



# The Association of *TLR2* and *TPA* Genetic Polymorphisms With Colorectal Cancer Risk

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## Abstract

**Background/Aim:** Colorectal cancer is the second most common cancer in women and the third most common in men. It is the third leading cause of cancer death worldwide. Statistics suggest a worrying increase in the incidence of this cancer in the coming years. Many factors, including family history, age, smoking habits and genetic variations, can increase susceptibility to colorectal cancer. Among these influential genetic variations, polymorphisms are of particular importance. This study aimed to investigate the influence of genetic polymorphisms, namely the 23 bp insertion/deletion polymorphism (rs111200466) within the *TLR2* gene and the Alu polymorphism within the *TPA* gene, on the risk of developing colorectal cancer.

**Methods:** The participants in this study consisted of 200 people who had been diagnosed with the disease and 224 healthy people who were carefully matched in terms of age and gender. Polymerase chain reaction (PCR) was the method of choice for identifying the genotypes of the Alu polymorphism in the *TPA* gene and the 23 bp insertion/deletion (I/D) polymorphism in the *TLR2* gene.

**Results:** No significant association was found between the I/D (OR = 0.85, 95 % CI = 0.56 - 1.29,  $p = 0.45$ ) and D/D (OR = 1.06, 95 % CI = 0.44 - 2.55,  $p = 0.88$ ) genotypes compared to the I/I genotype of the *TLR2* gene and the risk of developing colorectal cancer. Similarly, for the Alu polymorphism in the *TPA* gene, no significant association was found between the I/D (OR = 0.97, 95 % CI = 0.57 - 1.68,  $p = 0.94$ ) and D/D (OR = 0.94, 95 % CI = 0.53 - 1.67,  $p = 0.85$ ) genotypes compared to the Ins/Ins genotype in relation to colorectal cancer risk.

**Conclusions:** No statistically significant association was observed between colorectal cancer susceptibility and either the *TLR2* rs111200466 polymorphism or the *TPA* Alu polymorphism in the Iranian population studied.

**Key words:** *TLR2*; *TPA*; Colorectal neoplasms; INDEL mutation; Polymerase chain reaction.

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### Citation:

Javan-Fekr M, Sabzevari MH, Saadat I. The association of *TLR2* and *TPA* genetic polymorphisms with colorectal cancer risk. Scr Med. 2026 Jul-Aug;57(4):817-23.

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## Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third most commonly diagnosed cancer in men. It ranks third in terms of global mortality from cancer.<sup>1</sup> The

statistics show a worrying upward trend in the incidence of colorectal cancer, with the number of new cases predicted to rise from 1.8 million in 2018 to 2.5 million in 2035.<sup>2</sup> Several factors, such

as age, family history, genetic mutations, epigenetic changes, dietary habits, physical activity and tobacco use, have a significant impact on the development of colorectal cancer.<sup>3-7</sup>

The body's own immune system uses pattern recognition receptors to detect microbes that cause disease and damaged cells. One group of these pattern recognition receptors is known as Toll-like receptors (TLR). These receptors make up a group of receptor proteins that can be found on both the outer and the inner surface of cells.<sup>8</sup> TLR2, which is specifically located on the outer surface of cells, has been identified as a member of the Toll-like receptor family. The gene encoding this receptor is located at position 4q31.3 on the long arm of chromosome 4.<sup>8</sup> TLR2 plays a crucial role in recognising disease-causing viruses and bacteria.<sup>9</sup> Downstream in the signalling pathway of TLR2, other signalling pathways such as NF- $\kappa$ B are also activated. Activation of the NF- $\kappa$ B pathway leads to cell proliferation, inhibition of cell death (apoptosis) and enhancement of the inflammatory environment. These factors contribute to tumour initiation and progression, particularly in colorectal cancer, where chronic inflammation and inflammatory bowel disease have been shown to play a role in its malignancy.<sup>10</sup>

