International Journal of Science and Research Methodology (IJSRM)
Volume 29, Issue 6, June 2026 ijsrm.humanjournals.com ISSN: 2454-2008

Analysis of Functional SNPs in P53 and hTERT Genes and Their Association with The Risk of Leukemia Development

Fatema Ali Khan[1], Maliha Faheem[1], Krithika Badri[1], Dr. Vasavi Mohan[1,2]

1- Vasavi Medical & Research Centre, Lakdikapul, Khairatabad, Hyderabad - 500004 Telangana State, India.
2- Department of Genetics, Apollo Diagnostics, AHLL, Balanagar, Hyderabad. India.

Received: 20 April 2026 Revised: 11 May 2026 Accepted: 23 May 2026

ABSTRACT

Background: The TP53 and hTERT genes play critical roles in maintaining genomic stability through regulation of cell cycle progression, apoptosis, and telomere maintenance. Functional polymorphisms in these genes may influence susceptibility to leukemia and disease progression. **Objective:** This study aimed to evaluate the association of TP53 rs1042522 (C>G) and hTERT rs2736100 (C>A) polymorphisms with the risk of leukemia and preleukemic disorders. **Methods:** A total of 270 leukemic/preleukemic patients and 270 healthy controls were enrolled. Genomic DNA was isolated using the silica column method. TP53 rs1042522 was genotyped by PCR-RFLP, while hTERT rs2736100 was analyzed using Tetra-ARMS PCR. Genotype distributions, allele frequencies, Hardy–Weinberg equilibrium, and genetic association models were evaluated. **Results:** TP53 rs1042522 showed a significant association with leukemia risk. Individuals carrying the GG genotype demonstrated an increased risk of leukemia under the recessive model (OR=1.82, 95% CI=1.20–2.76, p=0.0051) and codominant models. The G allele was significantly associated with increased disease susceptibility (OR=1.38, 95% CI=1.09–1.76, p=0.0086). For hTERT rs2736100, the AA genotype was significantly associated with leukemia risk (OR=1.82, 95% CI=1.10–3.01, p=0.0192), whereas the heterozygous CA genotype exhibited a protective effect under the overdominant model (OR=0.56, 95% CI=0.40–0.78, p=0.0008).**Conclusion:** The TP53 rs1042522 GG genotype and hTERT rs2736100 AA genotype were associated with an increased risk of leukemia, while the heterozygous hTERT genotype appeared protective. These findings suggest that genetic variations affecting p53-mediated cell cycle regulation and telomere maintenance may contribute to leukemogenesis and could serve as potential genetic markers for leukemia susceptibility.

Keywords: TP53, hTERT, rs1042522, rs2736100, leukemia, polymorphism, telomere, p53, genetic susceptibility, PCR-RFLP.

Introduction

Cell cycle regulation is crucial for controlled cell division. The tumor suppressor gene *TP53* on chromosome 17q13 is a major tumor suppressor gene partaking in cell cycle regulation. The gene modulates cell cycle arrest, apoptosis, and senescence, and has been implicated in various cancers, as mutations in this gene lead to loss of tumor suppressor activity. The gene also regulates autophagy, metabolism, and the tumor immune microenvironment to suppress cancer development and progression. The *TP53* mutation rate is more than 70% in certain subtypes of cancers, including acute myeloid leukemia having complex karyotypes or CK (Wang, W. et al. 2026).

The p53 gene, also commonly known as the "guardian of the genome," encodes a transcription factor and modulates cell cycle regulation and progression. It plays a crucial role in recognizing DNA damage, helping cells proceed with DNA repair, and regulating the cell cycle at checkpoints. A common single-nucleotide polymorphic variant of p53, rs1042522 in exon 4 at position codon 72, results in a C to G change, changing the triplet codon from CGC-Proline to CCC-Arginine, which impacts the p53 activity. The results of the Pro to Arg amino acid substitution in the proline-rich region affect the p53-mediated apoptosis. The transcriptionally enhanced proline variant leads to G1 phase arrest, whereas the arginine variant is more adept at binding proapoptotic gene promoters to strongly trigger cellular apoptosis and reduce the risk of tumorigenic transformation. The association between the p53 gene codon 72 polymorphism has been associated with the malignant transformation and has been associated with the risk of ovarian, lung, cervical, and colon cancer, as well as prostate cancer. Some of the studies have supported the role of Pro72 with lower cancer risk, while others have supported the Arg72 with decreased cancer risk (Zhang, L., et al 2011).

