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The Relationship between Torque teno Virus and TLR2 rs5743708 Polymorphism with Breast Cancer

Majid Komijani[1], Ahmad Hamta[1*], Sajedeh Khanmohamadi Hezaveh[1]

[1]Department of Biology, Faculty of Science, Arak University, Arak, 38156-8-8349, Iran

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***Correspondence**
Email: A-hamta@araku.ac.ir
Tel: +988634173317
Fax: +988634173406

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ABSTRACT

Introduction: Breast cancer is one of the most important causes of mortality in women. Various factors are involved in the development of cancer, including viruses. Toll-like receptors (TLRs) have an essential role in the innate immune system. The present study investigated the relationship between TLR2 *rs5743708* polymorphisms and Torque teno virus (TTV) infection with breast cancer. **Methods:** Blood samples from 80 women with breast cancer and 80 healthy women were collected, and after DNA extraction, the presence of TTV was investigated by a PCR assay and polymorphism in the TLR2 gene (*rs5743708*) was explored using the PCR-RFLP method. Also, the physical and chemical properties of TLR2 protein in the two wild and mutant forms were analyzed using the ExPASy database. **Results:** Statistical analysis showed that there was no significant relationship between the age and TTV infection; TTV infection and breast cancer; the grade of cancer, and TTV infection; while there were significant relationships between *rs5743708* polymorphisms and breast cancer; GG genotype and increased incidence of cancer; TTV infection and *rs5743708* polymorphisms. Also, instability index, aliphatic index, grand average of hydropathicity, and molecular weight of TLR2 protein varied in wild and mutant states. **Conclusions:** Although there was no significant relationship between TTV infection and breast cancer, the *rs5743708* polymorphisms might be involved in TTV infection and breast cancer.

INTRODUCTION

Cancer is the second cause of death in the world after cardiovascular diseases. Half of the men and one-third of women in the United States experience cancer in their lifetime [1]. Breast cancer is considered one of the most common cancers (22% of all cancers) and contributes to 14% of cancer deaths worldwide. The incidence of breast cancer in different countries is increasing [2]

Many factors such as age, genetic susceptibility, early menstruation, and late menopause are involved in breast cancer development [3]. Also, viral infections contribute to 15%-20% of all human cancers [4]. Viruses encode proteins that influence and control the host cellular signaling pathways, affecting proliferation, differentiation, cellular death, and genome integration [4].

Since 1997, new groups of unevolved viruses with negative single-strand genomes of 3.6 to 3.9 kb have been identified, among which are Torque teno virus (TTV), Torque teno mini virus (TTMV), and Torque teno midi virus (TTMDV) in the genus *Aneloviruse*. These three viruses often exhibit high genomic diversity [5]. Torque teno virus, a circular single-strand virus DNA, was first identified in hepatitis patients. Based on ORF1, this virus comprises at least 16 genotypes [6]. The presence of this virus in white globules suggests that it can escape the immune system by infecting the immune system, and due to its similarity with the chicken anemia virus (CAV), it may grow in lymph like CAV [6].

Although there is not much data on the association of this infection with other diseases, high TTV infection rates are a concern [7]. The actual association of TTV pathogenesis with a particular disease is still unclear [7]. The innate immune system is essential for the early detection of invading viruses and activation of immunity in subsequent exposures. Dendritic cells and plasma cells use toll-like receptors (TLRs) to detect viruses [8]. TLRs are suitable membrane proteins for detecting viral components inside and outside the cell [9].

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The TLR2 gene in humans is located in cytogenetic locus 4q31.3 and produces a protein of the same name (also known as CD282) [10]. Studying polymorphisms helps identify the underlying causes of malignancies and cancer and provides new clinical and therapeutic approaches. The single nucleotide polymorphisms (SNPs) rs5743708 in the TLR2 gene represent three genotypes, AA, AG, and GG [11]. TLR2 in heterodimer state with TLR1 or TLR6 recognize different types of microbial ligands [12].

As mentioned above, viruses and the immune system are involved in the development and progress of some cancers [9]. Therefore, the present study aimed to investigate the relationship between *rs5743708* polymorphism and TTV infection and their association with breast cancer.

MATERIALS AND METHODS

Sample collection. The Ethics Committee of the Arak University of Medical Sciences approved this study (ARAKMU.REC.1395.288). Sampling was performed from May to Sep. 2018 at the Ayatollah Khansari Hospital, Arak. Blood samples were taken from 80 women with breast cancer and 80 healthy women and kept at -40°C. Information such as age, tumor grade, residence, and educational level was retrieved from the patients' clinical records.

DNA Extraction. The DNA extraction from whole blood was done according to the Erizole Kit protocol (Rena-Iran). The quality of the extracted DNA was examined by spectrophotometer. Finally, the extracted DNAs were stored at -20 °C until used.

