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Article

Detection of the Allelic Repeat in the TERT Gene At the Rs2736100 Locus in Diabetic Patients Using PCR and Sequencing Technology

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Abstract: Type 2 diabetes mellitus (T2DM) is a multifactorial condition that impacts multiple organs and might modify telomerase activity, expressed by the hTERT gene, potentially influencing telomere length. The study aimed to investigate of the allelic repeat in the TERT gene at the rs2736100 locus in diabetic patients using PCR and sequencing technology. A total of 4030 subjects (60 Diabetic patients; 10 age-matched healthy controls) were included. Peripheral blood was obtained for molecular analysis. Rs2736100 genotyping was conducted by PCR combined with Sanger sequencing, and genotyped for telomerase reverse transcriptase (TERT) rs2736100 using TaqMan custom SNP genotyping assay. The frequency of the wild-type genotype (GG) which was the references allele was more frequently in control groups at 100% than in patient group 53.33%. The mutant homozygous genotype (AA) appeared only in diabetic patients (1.34%), also the heterozygous genotype (AG) was observed in 33.33% of diabetic patients and not found in healthy individuals.The odds ratio (OR) for the AG and AA genotype was (19.727, 8.454) (95% CI: 1.063 - 365.978, 0.419 - 170.311; p = 0.01). At the allelic level, the G allele was highly frequent in the control group (100%) compared to the diabetic group (70%). Conversely, the A allele was observed in diabetic group only (30%). A single sharp G signal at the polymorphic location confirmed a homozygous wild genotype (GG) in numerous samples. Some chromatograms showed overlapping G and T nucleotide peaks at the same location, indicating a heterozygous genotype. The study investigates three genotypes (homozygous GG, heterozygous GT and mutant homozygous TT). The GT genotype was more frequent with 46% (12/26) followed by GG with 42%(11/26) while the TT was the least frequent with 11%(3/26). Based on allele frequency, G allele (normal) was more frequent with 65% (34/52) than T(mutant) with 35%(18/52). This particular variant, rs2736100, is an intron variant, meaning it is located outside of the gene's coding area. The polymorphism of telomerase reverse transcriptase(TERT) rs 2736100 variants are associated with the susceptibility of type 2 diabetes mellitus.

Keywords: rs2736100, Type 2 diabetes mellitus, hTERT, PCR, homozygous

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder primarily characterized by persistent hyperglycemia resulting from insulin resistance, impaired insulin secretion, or both. Often referred to as non-insulin-dependent diabetes mellitus, T2DM accounts for approximately 90% of all diabetes cases worldwide [1]. It represents a significant and growing public health burden in both developed and developing nations. In 2017, the global prevalence of diabetes was estimated at 8.8%, affecting approximately 415 million individuals, almost double the 4.6% (151 million) reported in 2000. Alarmingly, this figure is projected to rise to 10.4% (642 million) by 2040 [2].

Telomere biology is becoming a crucial element in a growing array of disorders [3]. Research has identified illness correlations with both atypical telomere length and genetic variations associated with telomere biology [4]. Telomeres are non-coding tandem repeats structured by specialized proteins that preserve the stability of chromosomal ends [5]. Moreover, telomeres act as a safeguard against chromosomal shortening, thus preserving essential genetic information [6]. Telomeres can be extended by the ribonucleoprotein telomerase to sustain replicative potential. Telomerase has a catalytic protein component, encoded by the telomerase reverse transcriptase (TERT) gene, and an RNA template, expressed by the telomerase RNA component gene[7].

Type 2 diabetes mellitus (T2DM) is a multifactorial condition that impacts multiple organs and might modify telomerase activity, expressed by the hTERT gene, potentially influencing telomere length[8]. Extensive data indicates that telomeres and telomerase play significant roles in senescence both in vitro and in vivo. The generation of elevated reactive oxygen species disrupts the redox equilibrium, inducing a condition of oxidative stress that ultimately causes premature senescence and telomere attrition [9]. Consequently, diabetes may be linked to the impairment of telomerase activity. Telomerase activity may diminish in the presence of diabetes [8]. Single nucleotide polymorphisms (SNPs) in the TERT region are associated with disorders of telomere biology, including bone marrow failure, aplastic anemia, myeloid dysplastic syndrome, combined pulmonary fibrosis and emphysema, and cancers of hematopoietic or epithelial origins [10]. Recently, two TERT gene single nucleotide polymorphisms (SNPs), specifically rs2736100 and rs2853669, have been previously linked to myeloproliferative neoplasms [11]. The study aimed to investigate of the allelic repeat in the TERT gene at the rs2736100 locus in diabetic patients using PCR and sequencing technology.