During replication and cell division, genomic stability is aided by the telomeres, which are the ends of chromosomes. Telomeric DNA consists of the TTAGGG repeat sequence and is crucial for chromosome structural integrity, preventing DNA damage and end-to-end fusion of chromosomes. The short length of telomeres results in chromosome destabilization and genomic instability,

catapulting into cancer development. Telomeres are maintained in cells with the help of an enzyme named Telomerase or terminal transferase, a reverse transcriptase enzyme encoded by the Telomerase reverse transcriptase or *TERT* gene located in 5p15.33, which replenishes the 3′ end of chromosomes by enhancing the synthesis of telomeric extensions. Altered telomerase activity alters telomere length and is associated with the risk of cancer initiation and progression.

The hTERT single-nucleotide polymorphic variant at rs2736100 arises in the second intron as a result of a T > G change and impacts the length of telomeres. The variant has been linked with shortened telomere length in gastric cancer. Cancer meta-analyses studies revealed an increased risk for glioma and lung cancer in individuals with the rs2736100 variant (Li, H. et al 2017). Studies conducted for rs2736100 C/A have linked this variant to telomere length. The study observed that the C-allele is associated with longer telomeres, while the A-allele is associated with shorter telomere length. The dual nature of this variant has been linked with various diseases, and both the alleles individually can predispose towards risk of a disease, depending on its association with telomere length and telomerase activity, as studies have implicated both short and long telomeres in different disease pathophysiology (Snetselaar R et al 2018).

The SNPs in this study, rs1042522 p53 gene and rs2736100 h-tert gene, have been linked to various diseases, and both sites generate polymorphism with dual functional implications, with both sets of alleles being implicated in some or the other disease pathology. The p53 Pro, C-allele variation has been linked to G1 cell cycle arrest and subsequent DNA repair, while the Arg, G-allele variant has been linked to enhanced pro-apoptotic activity. Similarly, the C-allele variant has been associated with longer length of telomeres, and the G-allele has been associated with shortened telomeres; both have opposite actions on telomere length, stability, as well as function, and both forms of variation have been implicated in various diseases. The current study has been carried out to evaluate both these functional SNPs in the context of leukemias, and the risk conferred to leukemia disease and its progression is under investigation in this study.

Materials and Methods

For this study, a total of 270 cases consisting of leukemic and preleukemic samples, along with 270 controls, were selected; patient details and consent, along with details of biopsy smear examination, were taken.

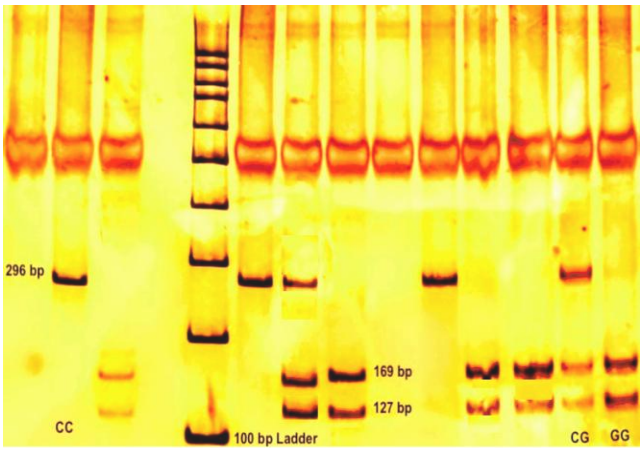
DNA isolation was done using the silica column method. The products were analyzed using the RFLP method for p53 (rs1042522), and the h-tert (rs2736100) gene was analyzed using the T- ARMS PCR method.

