparib) is approved to treat men with metastatic prostate cancer and a mutation in the CHEK2 gene. Lynparza can be used to treat men whose prostate cancer has progressed on enzalutamide (Xtandi) or abiraterone (Zytiga) [14,15].

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REFERENCES

1. Boukhatem N. Constitutional Oncogenetics. 1st ed. Wiley, 2021.
2. Bartek J, Lukas J. Chk1 and Chk2 kinases in checkpoint control and cancer. *Cancer Cell.* 2003;3(5):421-429.
3. Huzarski T, Cybulski C, Domagała W et al. Pathology of breast cancer in women with constitutional CHEK2 mutations. *Breast Cancer Res Treat.* 2005;90(2):187-9.
4. Apostolou P, Papasotiriou I. Current perspectives on CHEK2 mutations in breast cancer. *Breast Cancer* (Dove Med Press). 2017;9:331-335.
5. Smith J, Tho LM, Xu N, Gillespie DA. The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. *Adv Cancer Res.* 2010;108:73-112.
6. Schmidt MK, Hogervorst F, van Hien R, Cornelissen S, Broeks A, Adank MA et al. Age - and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. J Clin Oncol. 2016;34(23):2750-60.
7. Nevanlinna H, Bartek J. The CHEK2 gene and inherited breast cancer susceptibility. *Oncogene* 2006;25:5912–19.
8. Muranen TA, Blomqvist C, Dörk T, Jakubowska A, Heikkilä P, Fagerholm R et al. Patient survival and tumor characteristics associated with CHEK2:p.I157T – findings from the Breast Cancer Association Consortium. *Breast Cancer Res.* 2016;18:98.
9. Weischer M, Bojesen SE, Tybjaerg-Hansen A, Axelsson CK, Nordestgaard BG. Increased risk of breast cancer associated with CHEK2*1100delC. *J Clin Oncol.* 2007;25(1):57-63.
10. de Bock GH, Schutte M, Krol-Warmerdam EM, Seynaeve C, Blom J, Brekelmans CT et al. Tumour characteristics and prognosis of breast cancer patients carrying the germline CHEK2*1100delC variant. *J Med Gen.* 2004;41:731-35.
11. Chrisanthar R, Knappskog S, Løkkevik E, Anker G, Østenstad B, Lundgren S et al. CHEK2 mutations affecting kinase activity together with mutations in TP53 indicate a functional pathway associated with resistance to epirubicin in primary breast cancer. *PLoS One.* 2008;3(8):3062.
12. Desrichard A, Bidet Y, Uhrhammer N, Bignon YJ. CHEK2 contribution to hereditary breast cancer in non-BRCAfamilies. *Breast Cancer Res.* 2011;13:119.
13. Ansari N, Shahrabi S, Khosravi A, Shirzad R, Rezaeean H. Prognostic Significance of CHEK2 Mutation in Progression of Breast Cancer. *Lab Med.* 2019;50(3):36-41.
14. https://www.facingourrisk.org/info/hereditary-cancer-and-genetic-testing/hereditary-cancer-genes-and-risk/genes-by-name/chek2/cancer-treatment. Accessed at 19.03.2022
15. Kriege M, Hollestelle A, Jager A, Huijts PE, Berns EM, Sieuwerts AM et al. Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy. *Br J Cancer.* 2014;111:1004–13.