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Evaluation of the Association in the Chek2 Gene with Breast Cancer in the Uzbekistan Population

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KEYWORDS

CHEK2, Ile157Thr (rs 17879961), breast cancer, oncology, polymorphism

ABSTRACT:

A total of 200 cases of breast cancer were diagnosed in our experiment. Patients with stage I-IV breast cancer, aged 30-65 years, who received chemotherapy (the main group) and 100 healthy women (the control group) were selected. Information on histological examination of the tumour and blood biochemistry was obtained from the patients' medical records. DNA was isolated from the blood of women from the main and control groups using the “Ampli Prime Ribo-prep” kits (OOO “Next Bio”, Russia). PCRs were performed on the Corbett Research GRADIENT PALM CYCLER PCR Analysers CG1-96 (Australia) amplifier. The functionally dangerous allele T of the CHEK2 gene Ile157Thr polymorphism was statistically significantly more common in patients with breast cancer than in healthy donors (2.0% and 0.5%, respectively). The safe C allele, on the other hand, was more common in the control group than in the main group (99.5% and 98.0%, respectively).

The aim of the study is to determine the frequency of the Ile157Thr rs17879961 polymorphism of the tumour protein CHK2 in the development of breast cancer in the Uzbek female population, its association with onco markers and the Pro72Arg polymorphism of the Tp53 gene.

Materials and Methods. The quantity and quality of the isolated DNA were checked using a NanoDrop 2000 (Thermo Fisher Scientific, USA) spectrophotometer. Polymerase chain reaction was performed on a Corbett Research GRADIENT PALM CYCLER PCR Analyzers CG1-96 (Australia) amplifier, and statistical analysis of the results was calculated using the statistical computer programs “WinPEPI 2016, Version 11.65” and “EpiCalc 2000 Version 1.02”.

Rusults. A total of 200 women with breast cancer, who formed the main group, and 100 conditionally healthy Uzbek women in the control group, participated in the study. The results of biochemical blood tests of patients and immunohistochemistry (ER, PR, Her2/neu, Ki67) oncomarkers were obtained from the patients' medical records and the association with the CHEK2 gene Ile157Thr polymorphism was examined. The CHEK2 gene Ile157Thr polymorphism C/C (natural) and C/T (heterozygous) genotypes were detected in 200 patients from the main group.

Conclusion. The findings suggest that the G allele and the heterozygous C/G genotype of this polymorphism may be among the factors increasing the risk of breast cancer ($p > 0.05$).

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1. Introduction

1.1. It is known that 5% - 10% of oncological diseases are hereditary[1]. Several genes that determine hereditary predisposition have been identified, and the CHEK2 gene is one of these genes with moderate penetrance[2,1]. The CHEK2 checkpoint kinase is responsible for the synthesis of the CHK2 protein, and selective inhibitors of CHK2 have been shown to reduce the apoptosis process and increase the resistance of healthy cells to chemotherapy and radiation, which is why scientists are increasingly interested in the CHK2 protein[3].

The cell cycle checkpoint kinase 2 (CHEK2) gene (OMIM + 604373) encodes a serine/threonine kinase and is the human homolog of Saccharomyces cerevisiae RAD53 and S. pombe CDS1[4]. The gene was first identified in 1998 and is a polypeptide of 65 kD and 543 amino acid residues.

The CHEK2 gene plays a key role in regulating cell cycle checkpoints induced by DNA damage. In this cascade, CHK2 protein is phosphorylated and activated by ATM, which in turn activates TP53 and BRCA1/2 **(Fig. 1)**, which play important roles in regulating cell cycle checkpoints, apoptosis, and DNA damage repair[5,6]. CHK2 is considered a potential tumour suppressor, and the ATM-Chk2-Cdc25A-Cdk2 cascade is a mechanism that prevents radioresistant DNA synthesis and maintains genome integrity[7].

The CHEK2 gene (also known as CDS1; CHK2; LFS2; RAD53; TPDS4; hCds1; HuCds1; PP1425) is the most widely studied homolog of Rad53 and Cds1. CHK2 is located on the long arm of human chromosome 22q12.1 and is a tumour suppressor gene encoded by the serine/threonine kinase CHK2, which has been described as a gene with moderate penetrance for breast cancer susceptibility[8,9]. The presence of three functional domains of CHK2 is shown in **Fig. 2**: it consists of a Ser/Thr catalytic domain at the C-terminus, a SQ/TQ cluster domain (SCD) at the N-terminus, and an FHA domain with a hairpin head[10].

