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Research Article

Genetic Insights into Cervical Cancer: *in silico* approach

Duygu Kırkık[1,2]*, Gurkan Ozbey[3]

[1]Department of Immunology, Hamidiye Medicine Faculty, University of Health Sciences, Istanbul, Turkiye
[2]Department of Medical Biology, Hamidiye Medicine Faculty, University of Health Sciences, Istanbul, Turkiye
* **Corresponding Author Email:** duygu.kirkik@sbu.edu.tr - **ORCID:** 0000-0003-1417-6915

[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Adıyaman University, Adıyaman, Turkiye
Email: gozbey@adiyaman.edu.tr - **ORCID:** 0000-0001-7961-0087

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Abstract:

Cervical cancer is a major global health burden, particularly in developing regions where it remains a leading cause of cancer-related deaths among women. While high-risk human papillomavirus (HPV) types are the primary etiological agents, host genetic factors and their interplay with viral mechanisms significantly influence cervical cancer susceptibility and progression. This study focuses on the genetic contributions of RPL11, TP63, and CDKN2A, key genes involved in cell cycle regulation, apoptosis, and DNA repair.We performed an *in silico* analysis using advanced computational tools to identify and characterize missense single nucleotide polymorphisms (SNPs) in these genes. Protein-protein interaction networks were constructed using STRING and GeneMANIA databases, and disease associations were evaluated using the DISEASES and KEGG pathway databases. Our findings identified significant polymorphisms, such as rs1042522 in TP53, encoding the P72R variant, and rs769412 in CDKN2A, which may modulate cellular responses to HPV oncoproteins, contributing to tumorigenesis. RPL11 was shown to stabilize TP53 through MDM2 inhibition, underscoring its role in tumor suppression, while TP63 was associated with epithelial differentiation and HPV-related infections.These genetic variations may also play a role in HPV-negative cervical cancers, which exhibit distinct molecular profiles. The study highlights the importance of exploring genetic predispositions in cervical cancer to better understand its pathogenesis. These findings provide a foundation for future research into personalized therapeutic strategies targeting genetic and molecular pathways, particularly for cases with unique etiological mechanisms.

1. Introduction

Cervical cancer remains a significant global health challenge, particularly in developing countries where it ranks among the leading causes of cancer-related deaths in women [1]. It is the most common gynecological malignancy worldwide, with an estimated 604,127 new cases and 341,831 deaths reported in 2020, according to GLOBOCAN statistics from the International Agency for Research on Cancer (IARC) [2]. Notably, approximately 87% of cervical cancer cases occur in less developed regions, where disparities in healthcare access contribute to an 18-fold variation in mortality rates across the globe. Factors such as late-stage recurrence, metastasis, and limited access to effective treatments, including radiotherapy, chemotherapy, and combination therapies, further compound the burden of this disease [3].

In recent years, increasing evidence has highlighted the role of genetic polymorphisms in cervical cancer susceptibility, particularly in genes involved in key cellular processes such as the cell cycle, DNA repair, xenobiotic metabolism, and apoptosis [4-6]. Tumor suppressor genes, for example, are frequently associated with increased host susceptibility to cervical cancer when their expression is reduced. Case-control studies have investigated the association of several genes, including TP53, CDKN2A, CDKN1A, and MDM2, with cervical cancer [7], especially in the context of HPV infection. Among these, the TP53 gene, encoding the p53 tumor suppressor protein, has garnered significant attention due to its pivotal role in apoptosis [8]. Notably, studies have explored the

impact of polymorphisms within the TP53 gene, such as the P72R variant, and their association with cervical cancer risk [9]. While some research has reported a link between the P72R polymorphism and increased susceptibility to cervical cancer and adenocarcinoma, others have yielded conflicting results. This inconsistency underscores the need for further investigation to elucidate the precise role of genetic variations in cervical cancer pathogenesis [10-12].

This study aims to conduct *in silico* analysis to identify potential polymorphisms in key genes associated with cervical cancer. By leveraging advanced computational tools, we seek to gain deeper insights into the genetic predispositions underlying cervical cancer and their potential implications for disease risk and progression.