The fibrinolytic system is made up of a network of biochemical reactions that ultimately lead to the breakdown of fibrin clots. These reactions take place in the blood plasma.<sup>11</sup> The main enzyme of the fibrinolytic system is tissue plasminogen activator (tPA). This enzyme is a serine protease encoded by the *TPA* gene is located at position 8p12-q11.2.<sup>12</sup> An increase in the activity of this enzyme can lead to bleeding, while a decrease in the activity of this enzyme can lead to thrombosis.<sup>13</sup> A wide range of physiological and pathophysiological processes are controlled by the fibrinolytic system. In cancer, different elements of this system contribute to processes such as angiogenesis, cell migration, metastasis and cancer cell growth.<sup>14</sup>

Genetic alterations in the *TLR2* and *TPA* genes that affect protein expression and functionality may contribute to the development or worsening of cancer, given the functions of these genes. Genetic polymorphisms are an important type of genetic variation that can affect the function or products of genes. Specifically, a deletion polymorphism of 23 bp is located in the promoter region of the *TLR2* gene, suggesting that it may

affect gene expression levels.<sup>15</sup> The *TPA* gene contains an Alu polymorphism in intron 8, which is an insertion (Alu+) or deletion (Alu-) of a 311 bp sequence. Studies have shown that this polymorphism affects the levels of tPA in the bloodstream.<sup>16</sup>

Although the *TPA* Alu Ins/Del polymorphism has primarily been investigated in relation to cardiovascular disorders, there is growing evidence to suggest that the plasminogen activation system also plays a role in colorectal carcinogenesis by influencing extracellular matrix remodelling, angiogenesis, inflammatory responses and interactions with the tumour microenvironment. As the *TPA* Alu polymorphism has been linked to altered circulating tPA levels, it is a promising candidate for further research into its potential influence on individual susceptibility to colorectal cancer.<sup>14, 16</sup>

The *TLR2* rs111200466 polymorphism was selected because it is a functional promoter variant reported to influence *TLR2* transcription and gene expression.<sup>15</sup> TLR2 plays a central role in innate immune responses, recognising pathogen-associated molecular patterns and regulating inflammatory signalling pathways involved in intestinal immune homeostasis. However, dysregulation of TLR2 signalling has been implicated in colorectal carcinogenesis through persistent inflammation and altered host-microbiota interactions.<sup>17</sup> Nevertheless, studies evaluating the association between rs111200466 and colorectal cancer susceptibility have reported inconsistent findings among different populations.<sup>15, 17</sup> Therefore, further studies in larger, more ethnically diverse populations are needed to clarify its potential role in colorectal cancer susceptibility.<sup>15, 17</sup>

This study aimed to investigate the effect of the 23 bp insertion/deletion polymorphism (rs111200466) in the *TLR2* gene and the Alu polymorphism in the *TPA* gene on the susceptibility to CRC.

## Methods

### Participants

The study involved a total of 200 people with CRC, including 72 women and 128 men and 224 healthy cancer-free control subjects, including 65 women and 159 men. CRC were selected from the Hospital of Namazi. The participants were

**Table 1:** Primers used for genotyping *TLR2* 23bp I/D and *TPA* Alu polymorphisms

| Gene        | Primer sequence                           | Annealing temperature (°C) | Product size (bp) |
|-------------|-------------------------------------------|----------------------------|-------------------|
| <i>TPA</i>  | 5'-CCCCACCCTAGGAGAACTTCTCTTT-3' (forward) | 63                         | 424 Ins/ 113 Del  |
|             | 5'-GTAAGAGTTCCGTAACAGGACAGCT-3' (reverse) |                            |                   |
| <i>TLR2</i> | 5'-CACGGAGGCAGCGAGAAA-3' (forward)        | 58                         | 286 Ins / 263 Del |
|             | 5'-CTGGGCCGTGCAAAGAAG-3' (reverse)        |                            |                   |

*TLR2*: Toll-like receptor 2; *TPA*: tissue plasminogen activator;

carefully matched for age, with an average age of 54.4 years for patients and 53.5 years for healthy individuals. All participants gave informed consent and completed questionnaires. The population of Iran is one of the most heterogeneous in the world.<sup>18,19</sup> For this reason, the same ethno-religious group was used for both the selection of patients and control subjects (ie Persian Muslims living in Fars province, southern Iran).