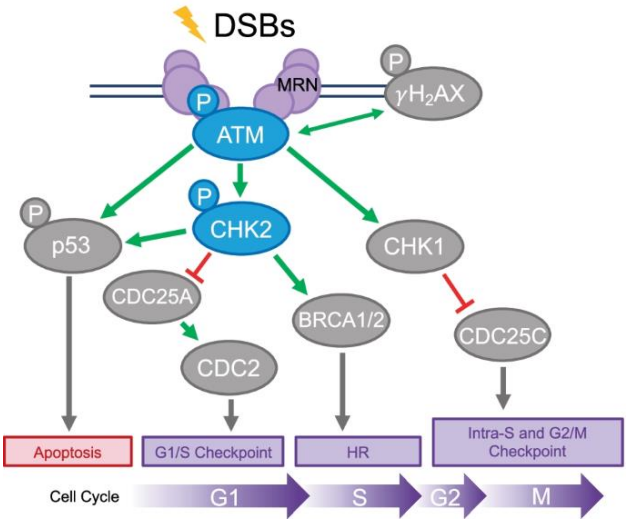

Figure 1. The cellular function of the CHK2 protein is described by8

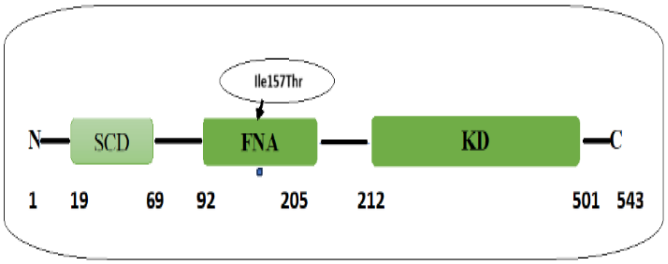

Figure 2. Primary structure of CHEK2

The SCD (residues 19–69) consists of 7 pairs of serine–glutamine or threonine–glutamine (SQ/TQ) residues that are phosphorylated by ATM and other kinases. The SQ/TQ domain contains the T68 residue, which is essential for CHK2 activation[11].

The FHA domain (residues 92–205) forms an 11-stranded β-sandwich structure. The serine–threonine kinase domain (residues 212–501) makes up almost half of CHK2. The KD domain consists of two segments, between which is a cleft that forms the ATP binding site (Fig. 2). The N-terminal segment is predominantly β-sheet and contains the conserved E273 amino acid residue, which is essential for catalytic activity. The C-terminal segment is mainly composed of α-helical structure and serves to transport the CHK2 molecule into the nucleus[12].

As the evidence for the association of the CHEK2 gene with breast cancer increases, the clinical importance of studying this gene and identifying its various variants is

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increasing. According to ClinVar (as of 13.12.2024), there are relatively dangerous (358) and dangerous (125) variants of the CHEK2 gene[13].

Polymorphism Ile157Thr rs17879961 (470T>C, I157T: ATT>ACT).

It is known that there are several polymorphisms of the CHEK2 gene, and in our scientific work we examined the frequency of the Ile157Thr (rs117879961) polymorphism in women of Uzbek ethnicity, who formed the main group of breast cancer patients and control groups. The Ile157Thr missense variant of the CHK2 protein is located in the FHA domain of CHEK2. The Ile157Thr missense variant occurs as a result of the substitution of isoleucine for threonine at the 157 locus of the domain and changes the binding of key substrates. As a result, CHK2 changes its ability to bind to BRCA1, Cds25A and TP53[14]. CDC25A activates the cyclin A/E-CDK2 complex, which causes the cell to enter the S phase of cell division and DNA replication. When DNA is damaged for various reasons, CDC25A is degraded, resulting in failure of DNA replication. The Ile157Thr CHEK2 mutation prevents the degradation of CDC25A, which leads to replication of damaged DNA and proliferation of tumor cells[15].

In patients with breast cancer, the Ile157Thr mutation of the CHEK2 gene causes a disruption of the suppressor function of p53 and the function of p21. Various studies have found that the Ile157Thr missense variant of CHEK2 is closely related to the development of various tumors, including breast cancer, colorectal cancer, colon cancer, testicular cancer, thyroid cancer, and kidney cancer[16,17].