2. Material and Methods

2.1 Protein sequence and missense SNPs retrieval

The analysis was performed using the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/) and the NCBI dbSNP database (https://www.ncbi.nlm.nih.gov/snp/). Protein sequences in FASTA format and single nucleotide polymorphisms (SNPs) for the genes TP53, CDKN2A, CDKN1A, and MDM2 were retrieved from these resources. Particular focus was placed on missense SNPs, as these mutations result in altered protein variants that may induce significant structural changes. Such changes have the potential to reduce binding affinity and disrupt the normal function of these proteins, making them critical targets for further analysis. Advanced bioinformatics tools were subsequently used to evaluate the potential impact of these mutations on protein structure and function [13,14].

2.2 Functional and Physical Interaction Analysis of Genes Similar to TP53, CDKN2A, CDKN1A, and MDM2

To investigate the functional and physical interactions of genes related to TP53, CDKN2A, CDKN1A, and MDM2, the STRING database ((version 11.5) was used with medium confidence score cutoff (≥0.4) for interaction prediction) [15] was utilized to construct a protein association network. Additionally, the GeneMania tool (version 3.5.2) [16] was applied to explore the relationships between TP53, CDKN2A, CDKN1A, MDM2 and other interacting genes. Functional and physical similarity analyses were performed using GeneMania to gain insights into the connections between these genes. The findings obtained through GeneMania were cross-validated using the STRING database to ensure consistency and reliability. All analyses were conducted between December 5–10, 2024**.**

2.3 Variant Analysis of TP63, RPL11 AND CDKN2A

To validate the identified SNPs, the Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org/) was used [17]. This database provides comprehensive allele frequency data and annotations, enabling further evaluation of the potential impact of the selected missense SNPs. By cross-referencing the data, high-confidence variants were identified for downstream structural and functional analysis.

2.4 Pathway and Diseases Analysis of RPL11, TP63, and CDKN2A

Pathway and disease analyses for the RPL11, TP63, and CDKN2A genes were conducted using the KEGG database [18] to identify their roles in key biological pathways, particularly those relevant to cervical cancer. KEGG pathway analysis was accessed via the KEGG API, and disease associations were retrieved from the DISEASES database (JensenLab, 2024 version). The KEGG database enabled systematic mapping of gene functions, highlighting their involvement in processes such as cell cycle regulation, apoptosis, and tumor suppression [18]. To validate these findings, protein-protein interaction networks were constructed using the STRING database [15]. Additionally, the DISEASES resource database was utilized to explore disease associations for these genes, providing insights into their relevance in cervical cancer and other related conditions [19].

3. Results and Discussions

3.1 Functional and Physical Interaction Analysis of Genes Similar to TP53, CDKN2A, CDKN1A, and MDM2

The genes shown in Figure 1 have a critical role in cell cycle regulation, DNA repair and cancer biology. Among the genes in the network, tumor suppressor genes such as TP53, MDM2, CDKN1A, CDKN2A, CDKN2B, CDKN2D, CDKN1B and CDKN1C stand out. Cyclin and cyclin-dependent kinase genes such as CCND1, CCND2, CCND3, CCNE1, CCNE2, CDK2, CDK3, CDK4 and CDK6, which play an important role in cell cycle regulation, are also present in the network.

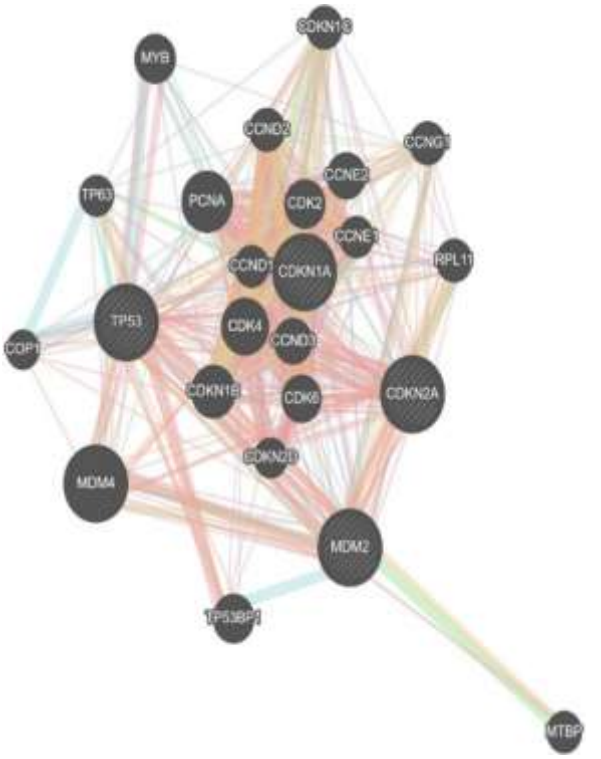

Figure 1. *Genes related to TP53, CDKN2A, CDKN1A, and MDM2. (The figure was retrieved from GeneMania database).*

