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The Role Of The Pro47ser Polymorphism Of The Tr53 Gene In Predisposition To Breast Cancer

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ABSTRACT

Numerous scientific studies have been carried out on the predisposition of the Pro47Ser polymorphism of the TR53 gene to breast cancer in women living in most countries of the world. However, no studies have been conducted on the susceptibility of this Pro47Ser gene polymorphism to breast cancer in Uzbek women. In this article, genotyping of the Pro47Ser polymorphism of the TR53 gene was performed for the first time in 207 Uzbek women. According to the results of our study, the functionally dangerous T allele of the Pro47Ser polymorphism of the TR53 gene was statistically significantly higher than that in healthy donors in patients with breast cancer; ($\chi^2 = 8.2$; $p = 0.004$; OR = 11.2; 95% CI: 1.422-88.38; RR = 10.7; 95% CI: 1.382-82.82). The safe C allele, on the other hand, was more common in the control group than in the main group. The natural S / C genotype was found in the control group with a higher frequency than in the control group. However, the limit of the statistical difference reached a significant level: ($\chi^2 = 8.4$; $p = 0.004$; OR = 0.08; 95% CI: 0.01066-0.676; $\chi^2 = 8.2$; $p = 0.004$; RR = 0.1 ; 95% CI: 0.8489- 0.9723). The S / T genotype of this polymorphism significantly

differs in the frequency of occurrence in the main and control groups. Relative risk according to statistical analysis: RR = 10.7; (95% CI: 1.395–82.07) and odds ratio: OR = 11.8; (95% CI: 1.479-93.77). It is known that the minor T allele and the S / T genotype of this polymorphism increase the risk of developing breast cancer by 10.7 times. It should be noted that the unique homozygous genotype of Pro47Ser polymorphism was not identified in patients and control groups studied by T / T.

Thus, the T allele and the C / T genotype of the Pro47Ser polymorphism of the TR53 gene are important factors that increase the risk of breast cancer ($r < 0.05$). The C allele and S / S genotype of this polymorphism are reliable protective markers against the development of this pathology. Therefore, we believe that the Pro47Ser polymorphism of the TR53 gene can be used as important genetic markers in determining the likelihood of developing breast cancer.

KEYWORDS

Tumor suppressor, TR53, rs 1800371 polymorphism, breast cancer, Pro47Ser, polymerase chain reaction, r53.

INTRODUCTION

Breast cancer (BC) is the leading cause of cancer among women, meaning that one in four women (24.2%) diagnosed with cancer is BC -related [1,2]. BC - more genetic disease (defect in BRCA I-II genes), consumed a lot of alcohol, did not have children, became a first-time mother over the age of 30, did not breastfeed, took estrogenic hormonal drugs for more than 1 year , is observed in women exposed to radiation [3,4].

Nowadays, as a result of studying the molecular mechanisms of the emergence and development of BC, ie the study of candidate genes that cause somatic mutations, polymorphisms of BC, there are opportunities for early diagnosis and treatment of the disease. One of them is a genetic modification of the 20 kb, 10 intron and 11 exon oncosuppressor TR53 (OMIM №191170) gene located on the short shoulder of chromosome 17p13.1, the most mutated in BC, including human cancer [5].

Figure 1. The location of the TR53 gene on the chromosome [6].

Start: 7,514,550 bp from pter . End: 7,533,728 bp from pter . Size: 19,178 bases

The TP53 gene is composed of 393 amino acid residues that play a key role in maintaining the integrity of the human genome and transcribes a 2.8 kb long mRNA that transmits nuclear phosphoprotein with a molecular mass of 53 kDa [7,8]. The R53 protein is located in the cell

nucleus and is directly bound to DNA, which is involved in controlling the cell cycle, regulating repair processes, and apoptosis [9,10].

Figure 2. Structure of R53 protein [5].

Because TP53 plays an important role in regulating the cell cycle and ensuring genome stability by preventing mutations, it is often referred to as the “guardian of the genome” or the “cellular gateway to growth and division” [11,12]. Recovers damaged DNA from cell damage, including chemicals, radiation, and ultraviolet light [13,14]. If the DNA is mutated or damaged and it is not possible to correct it, r53 transmits a signal, which induces cell apoptosis and prevents cell division and tumor transformation [15,16].

The TP53 gene is the most mutated and polymorphic gene in cancer, with more than 200 known polymorphisms (SNPs) and 27,580

somatic mutations in this gene [17,18]. Somatic mutations in TR53 occur in 15–71% of breast cancer cases [19,20]. Human susceptibility to cancer and other diseases is associated with genetic polymorphism, which may play an important role in susceptibility to disease [18].

One of these widely studied polymorphisms is the unique polymorphism in which the TP53 gene is formed by the exchange of C> T nucleotides at codon Pro47Ser (g1.11370 C> T, c, 139C> T, 47) of exonin 47 and converts the proline residue of r53 to cerine [18,21].