### Extraction of DNA and genotyping

Blood samples were taken from the participants in the study. They were stored in EDTA-containing tubes at -20 °C until further use. The boiling method was used to extract the DNA. Polymerase chain reaction (PCR) was used to determine the genetic variations, specifically the Alu polymorphism in the *TPA* gene and the 23 bp Ins/Del in the *TLR2* gene. Genotyping for the Alu polymorphism in the *TPA* gene and 23 bp Ins/Del in the *TLR2* gene was performed as previously described.<sup>15,20</sup> PCR amplification of the *TPA* rs4646972 polymorphism was performed with an initial denaturation at 94 °C for 2 min, followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 63 °C for 1 min and extension at 72 °C for 1 min. A final extension step was carried out at 72 °C for 5 min. Similarly, PCR amplification of the *TLR2* rs111200466 polymorphism was performed with an initial denaturation at 95 °C for 1 min, followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 58 °C for 1 min and extension at 72 °C for 1 min. A final extension step was carried out at 72 °C for 7 min. The genotyping results were verified by retesting 15 % of the randomly selected samples and a 100 % concordance was found. The primer sequences and PCR conditions used to determine the *TPA* and *TLR2* genotypes are shown in Table 1.

### Statistical analysis

To determine whether the control samples showed Hardy-Weinberg equilibrium, the Chi-square test

was performed for the polymorphisms. Unconditional logistic regression analysis was performed to estimate crude odds ratios (ORs) and 95 % confidence intervals (CIs). Additional adjusted logistic regression analyses were performed to assess the potential influence of confounding variables after controlling for smoking status (including cigarette and hookah use) and family history of cancer. Statistical analyses were performed using SPSS software version 24. The bar for statistical significance was set at  $p < 0.05$ .

## Results

The frequency of genotypes and alleles for the Ins/Del polymorphism of the *TLR2* gene ( $\chi^2 = 0.12$ ,  $df = 1$ ,  $p > 0.05$ ) and also for the Alu polymorphism in the *TPA* gene ( $\chi^2 = 0.045$ ,  $df = 1$ ,  $p > 0.05$ ) did not show any significant deviation from the Hardy-Weinberg equilibrium in healthy people.

According to the results described in Table 2, taking the Ins/Ins genotype as reference in the *TLR2* gene, no significant association was observed between the Ins/Del (OR = 0.85, 95 % CI = 0.56-1.29,  $p = 0.45$ ) and Del/Del (OR = 1.06, 95 % CI = 0.44-2.55,  $p = 0.88$ ) genotypes and the risk of CRC.

In addition, in relation to the Alu polymorphism in the *TPA* gene, no significant association was found between the Ins/Del (OR = 0.97, 95 % CI = 0.57-1.68,  $p = 0.94$ ) and Del/Del (OR = 0.94, 95 % CI = 0.53-1.67,  $p = 0.85$ ) genotypes and the risk of developing CRC when the Ins/Ins genotype was considered the baseline.

Additional logistic regression analyses were performed for both the *TLR2* rs111200466 and *TPA* rs4646972 (Alu) polymorphisms to evaluate the potential confounding effects of smoking status (including cigarette and hookah use) and family

**Table 2:** Distributions of the genotypes of the *TLR2* 23bp I/D and *TPA* Alu polymorphisms in colorectal cancer (CRC) and control subjects

| Genotype                                 | CRC (%)    | Control (%) | OR   | p-value |
|------------------------------------------|------------|-------------|------|---------|
| <b><i>TLR2</i> 23bp I/D polymorphism</b> |            |             |      |         |
| II                                       | 130 (65.0) | 139 (62.1)  | 1.00 | -       |
| ID                                       | 59 (29.5)  | 74 (33.0)   | 0.85 | 0.45    |
| DD                                       | 11 (5.5)   | 11 (4.9)    | 1.06 | 0.88    |
| <b><i>TPA</i> Alu polymorphism</b>       |            |             |      |         |
| II                                       | 34 (17.0)  | 37 (16.5)   | 1.00 | -       |
| ID                                       | 99 (49.5)  | 110 (49.1)  | 0.97 | 0.94    |
| DD                                       | 67 (33.5)  | 77 (34.4)   | 0.94 | 0.85    |