PCNA is involved in cell proliferation and DNA repair, while MYB is involved in the control of gene expression. RPL11, a ribosomal protein, is associated with tumor suppression and COP1 has ubiquitin ligase activity. In addition, genes such as MDM4, TP53BP1, TP63 and MTBP are involved in the network and are associated with the DNA damage response. The connections between these genes reveal the complexity of cellular mechanisms and the importance of interaction networks in biological functions. The colored links in the network represent different types of interactions: pink indicates physical interactions, purple indicates coexpression, orange indicates predicted interactions, blue indicates co-localization, and green indicates genetic interactions. In this context, genes associated with cell cycle regulation and DNA repair appear to be involved in the network.

3.2 Variant Analysis of TP63, RPL11 AND CDKN2A

Most of the SNPs found in the TP53 gene are rare variants (e.g. rs375444154, rs371409680) and generally have low frequency in the population. This suggests that these mutations are likely to be associated with disease or have a strong biological effect.

One of the most notable variants is rs1042522. This SNP is more commonly observed in the population (C=8193, G=4811) and is a mutation that may affect the function of TP53. This may be more frequently associated with diseases (Table 1).

The total allele frequency of rs769412 was 0.2054 (20.5%), indicating that the variant is relatively common in the population. In the genome analyses, the frequency was slightly lower, 0.1862 (18.6%). However, the Grpmax Filtering AF value was 0.2754 (27.5%), suggesting that it may occur at a higher frequency in population subgroups. This suggests that the variant may be more common in certain genetic subgroups and should be considered in population genetics studies. Furthermore, the number of individuals homozygous for the variant was 32,322, indicating that it has a prevalence level that may require more comprehensive analysis of its genetic effects. The total allele frequency of rs769412 was calculated as 6.2% (0.06219) and reported as 6.1% (0.06097) in exome regions and 7.4% (0.07392) genome wide. This suggests that the variant has a relatively widespread distribution in the population. However, the Grpmax Filtering AF value was 12.5% (0.1248) overall, indicating that the variant may occur at higher frequencies in population subgroups. The total number of homozygous individuals was 3502, which may warrant further investigation of the variant for recessive effects or specific phenotypic outcomes. In exome analyses, the number of homozygous individuals was 2992 and 510 genome-wide. The fact that the variant has been identified in dbSNP (rs769412) and ClinVar (1167676) suggests that it may have genetic and clinical significance. The ClinVar record in particular warrants further investigation to assess the potential for this variant to be associated with disease.

3.3 Pathway and Diseases Analysis of RPL11, TP63, and CDKN2A, MDM2, TP63

Figure 2 is taken from the KEGG Pathway database, describes the effects of high-risk HPV infection on cellular mechanisms. In particular, E6 and E7 oncoproteins are shown to disrupt cell polarity, causing hyperplasia, suppressing apoptosis and driving the cell cycle in an uncontrolled manner. Furthermore, the interaction between MDM2 and p53 is highlighted, detailing the critical role of p53 suppression on cell survival and tumorigenesis. Although the genes it interacts with (genes such as RPL11, TP63 and CDKN2A) are not directly included in the image, these genes are thought to have indirect roles in HPV-related cellular processes [20,21].

Table 1. *TP53 mutations*

Source	rs ID	Alleles	All Alleles	GVS Function
TP53	rs375444154	G>A	A=1/G=13005	missense
	rs372613518	C>G	G=1/C=13005	missense
	rs371409680	C>T	T=1/C=13005	missense
	rs149633775	G>A	A=5/G=13001	missense
	rs28934574	G>A	A=2/G=13004	missense
	rs11540652	C>T	T=1/C=13005	missense
	rs28934575	C>T	T=1/C=13005	missense
	rs144340710	T>C	C=2/T=13004	missense
	rs138983188	G>T	T=1/G=13005	missense
	rs146340390	G>A	A=2/G=13004	missense
	rs375275361	A>T	T=1/A=13005	missense
	rs368771578	A>G	G=1/A=13005	missense
	rs1042522	G>C	C=8193/G=4811	missense
	rs144386518	G>C	C=5/G=13001	missense
MDM2 and TP63	rs1801173	C>T		missense
MDM2 and CDKN2A	rs769412	A>G		missense