Figure 3. TR53 gene structure and role of polymorphism investigated [18].

With this in mind, this research paper is devoted to the study of the role of the TR53 gene Pro47Ser polymorphism in the development of breast cancer.

Analysis of the frequency of polymorphism of the TR53 gene Pro47Ser in Uzbek women and evaluation of its role in the pathogenesis of breast cancer.

METHODS OF RESEARCH

207 Uzbek women were included in the study, of whom the main group consisted of 100 patients with breast cancer and the control group consisted of 107 conditionally healthy women. On the basis of the results of mammography and histological examination in the mammology department of the Tashkent branch of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan were taken women diagnosed with breast cancer.

Molecular genetic testing of this study was conducted in the Department of Molecular Medicine and Cell Technology of the Republican Specialized Scientific-Practical

Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan as follows. DNA was isolated from the peripheral blood of the study groups using AmpliPrime Ribo-prep (OOO Next Bio, Russia) and Diatom™ DNA Prep 100 (Laboratory Isogen, Russia). DNA quantity and quality were checked using a NanoDrop 2000 (Thermo Fisher Scientific, USA) spectrophotometer. The detection of the polymorphism of the TR53 gene Pro47Ser was carried out on a polymer chain reaction (PCR) amplifier 2720 "Applied Biosystems" (USA) in accordance with the manufacturer's instructions using a test kit from Litex (01338-100 OOO NPF "Litex" Russia). The presence of PCR products was observed in electrophoresis in 3% agarose gel and transilluminator (Biocom UVT1) equipment [Figure 4].

Figure 4. Electrophoregram of TR43 gene Pro47Ser polymorphism detection

Note: K (-) control, K (+), control, 2,3,5,7,13-row heterozygote Pro / Ser;

4,6,8,9,10,11,12,14,15,16,17 series norm Pro / Pro.

Statistical analysis of the obtained results was performed using statistical computer programs "WINPEPI 2016, Version 11.65" and "EpiCalc 2000 Version 1.02".

In our study, a total of 207 women, including 100 KBS patients with an average age of 34-72 years and 107 conditionally healthy women with an average age of 32-72 years. The following results were obtained on the TR43

gene Pro47Ser polymorphism in our study groups [Figure 5].

Figure 5. Occurrence frequency of TR43 gene Pro47Ser polymorphism in study groups

The figure above describes the distribution levels of alleles and genotypes. At the same time, the functionally dangerous T allele of the TR53 gene Pro47Ser polymorphism was statistically significantly superior in patients with BC compared to traditionally healthy donors (5.0% and 0.5%, respectively); ($\chi^2 = 8.2$; $p = 0.004$; OR = 11.2; 95% CI: 1.422-88.38; RR = 10.7; 95% CI: 1.382-82.82). The safe C allele, by contrast, was more common in the control group than in the main group (99.5% and 95.0%, respectively). The homozygous natural S / S genotype of the TR53 gene Pro47Ser polymorphism was found in patients and

control groups, the highest in the control group - 99.1%, and in the group of patients with BC at 90.0%. However, the statistical difference limit reached a significant level: ($\chi^2 = 8.4$; $p = 0.004$; OR = 0.08; 95% CI: 0.01066-0.676; $\chi^2 = 8.2$; $p = 0.004$; RR = 0.1; 95% CI: 0.8489- 0.9723). The heterozygous S / T genotype of this polymorphism had encounter frequencies in the primary and control groups, 10.0% (10/100) and 0.9% (1/107), respectively. Relative risk according to statistical analysis: RR = 10.7; (95% CI: 1.395-82.07) and probability ratio: OR = 11.8; (95% CI: 1.479-93.77). It is known that the S / T genotype increases the risk of developing

breast cancer by 10.7 times. It should be noted that a unique homozygous genotype of Pro47Ser polymorphism was not identified in patients and control groups studied by T / T.

RESULT AND DISCUSSION

There are several risk genetic factors for the development of breast cancer, one such risk factor being the TR53 oncosuppressor gene and its Pro47Ser polymorphic variant [22,23]. Several studies have examined the involvement of this polymorphism in apoptotic activity and the risk of breast cancer, as well as differences in ethnic origin or race [18,24]. However, there is no data on the susceptibility of the TR53 gene Pro47Ser polymorphism in breast cancer in Uzbek women. With this in mind, the role of the TR53 gene Pro47Ser polymorphism in breast cancer among Uzbek women in this study is of scientific and practical importance.