To our knowledge, no scientific studies have been conducted in Uzbekistan on the association of CHEK2 gene polymorphisms with CHD.

1.2. In conclusion, the Ile157Thr mutation impairs the activity of tumour suppressors, which in turn leads to uncontrolled proliferation of tumour cells and a worsening prognosis of the disease[18,19].

1.3. Research objective. In addition, this scientific research is aimed at studying the Ile157Thr polymorphism of the CHEK2 gene in Uzbek women diagnosed with breast cancer.

1.4. The study involved 200 Uzbek women diagnosed with breast cancer and 100 healthy women. Scientific observations were also carried out. All analyses and observations during the studies were carried out without the consent or objection of patients and healthy women. All scientific procedures carried out in this study were carried out with the official permission of the management of the scientific institution.

2. Materials and methods of the study

The study included a total of 200 Uzbek women diagnosed with breast cancer (n=200) and a conditionally healthy control group (n=100). Demographic (ethnicity, age, marital status) and clinical data (blood, histological and biochemical tests) were obtained from the patients' medical history. For this study, blood samples were taken from 200 patients diagnosed with breast cancer based on the results of mammography and histological examination at the Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Republic of Uzbekistan and its Tashkent City Branch, mammalogy department, and 100 conditionally healthy Uzbek women as controls (control group). All molecular genetic tests were conducted at the Department of Molecular Medicine and Cell Technologies at the Republican Specialized Scientific and Practical Medical Center of Hematology. DNA was isolated from peripheral blood of patients and conditionally healthy Uzbek women using the “AmpliPrime Ribo-prep” (OOO “Next Bio”, Russia) kits. The quantity and quality of the isolated DNA were checked using a NanoDrop 2000 (Thermo Fisher Scientific, USA) spectrophotometer. CHEK2 gene I157Thr mutation was performed according to the instructions of the Litex (Russia) genetic test kit. Polymerase chain reaction was performed on a Corbett Research GRADIENT PALM CYCLER PCR Analyzers CG1-96 (Australia) amplifier, and statistical analysis of the results was calculated using the statistical computer programs “WinPEPI 2016, Version 11.65” and “EpiCalc 2000 Version 1.02”.

The following generally accepted abbreviations were also used:

CDC25 - cell division cycle 25 (CDC25)–family proteins. CDK2 - Cyclin-Dependent Kinase2.
PSR - Polymerase chain reaction
KBS - breast cancer

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CHEK2 - checkpoint kinase2
CHK2 - checkpoint kinase protein
DNA - deoxyribonucleic acid
DDR - DNA Damage Response
SSB - single-strand breaks
DSB - double-strand breaks

3. Results

Genes with not only high, but also moderate penetrance play an important role in the occurrence of breast cancer. The CHEK2 gene is in a group of such genes (CHEK 2 Gene – Gene Cards | CHK 2 Protein | CHK 2 Antibody n.d.; VCV000005591.103 – CLIN Var – NCBI n.d.)[20,21]. A total of 200 women with breast cancer, who formed the main group, and 100 conditionally healthy Uzbek women in the control group, participated in the study. The results of biochemical blood tests of patients and immunohistochemistry (ER, PR, Her2/neu, Ki67) oncomarkers were obtained from the patients' medical records and the association with the CHEK2 gene Ile157Thr polymorphism was examined. The CHEK2 gene Ile157Thr polymorphism C/C (natural) and C/T (heterozygous) genotypes were detected in 200 patients from the main group. Only 1 C/T genotype was detected in 100 women from the control group. The analysis of general pathological parameters of 8 patients from the main group was carried out **(Tab. 1)**.

Table 1

Characteristics of common pathological parameters of patients with Ile157Thr polymorphism diagnosed with breast cancer (total of 8 patients)

	Indicators	genotype
		C/T
Tumor size	>2 sm (T1)	2
	2-5 sm (T2)	4
	>5sm (T3)	2
	Tumors that have spread to various sized thoracic organs (T4)	-
Disease stage	I	-
	II	6
	III	2
	IV	-
Lymph node metastases	No lymph node metastases were detected.	2
	Metastases in the axillary lymph nodes	4
	Metastases in the adjacent axillary lymph nodes	2
Spread of metastases to other organs	No metastases in other organs (M0)	8
	Metastases have been detected in other organs (M1)	-
Hormonal receptors	ER	Positive (+) 5
		Negative (-) 3
	PR	Positive (+) 5
		Negative (-) 3
	Her2/neu	Positive (+) 2
		Negative (-) 6
An indicator of the proliferative activity of tumor cells	Ki67	<15% 2
		16-30% 2
		>30% 4