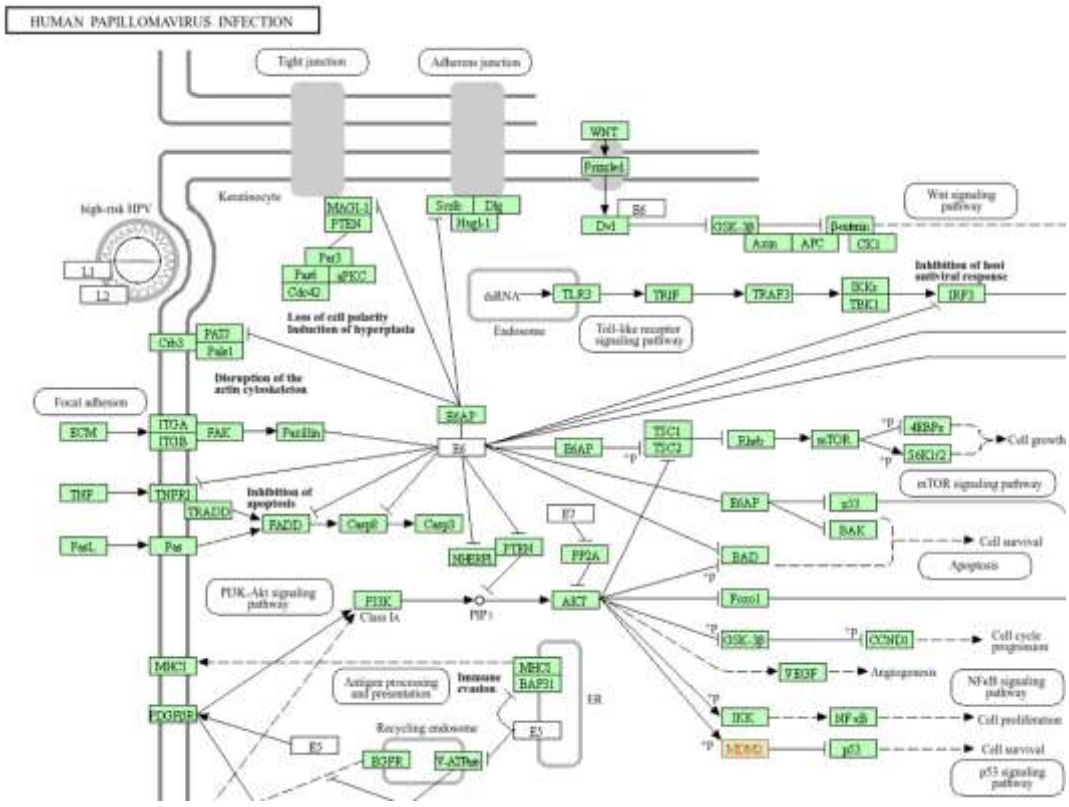

Figure 2. *Pathways of Human Papilloma Virus. (The figure was retrieved from KEGG Pathway database).*

Table 2 shows reported diseases and RPL11, TP63 and CDKN2A genes associations were indicated with Z score and confidence score obtained from the DISEASES database. Z score indicates the density of people of the same age, sex, and genetic background. Confidence score indicates a comparable value for different types and sources of evidence.Cervical cancer remains one of the leading causes of cancer-related deaths among women globally. Its development is primarily driven by high-risk human papillomavirus (HPV) types such

as HPV 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 66, 68, and 70 [22-25].

Table 2. *Reported diseases and RPL11, TP63 and CDKN2A genes associations were indicated with Z score and confidence score obtained from the DISEASES database.*

Gene	Diseases Name	Z-Score	Confidence
RPL11	Cancer	4.7	★★★★☆
TP63	Human papillomavirus infectious	3.8	★★★☆☆
CDKN2A	Papilloma	5.4	★★★★☆

However, the interplay between viral factors, host genetic predispositions, and environmental influences adds a layer of complexity to the disease [26]. While lifestyle factors such as multiple sexual partners, smoking, obesity, and co-infections with *Chlamydia trachomatis* or herpes simplex virus are recognized as significant risks, genetic variations in tumor suppressor and cell cycle-related genes also play critical roles in cervical cancer susceptibility and progression [27,28].