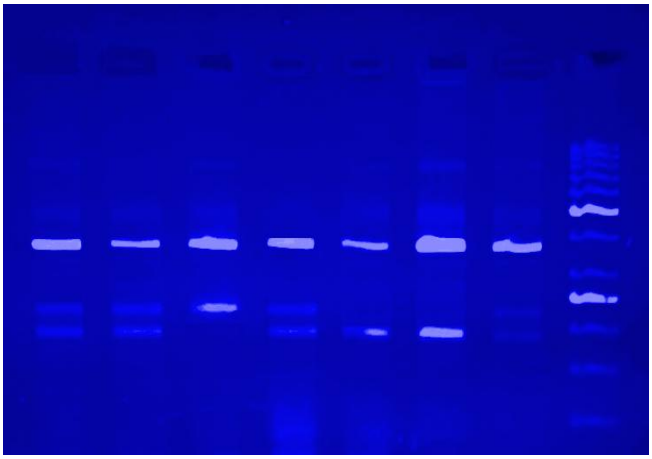
The PCR was standardized using already published primers, given below.

TP53	**rs1042522**	**C > G**	**F: 5'-ATCTACAGTCCCCCTTGCCG-3'** **R: 5'-GCAACTGACCGTGCAAGTCA-3'**	**BstUI**	**C-allele** **G-allele**	**296 bp** **169+127 bp**

hTERT	**rs2736100**	**C > A**	**F in: CAGGGCGGGGGCAAAGCCAA** **R in: AATATTGTTTTCCGTGTTGAGTGTTTTTG** **F out: TCTGTGCATCATAAGCAGAGGTCCCC** **R out:TCTGAAACATTGCTACCCTTGTCCTGAGC**	**A-allele** **C-allele**	**192bp** **233bp** **366bp**

Results





A) PAGE gel showing banding pattern of P53 gene
CC-allele = 296 bp
CG- allele = 296 bp + 169+127 bp
GG-allele = 169+127 bp

B) AGE gel showing banding pattern of h-TERT gene
AA-allele = 192 bp
CC-allele = 233 bp
Control band = 366 bp

STATISTICAL ANALYSIS - P53 gene

Genotype	Observed	Expected	%
HW	78	70.53	28.89%
HT	122	134.88	45.19%
HR	70	63.56	25.93%

Genotype	Observed	Expected	%
HW	94	94.22	34.81%
HT	131	130.55	48.52%
HR	45	45.22	16.67%

Case Group

Results (N = 270)
Allele Frequencies: p = 0.5148, q = 0.4852
χ^2 = 2.4626, p = 0.1166 (in HWE)

Control Group Results (N = 270)
Allele Frequencies: p = 0.5111, q = 0.4889
χ^2 = 3.3070, p = 0.0690 (in HWE)

Genetic Model	Comparison	Odds Ratio (95% CI)	Z-Score	p-value
Recessive	**HR vs (HT+HW)**	**1.75 (1.15-2.66)**	**2.6106**	**0.0090***
Dominant	**(HR+HT) vs HW**	**1.31 (0.91-1.89)**	**1.4762**	**0.1399**
Overdominant	**HT vs (HR+HW)**	**0.87 (0.62-1.23)**	**-0.7760**	**0.4378**
Allelic	**R vs W alleles**	**1.36 (1.07-1.73)**	**2.5066**	**0.0122***
Codominant (HR vs HW)	**HR vs HW**	**1.87 (1.16-3.03)**	**2.5662**	**0.0103***
Codominant (HR vs HT)	**HR vs HT**	**1.67 (1.07-2.62)**	**2.2424**	**0.0249***
Codominant (HT vs HW)	**HT vs HW**	**1.12 (0.76-1.66)**	**0.5822**	**0.5604**