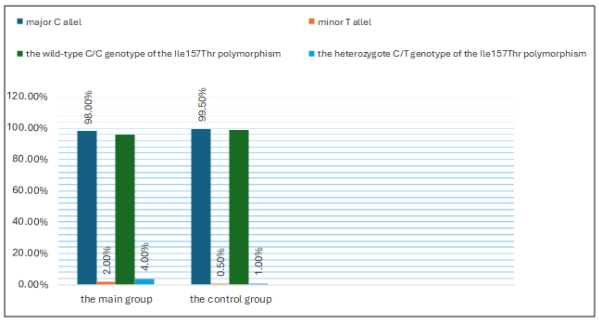

Figure 3. Frequency of CHEK2 gene Ile157Thr polymorphism in the study groups

The functionally dangerous allele T of the CHEK2 gene Ile157Thr polymorphism was statistically more common in breast cancer patients than in healthy donors (2.0% and 0.5%, respectively); ($\chi 2$=2.0; p=0.1; OR=4.1;

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95% CI:0.50-31.69; RR=4.0; 95% CI: 0.50-31.76). The safe allele C, on the other hand, was more common in the control group than in the main group (99.5% and 98.0%, respectively, $\chi2=2.0$; p=0.1; OR=0.2; 95% CI:0.03-1.98; RR=0.9; 95% CI:0.968-1.002) **(Fig. 3)**. Thus, it was found that the dangerous T allele increases the probability of developing breast cancer by 4.1 times and the relative risk by 4.0 times **(Tab. 2)**.

The functionally dangerous allele T of the CHEK2 gene Ile157Thr polymorphism was statistically more prevalent in patients with breast cancer than in traditionally healthy donors (2.0% and 0.5%, respectively). The harmless C allele, on the contrary, was more common in the control group than in the main group (99.5% and 98.0%, respectively). The functionally natural C/C genotype of this CHEK2 gene Ile157Thr polymorphism was found at the highest frequency in the control group - 99.0%, and in the group of patients with CHEK2 - 96.0%. At the same time, the statistical difference threshold reached a significant level: ($\chi2=2.1$; p=0.1; OR=0.2; 95% CI: 0.029-1.966; RR=0.9; 95% CI: 0.936-1.004). It was also observed that the frequency of occurrence of the functionally dangerous heterozygous C/T genotype of the CHEK2 gene Ile157Thr in the main and control groups was equal (4.0% (8/200) and 1.0% (1/100), respectively, $\chi2=2.1$; p=0.1; OR=4.1; 95% CI: 0.50-33.44; RR=4.0; 95% CI: 0.50-31.54).

Of the 200 patients **(Tab. 3)** 192 had the C/C genotype and 8 had the C/T genotype of the Ile157Thr polymorphism of the CHEK2 gene. Of the patients with the C/C genotype, 124 (62%) were ER positive, and the remaining 76 (38%) were ER negative. Of the patients with the C/T genotype, 5 (62.5%) were ER positive and 3 (34.5%) were negative. Of the 192 patients with the C/C genotype, 85 (42.5%) were PR negative, and 115 (57.5%) were positive. Of the patients with the C/T genotype, 5 (62.5%) were PR positive and 3 (34.5%) were negative. Of the 192 patients (with the C/C genotype), 54 (28.1%) were positive for the Her2/neu marker, 138 (71.8%) were negative, 161 (88.4%) were positive for Ki67, and 31 (16.1%) were negative. Of the patients with the C/T genotype, 2 (0.25%) were positive for Her2/neu, 6 (0.75%) were negative, 6 (0.75%) were positive for Ki67, and 2 (0.25%) were negative.

№	Group	Allele frequency				Genotype distribution frequency					
		C		T		C/C		C/T		T/T	
		n	%	n	%	n	%	n	%	n	%
1	Main group n = 200	392	98	8	2	192	96	8	4	0	0
2	Control group n = 100	199	99.5	1	0.5	99	99	1	1	0	0

Table 2

Prevalence of alleles and genotypes of the CHEK2 gene Ile157Thr (rs17879961) polymorphism in the main and control groups.