In our study, the distribution of alleles and genotypes of the TR53 gene Pro47Ser polymorphism was detected in the primary and control groups and compared with the frequency of occurrence in women from other countries. According to the results of our research, according to the genotype analysis of the TR53 gene Pro47Ser polymorphism in ethnic Uzbek women, the S / S genotype occurrence rate was 90.0% in the main group and 99.1% in the control group. The incidence

rate in the S / T genotype BC group was 10.0% and 0.9% in conditionally healthy women. This polymorphism in Kuwaiti women accounted for 99.6% of the S / S genotype in the main group and 100.0% in the control group. S / T genotype The incidence rate in the KBS group was 0.4%, the S / T genotype was not identified in conditionally healthy women, and T / T genotypes were not found in the primary and control groups [25]. In Saudi Arabia, the incidence rate of S / S genotype in women in the primary and control groups was 100.0% [26]. In India, this polymorphism accounted for 99.5% of the S / S genotype in the main group and 100.0% in the control group. The S / T genotype had a occurrence rate of 0.5% in the BC group, and this genotype was not detected in conditionally healthy women, while T / T genotypes were not found at all in women in the primary and control groups [27]. This polymorphism was found in African American women, with a S / S genotype occurrence rate of 96.8% in the main group and 97.2% in the control group. The incidence rate in the S / T genotype BC group was 3.2%, and in conditionally healthy women it was 2.8% [28]. In women in the African diaspora, this polymorphism accounted for 97.6% of the S / S genotype occurrence in the main group and 97.8% in the control group. The incidence rate in the S / T genotype BC group was 2.4%, and 2.2% in conditionally healthy women [28].

Table 1. Allelic and genotypic frequencies of the TR53 gene Pro47Ser polymorphism in breast cancer patients and healthy women in different countries

Countries	Alleles and genotypes	The main group		Control group		OR (95% CI)	p – value	χ^2	authors
		n	%	n	%				
Ўзбекистон	Pro	190	95.0	213	99.5	-	-	-	Avezov N.Sh. and others 2020
	Ser	10	5.0	1	0.5	11.2(1.422- 88.38)	0,004	8.2	
	Pro/Pro	90	90.0	106	99.1	0.08(0.01066- 0.676)		8.4	
	Pro/Ser	10	10.0	1	0.9	11.8(1.479- 93.77)			
	Ser/Ser	0	0.0	0	0.0	-	-	-	
Kuwait	Pro	453	99.8	210	100	1.00	-		Alawadi et al. (2011) DOI: 10.1007/s12032-010-9505-4
	Ser	1	0.2	0	0.0	0.683(0.649-0.720)	>0.999		
	Pro/Pro	226	99.6	105	100	1.00			
	Pro/Ser	1	0.4	0	0.0	0.682 (0.633–0.734)	>0.999		
	Ser/Ser	0	0.0	0	0.0	-	-		
Saudi Arabia	Pro	200	100	200	100	-	-		Al-Qasem et al. (2012) DOI: 10.3892/o.12012.581
	Ser	0	0.0	0	0.0	-	-		
	Pro/Pro	100	100	100	100	-	-		
	Pro/Ser	0	0.0	0	0.0	-	-		
	Ser/Ser	0	0.0	0	0.0	-	-		
India	Pro	399	99.75	400	100	-	-		Sharma S. et al. (2014) DOI:http://dx.doi.org/10.7314/APJCP.2014.15.16.6871
	Ser	1	0.25	0	0.0	-	-		
	Pro/Pro	199	99.5	200	100	-	-		
	Pro/Ser	1	0.5	0	0.0	-	-		
	Ser/Ser	0	0.0	0	0.0	-	-		
Afro- Americans	Pro	6160	98.4	7293	98.6	-	-		Murphy M. E. et al. (2017) doi:10.1038/s41523-017-0007-9
	Ser	100	1.6	103	1.4	1.17(0.84- 1.62)	0.34	0.971	
	Pro/Pro	3030	96.8	3595	97.2	0.868(0.57-1.148)	0.32	0.98	
	Pro/Ser	100	3.2	103	2.8	1.152(0.871-1.523)			
	Ser/Ser	0	0.0	0	0.0	-	-		
Among the African diaspora	Pro	3274	98.8	4013	98.9				
	Ser	40	1.2	45	1.1	1.1(0.710-1.672)	0.695	0.154	
	Pro/Pro	1617	97.6	1984	97.8	0.9(0.596-1.411)	0.694	0.156	
	Pro/Ser	40	2.4	45	2.2	1.1(0.709-1.678)			
	Ser/Ser	0	0.0	0	0.0	-	-	-	

Thus, based on the above analysis, the TR53 gene Pro47Ser polymorphism genotypes in

Uzbek women corresponded to the frequency of genotypes of Asian peoples.

CONCLUSION

Thus, the results confirmed that the Pro47Ser polymorphism of the TR53 gene in Uzbek women is important in the mechanism of development of breast cancer. The T allele and heterozygous C / T genotype of the TR53 gene Pro47Ser polymorphism have been shown to increase the risk of breast cancer, while the C allele and homozygous S / S genotypic variant have reliable protective (protective) functions against the development of this pathology. Hence, it follows that we believe that the Pro47Ser polymorphism of the TR53 gene can be used as important genetic markers in determining the likelihood of developing breast cancer.

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