STATISTICAL ANALYSIS- hTERT

Genotype	Observed	Expected	%
HW	97	96.00	35.93%
HT	128	129.99	47.41%
HR	45	44.00	16.67%

Genotype	Observed	Expected	%
HW	79	96.00	29.26%
HT	164	129.99	60.74%
HR	27	44.00	10.00%

Case Group Results (N = 270)
Allele Frequencies: p = 0.5963, q = 0.4037
χ^2 = 0.0634, p = 0.8011 (in HWE)

Control Group Results (N = 270)
Allele Frequencies: p = 0.5963, q = 0.4037
χ^2 = 18.4788, p = 1.7193e-5 (not in HWE)

Genetic Model	Comparison	Odds Ratio (95% CI)	Z-Score	p-value
Recessive	HR vs (HT+HW)	1.80 (1.08-3.00)	2.2571	**0.0240***
Dominant	(HR+HT) vs HW	0.74 (0.51-1.06)	-1.6504	0.0989
Overdominant	HT vs (HR+HW)	**0.58 (0.41-0.82)**	**-3.0991**	**0.0019***
Allelic	R vs W alleles	1.00 (0.78-1.28)	0.0000	1.0000
Codominant (HR vs HW)	HR vs HW	1.36 (0.77-2.38)	1.0656	0.2866
Codominant (HR vs HT)	HR vs HT	**2.14 (1.26-3.63)**	**2.8047**	**0.0050***
Codominant (HT vs HW)	HT vs HW	**0.64 (0.44-0.93)**	**-2.3595**	**0.0183***

DISCUSSION

Statistical analysis for P53 rs1042522 was carried out for Homozygous GG, CC & Heterozygous.

CG as follows (χ^2 = 0.0634, *p* = 0.8011)

rs1042522 CC- Homozygous OR = 1.31 (95 % C.I = 0.91-1.89), z-score = 1.4762; *p*-value = 0.1399

rs1042522 CG- Heterozygous OR = 0.87 (95 % C.I = 0.62-1.23), z-score = -0.7760; *p*-value = 0.4378

rs1042522 GG- Homozygous OR = 1.75 (95 % C.I = 1.15-2.66), z-score = 2.6106 = ; *p*-value = **0.0090***

In the present study, we analyzed the P53 gene SNP rs1042522 C > G polymorphism in pre-leukemic and leukemic cases. This study found the role of GG alleles rs1042522 to be significantly associated with increased risk for development of leukemia with an OR = 1.75 (95 % C.I = 1.15-2.66) and *p*-value <0.0090* . The presence of the homozygous GG-allele in the p53 gene conferred increased risk of leukemia initiation. The Codominant models (HR vs HW) and (HR vs HT) OR = 1.87 (95 % C.I = 1.16-3.03), *p*-value < 0.0103* and OR = 1.67 (95 % C.I =1.07-2.62), *p*-value <0.0249* respectively, were both statistically significant indicating that the presence of G-allele was associated with the risk of leukemia development. The allelic model (R vs W alleles), OR = 1.36 (95 % C.I = 1.07-1.73), *p*-value < 0.0122* was also found to be a statistically significant value.

Statistical analysis for hTERT rs2736100 (C > A) was carried out for Homozygous CC, AA &

Heterozygous CA (χ^2 = 0.0634, *p* = 0.8011)

rs2736100 CC- Homozygous OR = 0.74 (95 % C.I = 0.51-1.06), z-score = -1.6504; *p*-value = 0.0989

rs2736100 CA- Heterozygous OR = 0.56 (95 % C.I = 0.40-0.78), z-score = -3.3498; *p*-value = **0.0019***

rs2736100 AA- Homozygous OR = 1.80 (95 % C.I = 1.08-3.00), z-score = 2.2571; *p*-value = **0.0240***

The other polymorphism we analyzed in this study was the SNP rs2736100 C > A in the h-TERT gene in pre-leukemic and leukemic cases. We found the AA was significant in the cases than the control samples with 1.80 ((95 % C.I =1.08-3.00) p-value <0.0240*. The presence of the homozygous AA-allele in the h-TERT gene was found to be associated with increased risk of development of leukemia. The statistical analysis of the Overdominant model (HT vs (HR+HW) p-value <0.0019* was significant, the heterozygous genotype was more pronounced in the controls compared to cases and OR = 0.58 (95 % C.I = 0.41-0.82) indicating it might be associated with reduced risk of leukemia development.