Note: The natural C/C genotype of the Ile157Thr polymorphism, the heterozygous C/T genotype of the Ile157Thr polymorphism.

Ile157Thr rs17879961		ER status		PR status		Her2/neu status		Ki67 status	
Genotypes	n	+	-	+	-	+	-	+	-
C/C	192	119	73	110	82	54	138	161	31
C/T	8	5	3	5	3	2	6	6	2
Total:	200	124	76	115	85	56	144	167	33

Table 3

Genotopic association of the CHEK2 gene with the Ile157Thr polymorphism in the main group of patients with IGK results (T/T genotype was not detected in the main group)

Note: Ki67 <15 is considered Ki67 negative, Ki67 >15 is considered Ki67 positive

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4. Discussion

Several studies have reported that the frequency of CHEK 2 polymorphisms varies in different populations and ethnic groups[22,6,23]. The Ile157Thr polymorphism of CHK2 in the Brazilian population is 7.2%[24], 1.9% in Latvia, 8.6% in the Baltic regions[25], 5.3% in the Finnish population, 4.8% in Poland[26], 5% in the Slavic population18, and the frequency of the I157Thr missense mutation in the Polish and German populations is 2.2-7.4%[27]. We know that the Ile157Thr missense mutation of the CHEK2 gene is more common in European populations than in Asian populations[28,27]. In particular, when the frequency of the CHEK2 gene Ile157Thr polymorphism was studied in the Turkish population, this indicator was 0%[29], 1.47% in the Burkina Faso (West Africa) population[30], and 1.54% in the Chinese population[31,32].

4.1. Summary of the discussion: The main aim of our study was to investigate the association of CHEK2 gene Ile157Thr (rs17879961) polymorphism with CHEK2 in the Uzbek population. The results showed that out of 200 patients, 192 were carriers of the C/C and 8 of them were carriers of the C/T genotype. The frequency of occurrence of the dangerous T allele in donors with CHEK was statistically higher than in healthy donors (2.0% and 0.5%, respectively; $\chi2=2.0$; p=0.1; OR=4.1; 95% CI:0.50-31.69; RR=4.0; 95% CI: 0.50-31.76). The frequency of the C allele, which was considered safe, was 98.0% in the main group and 99.5% in the control group ($\chi2=2.0$; p=0.1; OR=0.2; 95% CI:0.03-1.98; RR=0.9; 95% CI:0.968-1.002). Thus, it was found that the dangerous T allele increases the probability of developing breast cancer by 4.1 times and the relative risk by 4.0 times. The frequency of occurrence of the functionally dangerous heterozygous G/C genotype of the CHEK2 gene Ile157Thr was equal in the main and control groups (4.0% (8/200) and 1.0% (1/100), respectively, $\chi2=2.1$; p=0.1; OR=4.1; 95% CI: 0.50-33.44; RR=4.0; 95% CI: 0.50-31.54). Carrying this G/C genotype increased the risk of developing CHD by 4.1 times the odds ratio and 4.0 times the relative risk compared to women without this genotype. The Ile157Thr polymorphism of the CHEK2 gene was found to be associated with ER/PR positive CHD.

5. Conclusion

Our research, conducted for the first time in Uzbek women, examines the CHEK2 gene Ile157Thr polymorphism and its association with breast cancer risk. The findings suggest that the G allele and the heterozygous C/G genotype of this polymorphism may be among the factors increasing the risk of breast cancer ($p > 0.05$). Conversely, the C allele and the homozygous C/C genotype appear to serve as protective factors against the development of this pathology. These results indicate that the CHEK2 gene Ile157Thr polymorphism could be a useful genetic marker for assessing breast cancer susceptibility.

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Authors' share in the article: N.V. Khudoyberdiyeva Formulating a problematic scientific topic, conducting it, and coordinating with volunteers. Conducting scientific research, collecting scientific materials. M.M.Abdullayeva and Q.T.Boboyev Organizing and conducting all genetic and biological analysis work carried out in scientific research. Mathematical re-synthesis. Processing and analysis of collected materials. M.J.Toshtemirova organizing and conducting all genetic and biological analysis work carried out in scientific research. Mathematical re-synthesis. Processing and analysis of collected materials. Partially formulate a literature analysis, participate in the discussion section of the article. U.A.Tashbayeva, Kh.M.Rakhimova, N.T.Temirova and D.O.Aminova article design, preparation for publication, technical work. Preparing an article for publication in an appropriate scientific journal and participating in the processes leading up to its publication, financing processes.