Virus detection. Primers from previous studies were deployed to identify TTV in the samples using a PCR assay (Table 1). All 25 µl reactions included 1 µl of each primer (10 pmol), 0.4 µl of dNTPs (25 mM), 5 µl of extracted DNA, 2.5 µl of 10X *Taq* buffer (Sina Gene Iran), 1 µl of $MgCl_2$ (25 mM), 0.2 µl of Smar *Taq* DNA polymerase enzyme (Sina Gene, Iran) and water to the final volume. Ten microliters of PCR products were electrophoresed in 2% agarose gels containing the Safe stain, and amplicon sizes were estimated alongside a 100 bp DNA ladder.

Genotyping of *TLR2*. The TLR2 *rs5743708* polymorphisms comprise three genotypes, AA, AG, and GG. The genotypes of this polymorphism were detected by a nested PCR-RFLP assay using primers from previous studies (Table 1). All reactions included 0.6 µl of each primer (10 pmol), 0.4 µl of dNTPs (2.5 mM), 2 µl of target DNA, 2.5 µl of 10X Taq buffer, 0.5 µl of $MgCl_2$ (2.5 mM), 0.2 µl of Smar *Taq* DNA polymerase enzyme, and water to 25 µl final volume. Ten microliters of PCR products were electrophoresed in 2% agarose gels containing the Safe stain, and amplicon sizes were estimated alongside a 100 bp DNA ladder. The products from the second stage of nested PCR were digested by the *Pst*I enzyme [13]. The reactions included 2.5 µl of buffer, 5 µl of amplified product and 0.5 µl of *Pst*I enzyme, and 17 µl of water. The digestion was performed at 37 °C for three hours, and the products were electrophoresed on 3% agarose gel. The genotypes were determined based on the produced pattern.

Physicochemical analysis of protein structure TLR2. The physical and chemical properties of the protein related to the *rs5743708* polymorphism were examined in the mutant and wild form in the ExPASy database (https://web.expasy.org/protparam/).

Table 1. Primer sequences annealing temperatures and amplicon size for TTV detection and rs5743708 genotyping.

Virus/SNP	Sequence (5' to 3')	PCR Program (30Cycle)	Amplicon Size (bp)	Reference
rs5743708	F: GCTACGTCACTAACCACGT R: CTBCGGTGTGTAAACTCACC	Denaturation: 94°C, 60 sec Annealing: 55°C, 45 sec Extension: 72°C, 60 sec	199	[35]
TTV	External F: CGGAATGTCACAGGACAGC R: GGACTTTATCGCAGCTCTCAG	Denaturation: 94°C, 60 sec Annealing: 51°C, 45 sec Extension: 72°C, 60 sec	605	[11]
	Internal F: GCCTACTGGGTGGAGAACCT R: GGCCACTCCAGGTAGGTCTT	Denaturation: 94°C, 60 sec Annealing: 53°C, 45 sec Extension: 72°C, 60 sec	340	

Statistical analysis. The results were analyzed by SPSS software, version 20, using Chi-square test, and p-values ≤0.05 were considered statistically significant, and odds ratio (OR) was calculated with 95% confidence interval through the statistical method of logistic regression.

RESULTS

The mean age of the patients was 49 years. The youngest patient in this study was 26, and the oldest was 86 years old. Among the studied patients, 5, 28, 31, and 4 had cancers with grades I, II, III, and IV, respectively, and 12 had no information.

TTV detection. Among the 80 healthy individuals and 80 cancer patients, 60 (75%) and 56 (70%) had a TTV infection, respectively. Our statistical analysis results showed no significant relationship (P=0.479 and X^2=0.502) between TTV infection and breast cancer.

The mean age of women infected with TTV was 45.8 years, and the mean age of those without this virus was

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48 years. The T-test results showed no significant relationship between age and TTV infection (*P*= 0.334 and T= 0.970). Also, There was no significant relationship between cancer grade and TTV infection (P= 0.954 and X^2= 0.331).

Genotyping of *TLR2*. According to the obtained results, the frequency of different genotypes of the *rs5743708* polymorphism was different in healthy and patient groups (Table 2) and statistical analysis showed a significant relationship between this polymorphism and breast cancer (X^2= 14.423 and *P*= 0.001). Allele A was associated with a reduced risk of incidence of cancer phenotype and had a higher rate in healthy individuals (OR= 1.506, X^2= 10.995, and *P*= 0.001). The AG genotype has a higher rate among healthy individuals (OR= 1.777, X^2= 12.911 and *P*= 0.000); on the other hand, the GG genotype has a higher rate among women with cancer (OR= 0.491, X^2= 13.592 and *P*= 0.000). The difference in AA genotype between the healthy and cancer groups was not significant (OR= 0.695, X^2= 0.36, and *P*= 0.548).