*TLR2*: Toll-like receptor 2; *TPA*: tissue plasminogen activator; OR: odds ratio;

**Table 3:** Adjusted logistic regression analysis of *TLR2* rs111200466 and *TPA* rs4646972 polymorphisms after adjustment for smoking status and family history of cancer

| Gene               | Adjusted variable        | Genotype | OR   | 95 % CI   | p-value |
|--------------------|--------------------------|----------|------|-----------|---------|
| <b><i>TPA</i></b>  | Smoking                  | II       | 1.00 | -         | -       |
|                    |                          | ID       | 0.95 | 0.55-1.65 | 0.869   |
|                    |                          | DD       | 0.86 | 0.48-1.54 | 0.622   |
|                    | Family history of cancer | II       | 1.00 | -         | -       |
|                    |                          | ID       | 1.05 | 0.59-1.86 | 0.862   |
|                    |                          | DD       | 0.87 | 0.47-1.59 | 0.659   |
| <b><i>TLR2</i></b> | Smoking                  | II       | 1.00 | -         | -       |
|                    |                          | ID       | 0.88 | 0.58-1.35 | 0.571   |
|                    |                          | DD       | 0.93 | 0.37-2.33 | 0.880   |
|                    | Family history of cancer | II       | 1.00 | -         | -       |
|                    |                          | ID       | 0.83 | 0.53-1.30 | 0.430   |
|                    |                          | DD       | 1.25 | 0.50-3.01 | 0.632   |

*TLR2*: Toll-like receptor 2; *TPA*: tissue plasminogen activator; OR: odds ratio; CI: confidence interval;

history of cancer. The adjusted odds ratios are presented in Table 3. After adjusting for smoking status and family history of cancer, the estimated odds ratios did not change significantly and no association between either polymorphism and colorectal cancer susceptibility was observed after controlling for these potential confounding factors.

## Discussion

In presented study, the association between the Alu polymorphism in the *TPA* gene and the 23bp I/D polymorphism in the *TLR2* gene with the risk of CRC was investigated. Results indicate that there is no significant association between

these two polymorphisms and the susceptibility to CRC.

Colorectal cancer is a multifactorial disease resulting from the complex interplay of genetic susceptibility, environmental exposure, chronic inflammation, gut microbiota and host immune responses. Therefore, the contribution of a single genetic polymorphism to disease susceptibility is expected to be modest at best and this contribution may vary among different ethnic populations. This heterogeneity may partly explain the discrepancies observed in previous genetic association studies investigating *TLR2* polymorphisms in colorectal cancer. Furthermore, the impact of low-penetrance genetic variants is frequently affected by interactions with environmental factors, which makes replicating genetic

association studies across different populations particularly challenging.<sup>15, 17</sup>

However, in contrast to presented findings, a previous study conducted by Proenca et al in 2016 in the Brazilian population found an association between the Del allele in the *TLR2* gene and an increased risk of CRC.<sup>15</sup> The differences in reported associations between studies may be explained by variations in ethnic background, environmental exposure and host-microbiota interactions, all of which may influence susceptibility to colorectal cancer.<sup>15, 17</sup> The effect of a single susceptibility polymorphism may vary across different populations because colorectal cancer is a multifactorial disease influenced by genetic and environmental factors.<sup>17</sup> To the best of authors' knowledge, no previous study has investigated the association between the *TPA* Alu polymorphism and susceptibility to colorectal cancer.