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References

1. Ahn, Jinwoo, Marshall Urist, and Carol Prives. 'The Chk2 Protein Kinase'. DNA Repair 2004; 3(8–9): 1039-47. doi:10.1016/j.dnarep.2004.03.033.
2. Badgujar, Nutan V., Bhoomi V. Tarapara, and Franky D. Shah. 'Computational Analysis of High-Risk SNPs in Human CHK2 Gene Responsible for Hereditary Breast Cancer: A Functional and Structural Impact' ed. Amanda Ewart Toland. Plos One 2019; 14(8): e0220711. doi:10.1371/journal.pone.0220711.
3. Lountos, George T., Andrew G. Jobson, Joseph E. Tropea, Christopher R. Self, Guangtao Zhang, Yves Pommier, Robert H. Shoemaker, and David S. Waugh. 'Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2), a Drug Target for Cancer Therapy'. Journal of Structural Biology 2011; 176(3): 292–301. doi:10.1016/j.jsb.2011.09.008
4. Desrichard, Alexis, Yannick Bidet, Nancy Uhrhammer, and Yves-Jean Bignon. 'CHEK2 Contribution to Hereditary Breast Cancer in Non-BRCAfamilies'. Breast Cancer Research 2011; 13(6): R119. doi:10.1186/bcr3062.
5. Agaoglu, Nihat Bugra, Ozden Hatirnaz Ng, Busra Unal, Ozlem Akgun Dogan, Ufuk Amanvermez, Jale Yildiz, Levent Doganay, Arezou A. Ghazani, and Huma Q. Rana. 'Concurrent Pathogenic Variants of BRCA1, MUTYH and CHEK2 in a Hereditary Cancer Family'. Cancer Genetics 2022; 268-269: 128-136. doi:10.1016/j.cancergen.2022.10.144
6. Icen-Taskin, Irmak, Sevgi Irtegun-Kandemir, and Omer Munzuroglu. 'TP53 Rs1042522 Polymorphism and Early-Onset Breast Cancer'. Journal of Research in Medical Sciences 2020; 25(1): 25. doi:10.4103/jrms.JRMS_506_19
7. Falck, Jacob, Niels Mailand, Randi G. Syljuåsen, Jiri Bartek, and Jiri Lukas. 'The ATM–Chk2–Cdc25A Checkpoint Pathway Guards against Radioresistant DNA Synthesis'. Nature 2001; 410(6830): 842–47. doi:10.1038/35071124
8. Stubbins, Ryan J., Sophia Korotev, and Lucy A. Godley. 'Germline CHEK2 and ATM Variants in Myeloid and Other Hematopoietic Malignancies'. Current Hematologic Malignancy Reports 2022; 17(4): 94–104. doi:10.1007/s11899-022-00663-7.
9. Ansari, Narges, Saeid Shahrabi, Abbas Khosravi, Reza Shirzad, and Hadi Rezaeean. 'Prognostic Significance of Chek2 Mutation in Progression of Breast Cancer'. Lab Medicine 2019; 50(3): e36–41. doi:10.1093/labmed/lmz009.
10. Gabant, Guillaume, Alain Lorphelin, Nathalie Nozerand, Charles Marchetti, Laurent Bellanger, Alain Dedieu, Eric Quéméneur, and Béatrice Alpha-Bazin. 'Autophosphorylated Residues Involved in the Regulation of Human Chk2 In Vitro'. Journal of Molecular Biology 2008; 380(3): 489–503. doi:10.1016/j.jmb.2008.04.053
11. Wu, Xianglin, Shelley R. Webster, and Junjie Chen. 'Characterization of Tumor-Associated Chk2 Mutations'. Journal of Biological Chemistry 2001; 276(4): 2971–74. doi:10.1074/jbc.M009727200.
12. Laura Zannini, Domenico Delia, Giacomo Buscemi. CHK2 kinase in the DNA damage response and beyond. Journal Mol. Cell boil. 2014 Dec; 6(6):442-57. doi: 10.1093/jmcb/mju045. Epub 2014 Nov 17.
13. Boonen, Rick A.C.M., Wouter W. Wiegant, Nandi Celosse, Bas Vroling, Stephan Heijl, Zsofia Kote-Jarai, Martina Mijuskovic, et al. 'Functional Analysis Identifies Damaging CHEK2 Missense Variants Associated with Increased Cancer Risk'. Cancer Research 2022; 82(4): 615–31. doi:10.1158/0008-5472.CAN-21-1845.
14. Ge, Yuqiu, Yunyan Wang, Wei Shao, Jing Jin, Mulong Du, Gaoxiang Ma, Haiyan Chu, Meilin Wang, and Zhengdong Zhang. 'Rare Variants in BRCA2 and CHEK2 Are Associated with the Risk of Urinary Tract Cancers'. Scientific Reports 2016; 6(1): 33542. doi:10.1038/srep33542.
15. Michael R. Sargen, Jung Kim, Jeremy S. Haley, David J. Carey, Alisa M. Goldstein and Douglas R. Stewart. "Increased frequency of CHEK2 germline pathogenic variants among individuals with dermatofibrosarcoma protuberans". Genetics in Medicine Open 2024; 2, 101895: doi.org/10.1016/j.gimo.2024.101895
16. Han, Fei-fei, Chang-long Guo, and Li-hong Liu. 'The Effect of CHEK2 Variant I157T on Cancer Susceptibility: Evidence from a Meta-Analysis'.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 2485-2493 | ISSN:2251-6727