Table 2. Distribution of alleles and *rs5743708* genotypes among patients and controls

Group	Distribution of genotypes			Distribution of alleles	
	GG	AG	AA	G	A
	Number (%)				
Patients	64 (80.0)	11(13.8)	5 (6.3)	115 (71.87)	45 (28.13)
Controls	42 (52.5)	31 (38.8)	7 (8.8)	139 (86.87)	21 (13.13)
Total	106 (66.3)	42 (26.3)	12 (7.5)		

Relationship between TTV infection and *rs5743708* polymorphism. There was a significant relationship between virus infection and the *rs5743708* polymorphism (*P*= 0.000, X^2= 16.441). In other words, individuals with a co-dominant phenotype (AG) were more likely to be infected with TTV (Table 4).

Physicochemical analysis of protein structure. The TLR2 protein physicochemical structure was examined in the ExPASy database for wild and mutant types (Table 3), with G and A representing wild and mutant types, respectively. Our results showed that amino acid changes in the TLR2 protein caused no changes in the isoelectric pH of this protein. Also, the GRAV index, which indicates the degree of the protein tendency to non-polar environments, was more positive in the mutant state. As a result, the tendency of this protein in the mutant state to non-polar environments has slightly increased. Also, the aliphatic index increased in this protein in the mutant state, indicating increased hydrophobicity and temperature tolerance after mutation in the genome. Moreover, the instability index in the TLR2 protein showed an increase in the mutant type, indicating a decrease in the stability of this protein (Table 3). In general, except for length and PI, the rest of the studied indices for the TLR2 protein in two wild and mutant types (SNPs *rs5743708*) had changed, which may affect TLR2 protein function.

Table 3. Computation of various physical and chemical parameters in wild and mutant *rs5743708* types in TLR2 protein.

PI	GRAVY[2]	Aliphatic index	Instability index	Number of amino acids	Molecular weight	Gene type[1]
6.17	-0.117	101.07	40.32	784	89823.57	TLR2(G)
6.17	-0.115	101.20	40.53	784	89837.59	TLR2(A)

1: G is the wild-type allele, and A is the mutant allele
2: Grand average of hydropathicity

Table 4. Frequency of TTV and *rs5743708* genotypes.

Genotype	TTV infection					
	All cases		Control		Patient	
	Number (%)		Number (%)		Number (%)	
	P	N	P	N	P	N
GG	73 (45.6)	33 (20.6)	28 (35)	14 (17.5)	45 (56.2)	19 (23.7)
AG	35 (21.8)	7 (4.3)	28 (35)	3 (3.7)	7 (8.7)	4 (5)
AA	8 (5)	4 (2.5)	4 (5)	3 (3.7)	4 (5)	1 (1.2)

P= Positive, N= Negative

DISCUSSION

No thorough investigation is available on the TTV role in the development and progression of cancers, while infection with this virus is common among people and has a similar distribution worldwide [14].

The immune system always fights viral infections, and one of the innate immune system molecules involved in the identification of viruses is TLRs [8]. In addition to their role in defending invasion against pathogens, TLRs have antitumor effects.

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In the present study, we found no association between TTV and cancer (*P*= 0.479).

Some studies have investigated the relationship between human *anelloviruses* and breast cancer [15, 16]. Among 162 biopsy specimens from various cancers and intestinal polyps, 54.3% had TTV infections. The presence of this virus in hypopharynx, larynx, endometrial, ovarian, and bladder cancers ranged from 14 to 35%, and in digestive system cancers (stomach, colon, and rectum) and intestinal polyps ranged from 57% to 100%. Lung cancers, breast cancers, multiple myelomas, and leukemia with 68.4%, 50%, 85.7%, and 53.3% also showed a high prevalence of TTV infection. Since normal control tissues were not included in the study, no conclusions could be made about the possible relationship between virus infection and carcinogenesis. On the other hand, this study found new TTV types; in some cases, there were up to five different virus types in one tumor, which needs more attention [17].

Tokita *et al.* (2002) measured TTV DNA viral load in 237 patients with hepatocellular carcinoma; among them, 18 (8%) had a low viral load, 87 (37%) a moderate viral load, and 132 (56%) had a high viral load. The results suggested that a high TTV load was associated with HCC hepatocellular carcinoma complications [18].

Studies showed that this virus probably affects leukemia and lymphoma in children [19]. In addition to different types of lymphoma, the TTV genome has been identified with similar rates in healthy individuals, and the virus also occurs in non-cancerous cells. TTV is believed to infect T lymphocytes and plays a role in the development of lymphomas [20].

Investigating TTV in 46 Hodgkin's lymphoma (HL) patients and 19 healthy individuals (all 15-34 years old) exhibited the virus in 52% of patients and 60% of the control group, suggesting a possible role for TTV in the HL pathogenesis in young adults [21].