CONCLUSION

In all the research carried out to date, P53 functions as a tumor suppressor and has been highly significant, as various mutations in the gene have been observed in various cancer conditions. TP53 mutations affect not only the tumor suppressor action of the gene but also initiate oncogenic activity via the mutated gene (Wang, W. et al. 2026).

The p53 mutations and functional variations disrupt gene function, promoting chromosomal and genomic instability, resulting in aneuploidy, translocations, and the acquisition of a gain-of-function feature, which promotes cancer progression and metastasis. The process of telomere capping proteins may protect telomeres from mutated p53 action, which may otherwise lead to telomere damage, breakage, or triggering chromosomal translocations. This view was suggested by the presence of telomeric DNA at the site of translocations. Therefore, normal p53 function might be essential in suppressing chromosomal damage and preventing chromosomal translocation events (Hanel, W., 2012).

A detailed study on the route undertaken by the arg72 association with higher body mass index and diabetes risk analysed the response of this variant with nutrient excess and nutrient deficit pathways. In response to nutrient excess, the arg72 variants were associated with increased fat accumulation and storage. The transactivation of Tnf and Npc1l1 genes via p53 helps control inflammation and cholesterol uptake, respectively. The study also suggested that this change in nutrient uptake and storage was a consequence of cold environmental conditions frequently observed in northern latitudes, allowing individuals to accumulate fats as a fuel source to sustain them during winters when food availability is low. Their mouse model and cell line-based experimental study also indicated that during nutrient stress induced by low glucose levels, the arg72 variant displayed increased stability and triggered activation of the protein cyclin-dependent kinase (Cdk) inhibitor p21 more effectively than the pro72 variant. The presence of the arg72 variant in cells resulted in diverting the cells from cell cycle progression to arrest rather than the usual route leading to apoptosis, which indicates the improved overall chances of cell survival. The arg72 variants, therefore, displayed increased fat accumulation and better survival capabilities under nutrient-induced stress conditions and could also help cancer cells survive and propagate in nutrient-depleted conditions (Kung, C. P et al 2017).

A study presented the role of the arg72 variant in p53 mutants. These mutants at different positions, R175H, R273H, and A138V, when present along with arg72, promoted metastasis by enhancing migration and invasiveness of cancer cells compared to the pro72 variant, in different cancers such as osteosarcoma, prostate, and lungs. Further analysis of gene expression data revealed that the R72 variant was associated with enhanced expression of genes regulated by the crucial metabolic pathway gene PGC-1α, and the codon 72 SNP impacts the ability of p53 to bind and inhibit PGC-1α and trigger the Warburg effect. This feature of the arg72 variant has shown significant association with the risk of breast cancer in women and poor prognosis for breast cancer (Barnoud, T et al 2019).

Human telomerase catalytic subunits (hTERT) are essential for the overall maintenance and stability of telomeres and crucial for genomic stability. Studies have revealed that tert overexpression is conducive to malignant transformation as it promotes cell growth with diminished DNA damage response and p53 inactivation. Whereas loss of Tert activity restores p53 activity and DNA damage response in various cancer cell lines (Jin, X et al 2010). Maintenance of telomere length is essential for overall genomic and chromosomal integrity, and abnormal telomerase activity can therefore lead to derailed structural chromosomal organization with frequent non-reciprocal translocations driving cells towards cancer (O'Sullivan, R. J et al 2010).