DNA and Cell Biology 2013; 32(6): 329–35. doi:10.1089/dna.2013.1970

17. Stolarova, Lenka, Petra Kleiblova, Marketa Janatova, Jana Soukupova, Petra Zemankova, Libor Macurek, and Zdenek Kleibl. 'CHEK2 Germline Variants in Cancer Predisposition: Stalemate Rather than Checkmate'. Cells 2020; 9(12): 2675. doi:10.3390/cells9122675
18. Wagener, Rabea, Carolin Walter, Franziska Auer, Deya Alzoubi, Julia Hauer, Ute Fischer, Julian Varghese, et al. 'The CHK2 Kinase Is Recurrently Mutated and Functionally Impaired in the Germline of Pediatric Cancer Patients'. International Journal of Cancer 2023; 152(7): 1388–98. doi:10.1002/ijc.34390.
19. Liu, Chuan, Ying Wang, Qing-Shui Wang, and Ya-Jie Wang. 'The CHEK2 I157T Variant and Breast Cancer Susceptibility: A Systematic Review and Meta-Analysis'. Asian Pacific Journal of Cancer Prevention 2012; 13(4): 1355–60. doi:10.7314/APJCP.2012.13.4.1355
20. Woodward, Emma R., Elke M. van Veen, Claire Forde, Elaine F. Harkness, Helen J. Byers, Jamie M. Ellingford, and George J. Burghel. 'Clinical Utility of Testing for PALB2 and CHEK2 c.1100delC in Breast and Ovarian Cancer'. Genetics in Medicine 2021; 23(10): 1969–76. doi:10.1038/s41436-021-01234-6.
21. Yu Pei, Xiong Zhu, Jia-Le Zhu, Yu-Bao Han, Hao Zhang, Xiang Zhou, and Lei Yang. 'The Chk2-PKM2 Axis Promotes Metabolic Control of Vasculogenic Mimicry Formation in P53-Mutated Triple-Negative Breast Cancer'. Oncogene 2021; 40(34): 5262–74. doi:10.1038/s41388-021-01933-z.
22. Pavlovica, Kristine, Arvids Irmejs, Margit Noukas, Marili Palover, Mart Kals, Neeme Tonisson, and Andres Metspalu. 'Spectrum and Frequency of CHEK2 Variants in Breast Cancer Affected and General Population in the Baltic States Region, Initial Results and Literature Review'. European Journal of Medical Genetics 2022; 65(5): 104477. doi:10.1016/j.ejmg.2022.104477
23. Santana, Thaiana Aragao, Carolina De Bustamante Fernandes, Ana Carolina Branco Neves Silva, Fernanda Orpinelli Ramos Do Rego, Fernanda Christtanini Koyama, Layla Testa Galindo, and Daniela Tiaki Uehara. 'Frequency and Spectrum of CHEK2 Variants in a Large Brazilian Set of Germline-Tested Patients.' Journal of Clinical Oncology 2023; 41(16_suppl): e22539–e22539. doi:10.1200/JCO.2023.41.16_suppl.e22539.
24. Santana, Thaiana Aragao, Carolina De Bustamante Fernandes, Ana Carolina Branco Neves Silva, Fernanda Orpinelli Ramos Do Rego, Fernanda Christtanini Koyama, Layla Testa Galindo, and Daniela Tiaki Uehara. 'Frequency and Spectrum of CHEK2 Variants in a Large Brazilian Set of Germline-Tested Patients.' Journal of Clinical Oncology 2023; 41(16_suppl): e22539–e22539. doi:10.1200/JCO.2023.41.16_suppl.e22539.
25. Pavlovica, Kristine, Arvids Irmejs, Margit Noukas, Marili Palover, Mart Kals, Neeme Tonisson, and Andres Metspalu. 'Spectrum and Frequency of CHEK2 Variants in Breast Cancer Affected and General Population in the Baltic States Region, Initial Results and Literature Review'. European Journal of Medical Genetics 2022; 65(5): 104477. doi:10.1016/j.ejmg.2022.104477.
26. Badgujar, Nutan V., Bhoomi V. Tarapara, and Franky D. Shah. 'Computational Analysis of High-Risk SNPs in Human CHK2 Gene Responsible for Hereditary Breast Cancer: A Functional and Structural Impact' ed. Amanda Ewart Toland. Plos One 2019; 14(8): e0220711. doi:10.1371/journal.pone.0220711.
27. Mohamad, Suriati, Nurismah Md Isa, Rohaizak Muhammad, Nor Aina Emran, Nor Mayah Kitan, Peter Kang, and In Nee Kang. 'Low Prevalence of CHEK2 Gene Mutations in Multiethnic Cohorts of Breast Cancer Patients in Malaysia' ed. Alvaro Galli. Plos One 2015; 10(1): e0117104. doi:10.1371/journal.pone.0117104
28. Bayram, Süleyman, Mehmet Topaktaş, Hikmet Akkız, Aynur Bekar, and Ersin Akgöllü. 'CHEK2 1100delC, IVS2+1G>A and I157T Mutations Are Not Present in Colorectal Cancer Cases from Turkish Population'. Cancer Epidemiology 2012; 36(5): 453–57. doi:10.1016/j.canep.2012.03.008.
29. Topaktaş, Mehmet, Hikmet Akkız, Aynur Bekar, and Ersin Akgöllü. 'CHEK2 1100delC, IVS2+1G>A and I157T Mutations Are Not