TLR2 is a key regulator of the immune system's natural defences against infection and has been shown to play a significant role in cancers associated with inflammation.<sup>21</sup> The strongest link between inflammation and cancer development is observed in colorectal cancer; for instance, people suffering from Crohn's disease are more likely to develop colorectal cancer.<sup>22</sup> TLR2 promotes cell proliferation through PI3K/Akt and NF- $\kappa$ B signalling pathways and is associated with increased expression of anti-apoptotic genes such as *BCL2A1*, *WISP1* and *BIRC3*.<sup>21</sup> In a study by Proenca et al, it was demonstrated that the Del allele of the 23bp Ins/Del polymorphism leads to increased TLR2 expression in colorectal tumour tissue compared to adjacent normal tissue. This upregulation contributes to enhanced tumour cell proliferation.<sup>15, 23</sup> Another study showed that *TLR2* is highly expressed in the majority of patients with gastric cancer.<sup>24</sup> Further studies confirm that *TLR2* also promotes tumour cell proliferation in pancreatic and breast cancers.<sup>25, 26</sup>

Given the important role of TLR2 signalling in colorectal tumour development, the biological consequences of functional polymorphisms may be considerably smaller than those observed following experimental activation of the receptor. Therefore, alterations in *TLR2* expression caused by the rs111200466 polymorphism may not necessarily result in measurable differences in colorectal cancer susceptibility in all populations. These observations suggest that, although TLR2 is biologically involved in colorectal carcinogen-

esis, inherited polymorphisms may exert only modest effects on disease susceptibility when evaluated in population-based association studies. These observations suggest that, although *TLR2* is biologically involved in colorectal carcinogenesis, inherited polymorphisms may only have a modest effect on disease susceptibility when evaluated in population-based association studies.<sup>17, 21, 23</sup>

The development of colorectal cancer is marked by an early event: the dysregulation of plasminogen activator activity.<sup>27</sup> Significant alterations in the tissue levels of the plasminogen activation system are observed during colorectal tumorigenesis. As the normal mucosa progresses to adenomatous polyps, then to adenocarcinoma and eventually to metastasis, the levels of uPA, uPA receptor, PAI-1 and PAI-2 increase, while tPA simultaneously decrease.<sup>16</sup> Research studies have shown that the I/I genotype of the Alu polymorphism in the *TPA* gene results in an increased release of tPA from the cells.<sup>28</sup> Elevated levels of tPA can promote carcinogenesis through several mechanisms, including the upregulation of MMP-9, an enzyme that degrades the extracellular matrix (ECM), thereby promoting metastasis.<sup>29</sup>

As smoking and family history are recognised risk factors for colorectal cancer, additional adjusted analyses were performed to evaluate their potential confounding effects. However, adjustment for these variables did not significantly alter the observed associations for either the *TLR2* rs111200466 polymorphism or the *TPA* Alu insertion/deletion polymorphism. This suggests that the absence of significant associations in the present study was not likely to be explained by these confounding factors.

One limitation of the present study is the lack of detailed clinicopathological information, including tumour location, TNM stage, histopathological subtype and metastatic status. Consequently, we were unable to evaluate the potential association between the investigated polymorphisms and specific clinical features or disease progression. Further clarification of these relationships requires future studies with comprehensive clinicopathological data. Future investigations involving larger sample sizes, different ethnic populations and functional analyses are required to further clarify the role of these polymorphisms in colorectal cancer susceptibility.

## Conclusion

This study investigated the association between Alu polymorphisms in the *TPA* gene and 23bp I/D polymorphisms in the *TLR2* gene and their impact on the risk of developing colorectal cancer. In conclusion, no statistically significant association was observed between colorectal cancer susceptibility and either the *TLR2* rs111200466 polymorphism or the *TPA* Alu polymorphism in the Iranian population studied. However, larger, multicentre studies involving different ethnic populations, together with functional analyses, are required to validate these findings and further clarify the biological role of these variants in colorectal carcinogenesis.

## Ethics

The study was approved by the Ethics Committee of Shiraz University's Biology Department (decision No ECBD-SU 9831489, dated 6 December 2021).

## Acknowledgement

The authors are indebted to the participants for their close cooperation. This study was supported by Shiraz University.

## Conflicts of interest

The authors declare that there is no conflict of interest.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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