Another study suggested that TTV infection may be associated with the development of lung cancer [22].

Investigation of endothelial nitric oxide synthase (eNOS), angiotensin-converting enzyme (ACE), angiotensin II type I receptor (AGTR1) polymorphisms, and TTV genome in 100 women with breast cancer and 100 healthy women showed that TTV infection in women with breast cancer had significantly higher rates of *eNOS bb* variant and *ACEI* variant [16].

Apart from some similarities in our results and other studies, differences between this study and other studies may be due to differences in TTV distribution at different geographic regions. The primers utilized in PCR can also influence the results due to the variations in TTV strains. Also, differences in study results may be due to the type of cancer and the type of tissue being studied.

Recent studies on the relationships between TTV and the host immune system have led to new hypotheses for the potential pathological mechanisms of TTV. TTV escapes the immune system or assists other microorganisms in pathogenesis, probably affecting the NF-κB pathway [23]. Another study has shown the TTV's role in reducing interferon response and inhibiting interferon signaling by producing microRNAs [24].

TLRs play an essential role in regulating innate immunity. Ligand connection to TLRs activates downstream signaling cascade and causes the activation of several other genes. TLR2 in heterodimer state with TLR1 or TLR6 detects different types of microbial ligands [25]. Our results showed that TLR2 polymorphism was significantly related to breast cancer (*P*=0.001). The frequency of *rs5743708* (G/A) polymorphism for allele A in patients and healthy individuals was 13.1% and 28.1%, respectively, and for allele G in patients and the control group was 86.9% and 71.9%, respectively. Our statistical analysis showed a significant relationship between allele frequency and breast cancer (*P*= 0.001). In patients and controls, the frequency for AA genotype was 6.3% and 8.8%, AG genotype 13.8% and 38.8%, and GG genotype 80% and 52.5%. Statistical analysis results showed a significant relationship between breast cancer and GG and AG genotypes (*P* = 0.000). In other words, AG genotype was more frequent in healthy people, while GG genotype was more observed in people with breast cancer and therefore seemed to be involved in developing breast cancer. In the present study, the AA genotype was not associated with susceptibility to breast cancer.

Kutikhin *et al.* (2013), reported that TLR2 gene polymorphism is probably related to the risk of lymphoma, cervical cancer, breast cancer, gastric cancer, colon cancer, liver cancer, gallbladder cancer, and bladder cancer [26].

A study on glioblastoma patients showed that GG genotype in *rs5743708* polymorphism was more frequent among healthy individuals [27], which contrasts our finding indicating the association of GG genotype with breast cancer. A meta-analysis study on 3650 patients mainly with the digestive tract, liver, and prostate cancers and 4629 healthy individuals showed that the polymorphism *rs5743708* was not related to cancer [28]. Real-time PCR examination of *rs5743708* polymorphism in 191 patients with endometrial cancer and 291 controls revealed no role for this polymorphism in endometrial cancer [29]. In a study on 189 patients with hepatocellular carcinoma and 192 patients with HCV, no significant relationship was found between *rs5743708* polymorphism and hepatocellular carcinoma, while there was a significant relationship between this polymorphism and HCV infection [30]. These variations in the studies mentioned above and our results might be due to the cancer types, races, the dual role of TLR2 in causing cancer [28, 31].

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A study in the south of Iran on 150 patients with colorectal cancer and 150 control people showed a significant relationship between the TLR2 *Arg753Gln* polymorphism and colorectal cancer [32]. A meta-analysis study revealed that *rs5743708* polymorphism was related to hepatocellular carcinoma (HCC) and decreased survival of patients with stages III and IV of advanced colon cancer [33]. Therefore, regardless of whether the *rs5743708* polymorphism has a positive or negative effect on cancer, most studies have pointed out the influential role of this polymorphism in cancer.

Nucleotide changes can affect protein structure. Our physicochemical analysis of TLR2 protein in the wild and mutant type of *rs5743708* polymorphism showed no change in the isoelectric pH. Changes in GRAV and aliphatic indices resulted in a higher tendency of this protein to non-polar environments and increased hydrophobicity and temperature tolerance, respectively, in the mutant *rs5743708* type. On the other hand, the instability index in the TLR2 gene increased in the mutant type, decreasing the protein's stability. Although minor, when co-occurring in a protein, these changes can alter the protein function [34], confirmed by our results. For the first time, the present study simultaneously examined the relationship between TTV infection, *rs5743708* polymorphism, and the simultaneous relationship of these two with breast cancer. Future studies can elucidate the relationship between various types of this virus in different cancers and their relationship with different TLR polymorphisms.

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CONFLICT OF INTEREST

The athors declare that there are no conflicts of interest associated with this manuscript.

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