Present in Colorectal Cancer Cases from Turkish Population'. Cancer Epidemiology 2012; 36(5): 453–57. doi:10.1016/j.canep.2012.03.008.

30. Dabre, Soayebo, Abdou Azaque Zoure, Touwendpoulimdé Isabelle Kiendrébéogo, Nayi Zongo, Lanyo Jospin Amegnona, Herman Karim Sombie, and Marc Donald Wilfried Adico. 'Involvement of p.R72P and PIN3 Ins16bp (TP53) Polymorphisms and the I157T (CHEK2) Mutation in Breast Cancer Occurrence in Burkina FasO'. Asian Pacific Journal of Cancer Biology 2023; 8(2): 135–45. doi:10.31557/apjcb.2023.8.2.135-145.
31. Dabre, Soayebo, Abdou Azaque Zoure, Touwendpoulimdé Isabelle Kiendrébéogo, Nayi Zongo, Lanyo Jospin Amegnona, Herman Karim Sombie, and Marc Donald Wilfried Adico. 'Involvement of p.R72P and PIN3 Ins16bp (TP53) Polymorphisms and the I157T (CHEK2) Mutation in Breast Cancer Occurrence in Burkina FasO'. Asian Pacific Journal of Cancer Biology 2023; 8(2): 135–45. doi:10.31557/apjcb.2023.8.2.135-145.
32. Fu, Fenfen, Dongjie Zhang, Li Hu, Senthil Sundaram, Dingge Ying, Ying Zhang, and Shuna Fu. 'Association between 15 Known or Potential Breast Cancer Susceptibility Genes and Breast Cancer Risks in Chinese Women'. Cancer Biology and Medicine 2021; 18: 0–0. doi:10.20892/j.issn.2095-3941.2021.0358.