Our study specifically investigated the polymorphisms and disease associations of RPL11, TP63, and CDKN2A, genes that are pivotal in cell cycle regulation, DNA repair, and tumor suppression. These analyses provide valuable insights into their contributions to cervical cancer pathogenesis, particularly in HPV-associated and HPV-negative contexts. To validate the functional impact of the identified polymorphisms, future studies should consider experimental models. For instance, CRISPR/Cas9-mediated gene editing in HPV-positive cervical cancer cell lines could help assess the phenotypic effects of SNPs such as rs1042522 (TP53) and rs769412 (CDKN2A). Additionally, protein interaction disruptions may be investigated using co-immunoprecipitation or yeast two-hybrid assays to evaluate how mutations alter binding with MDM2 or other partners.

Among the notable findings, the rs1042522 polymorphism in the TP53 gene stands out due to its functional impact and prevalence in the population. This variant, encoding the P72R substitution, has been previously linked to cervical cancer susceptibility [29], and our results reaffirm its potential relevance. Polymorphisms such as rs769412 in CDKN2A also emerged as significant due to their relatively high allele frequencies, indicating a role in genetic susceptibility across population subgroups. These variants could potentially modulate cellular responses to HPV oncoproteins, such as E6 and E7, further influencing tumorigenesis [30]. Furthermore, the results suggest that RPL11, a ribosomal protein involved in stabilizing TP53 through MDM2 inhibition, indirectly contributes to tumor suppression. Polymorphisms in RPL11 could potentially compromise this protective mechanism, especially in HPV-driven cancers where TP53 is already targeted for degradation. The disease association analysis reinforces the role of RPL11 in cancer pathways, with a high-confidence connection (Z-score 4.7) to tumorigenesis. TP63, a member of the TP53 gene family, is closely linked to epithelial differentiation and responses to cellular stress, which are critical processes in cervical tissue homeostasis [31-33]. Our analysis revealed its significant association with HPV-related infections (Z-score 3.8), suggesting a potential role in modulating epithelial integrity in HPV-driven carcinogenesis.

CDKN2A, a key regulator of the G1/S cell cycle transition, emerged as a critical gene directly disrupted by HPV oncoproteins [34,35]. Variants like rs769412, which exhibit moderate allele frequencies across populations, may have a significant impact on cell cycle dysregulation caused by HPV E7. The strong association of CDKN2A with papillomas and cervical cancer (Z-score 5.4) underscores its importance as a molecular target for further exploration.

An intriguing aspect of this study is its implications for HPV-negative cervical cancers, which exhibit distinct molecular and genetic profiles. Our findings suggest that genetic variants in RPL11, TP63, and CDKN2A may also contribute to tumorigenesis in the absence of HPV infection. Advanced genotyping and genome-wide association studies could uncover additional polymorphisms or mutations that define these cases, paving the way for novel diagnostic and therapeutic approaches.

4. Conclusions

This study highlights the genetic and functional significance of RPL11, TP63, and CDKN2A in cervical cancer development. Polymorphisms in these genes, particularly those impacting pathways disrupted by HPV oncoproteins, represent valuable targets for further investigation. The interplay between viral mechanisms and host genetic factors underscores the complexity of cervical cancer pathogenesis. Our study specifically investigated the polymorphisms and disease associations of RPL11, TP63, and CDKN2A, genes that are pivotal in cell cycle regulation, DNA repair, and tumor suppression. These analyses provide valuable insights into their contributions to cervical cancer

pathogenesis, particularly in HPV-associated and HPV-negative contexts. To validate the functional impact of the identified polymorphisms, future studies should consider experimental models. For instance, CRISPR/Cas9-mediated gene editing in HPV-positive cervical cancer cell lines could help assess the phenotypic effects of SNPs such as rs1042522 (TP53) and rs769412 (CDKN2A). Additionally, protein interaction disruptions may be investigated using co-immunoprecipitation or yeast two-hybrid assays to evaluate how mutations alter binding with MDM2 or other partners. Future research focusing on these genetic variants could provide deeper insights into personalized risk assessment and therapeutic strategies, particularly for HPV-negative cervical cancers or cases with unique molecular profiles.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
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- **Author contributions:** DK conceptualized and designed the study, conducted bioinformatics analyses, interpreted the data, and wrote the original draft of the manuscript. She was also responsible for preparing the figures and tables and managing the overall coordination of the project. GO contributed to the interpretation of the clinical relevance of the genetic findings, supervised the methodological framework related to gynecologic oncology, and provided critical revisions to the manuscript for intellectual content. Both authors read and approved the final version of the manuscript.
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- **Data availability statement:** The data that supports the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

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