Methods

Study design

A total of 40 samples were collected for this study, comprising 30 patients diagnosed with type 2 diabetes mellitus (T2DM) and 10 healthy control subjects [12]. The participants included both males and females, with ages ranging from 20 to 70 years [13]. Sample collection was conducted in September 2025 [14].

The diagnosis of T2DM in patients was confirmed by specialist physicians from the diabetes unit within the hospital, based on clinical assessments and diagnostic criteria [15]. The control group consisted of individuals without a personal or family history of diabetes, ensuring the selection of metabolically healthy participants for comparative analysis [16].

Sample collection

About 2.5 mL of blood was collected into a tube containing EDTA as an anticoagulant [17]. This sample was gently mixed and shaken for 5 minutes to prevent clotting. The tube was then stored at -30 °C until required for DNA extraction to be used in molecular genetic analysis [18].

DNA Extraction and Genotyping

Genomic DNA was extracted from whole blood samples using the Genomic DNA Extraction Kit (Bioneer, South Korea), following the manufacturer's protocol. The quantity and purity of the extracted DNA were assessed using a Nanodrop spectrophotometer (Thermo Fisher Scientific, USA) [19].

Genotyping of the TERT rs2736100 variant was performed using the Tetra-primer Amplification Refractory Mutation System PCR (Tetra-ARMS PCR) technique. An annealing temperature of 54°C was used for all primer sets. Optimized primer concentrations were selected based on preliminary testing to ensure amplification efficiency and specificity.

PCR products were resolved by agarose gel electrophoresis and stained with Safe Dye. The amplified fragments were visualized using a gel documentation system to determine genotype profiles.

Genotype determination

The TERT (rs2736100) gene polymorphism is detected using RFLP technology, where the gene segment to be studied is amplified using specialized primers via a reaction.

Table 1. Primers used in the study.

Gene	primers	Nucleotides Sequence	Final concentration
rs2736100 C/A	Inner F Inner R Outer F Outer R	AAAAGCAGGGCGGGGGCAAAGCCAA 25 AATATTGTTTTCCGTGTTGAGTGTTTTTG 29 GCCCTCCTCGTGAGTCTCCACATCTTC 27 TGAAACATTGCTACCCTTGTCCTGAGCAA 29	66

Product size for A allele: 195
Product size for G allele: 251
Product size of two outer primers: 392

Table 2. Polymerase chain reaction condition.

Steps	Temperature	Time	Cycles
Pre Denaturation	95℃	10min	1
Denaturation	95℃	30sec	35
Annealing	66℃	30sec	
Elongation	72℃	30sec	
Final Elongation	72℃	5min	1

Statistical analysis

Analysis was carried out using the validity or reliability option in SPSS version 26.0. Differences in the distributions of genotypes and alleles between cases and controls were evaluated with the Chi-square test, whereas ORs (95% CI) were used to calculate the association between Diabetes risk and TERT rs2736100 polymorphism. TERT gene expression levels among groups were compared by Student's t test or ANOVA. A value of $P < 0.05$ was considered to be statistically significant.

Results

rs2736100 SNP of TERT gene analysis

Various samples showed variance in the rs2736100 polymorphic site sequencing chromatogram. The reference sequence exhibited a single, well-defined peak for the G nucleotide, indicating that G is the wild-type allele at this site(fig**1**).

A single sharp G signal at the polymorphic location confirmed a homozygous wild genotype (GG) in numerous samples. Some chromatograms showed overlapping G and T nucleotide peaks at the same location, indicating a heterozygous genotype. This pattern shows that one person has wild and mutant alleles.