Studies conducted in mice have shown that the cells that randomly lose p53 function are able to avoid the senescence checkpoint and proceed with shortened telomeres, and subsequently end up having frequent events of chromosomal fusion and non-reciprocal translocations, accelerating chromosomal instability. Also, an in vivo study conducted in mice reported that null mice not expressing telomerase give rise to abnormal telomeres, and the additional absence of p53 propelled the genome towards oncogenic modifications, triggering early cancer onset. Whilst ~90% of human tumors replenish their telomeres via telomerase activity, some of them use an alternate recombination-mediated route of telomere maintenance via a telomerase-independent process termed ALT (for alternative lengthening of telomeres), highlighting the significance of the p53 pathway in regulating cancer development and reinforcing the importance of telomere integrity and its maintenance via telomerase in cancer development and progression (Deng, Y. et al 2007). The loss of telomeric ends and pro-survival p53 variants can thus contribute to the genomic instability, thereby

increasing the risk of initiation and evolution of pro-oncogenic events in preleukemic cells, leading to their transformation into leukemic cancers.

REFERENCES

1. Wang, W., Liu, X., Liu, H. et al. p53: from understanding its structure to advances in therapeutic targeting. Sig Transduct Target Ther 11, 121 (2026). https://doi.org/10.1038/s41392-025-02549-5
2. Zhang, L., Shao, N., Yu, Q., Hua, L., Mi, Y., & Feng, N. (2011). Association between p53 Pro72Arg polymorphism and prostate cancer risk: a meta-analysis. Journal of biomedical research, 25(1), 25–32. https://doi.org/10.1016/S1674-8301(11)60003-1
3. Hanel, W., & Moll, U. M. (2012). Links between mutant p53 and genomic instability. Journal of cellular biochemistry, 113(2), 433–439. https://doi.org/10.1002/jcb.23400
4. Li, H., Xu, Y., Mei, H., Peng, L., Li, X., & Tang, J. (2017). The TERT rs2736100 polymorphism increases cancer risk: A meta-analysis. Oncotarget, 8(24), 38693–38705. https://doi.org/10.18632/oncotarget.16309
5. Snetselaar R, van Oosterhout MFM, Grutters JC and van Moorsel CHM (2018) Telomerase Reverse Transcriptase Polymorphism rs2736100: A Balancing Act between Cancer and Non-Cancer Disease, a Meta-Analysis. Front. Med. 5:41. doi: 10.3389/fmed.2018.00041
6. Jin, X., Beck, S., Sohn, YW. *et al.* Human telomerase catalytic subunit (hTERT) suppresses p53-mediated anti-apoptotic response via induction of basic fibroblast growth factor. *Exp Mol Med* **42**, 574–582 (2010). https://doi.org/10.3858/emm.2010.42.8.058
7. Kung, C. P., Liu, Q., & Murphy, M. E. (2017). The codon 72 polymorphism of p53 influences cell fate following nutrient deprivation. Cancer Biology & Therapy, 18(7), 484–491. https://doi.org/10.1080/15384047.2017.1323595
8. Barnoud, T., Parris, J. L. D., & Murphy, M. E. (2019). Common genetic variants in the TP53 pathway and their impact on cancer. Journal of Molecular Cell Biology, 11(7), 578–585. https://doi.org/10.1093/jmcb/mjz052
9. O'Sullivan, R. J., & Karlseder, J. (2010). Telomeres: protecting chromosomes against genome instability. Nature reviews. Molecular cell biology, 11(3), 171–181. https://doi.org/10.1038/nrm2848
10. Deng, Y., Chang, S. Role of telomeres and telomerase in genomic instability, senescence and cancer. Lab Invest 87, 1071–1076 (2007). https://doi.org/10.1038/labinvest.3700673

How to cite this article:
Fatema Ali Khan et al. Ijsrm.Human, 2026; Vol. 29 (6): 1-6.

Conflict of Interest Statement: All authors have nothing else to disclose.