Occasionally, a single peak for the T nucleotide indicated a homozygous mutant genotype (TT). This nucleotide substitution (G→T) indicates a single nucleotide polymorphism (SNP) at this location**.**These data suggest that the G allele is the wild-type allele and the T allele is the mutant variant, contributing to genetic diversity in the samples.

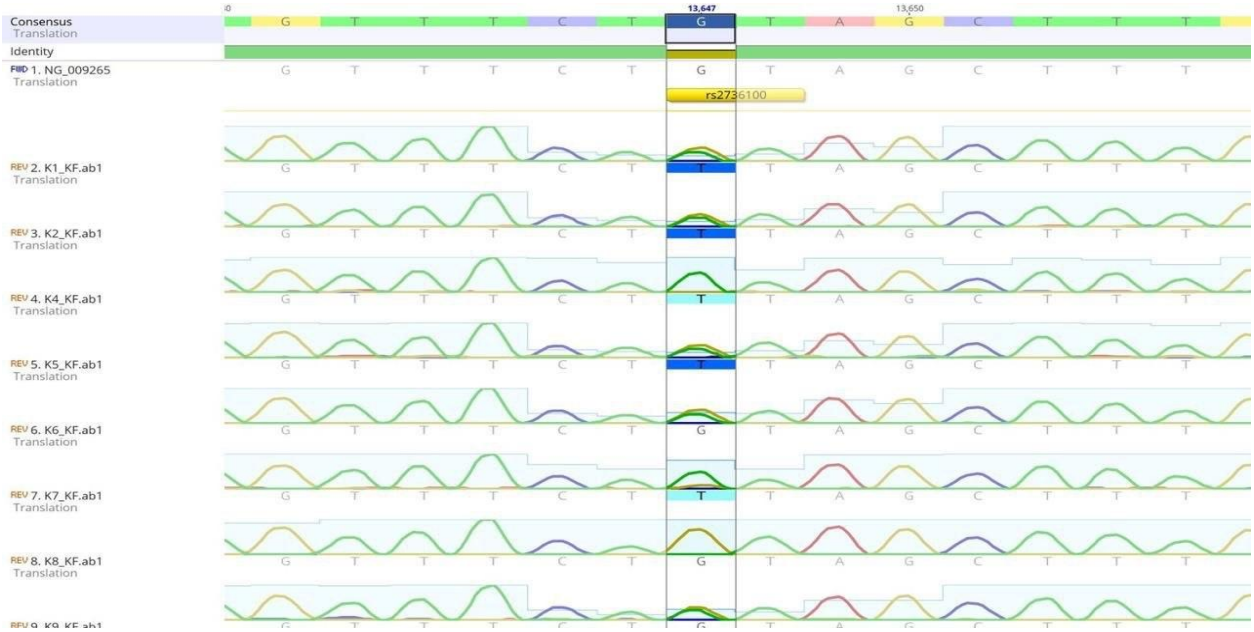

Figure 2. Analysis of rs2736100 SNP of TRET gene using Sanger sequencing. Single "T" peak indicative of a T homozygous allele. Single "G" peak indicative of a G homozygous allele.Presence of the "T" and "G" peak indicative of T/G heterozygous allele.

The genotypic distribution of the rs2736100 (G/A) polymorphism in the TERT gene was found to be in Hardy–Weinberg equilibrium in both T2DM patients and control groups (Table 3). The frequency of the wild-type genotype (GG) which was the references allel was more frequently in control groups at 100% than in patient group 53.33%. The mutant homozygous genotype (AA) appeared only in diabetic patients (1.34%), also the heterozygous genotype (AG) was observed in 33.33% of diabetic patients and not found in healthy individuals. However, these differences were statistically high significant ($p = 0.01$).

The odds ratio (OR) for the AG and AA genotype was (19.727, 8.454) (95% CI: 1.063 - 365.978, 0.419 - 170.311; $p = 0.01$), suggesting a significant trend toward increased risk of T2DM among carriers of the homozygous and heterozygous mutant allele.

At the allelic level, the G allele was highly frequent in the control group (100%) compared to the diabetic group (70%), which was also statistically significant (G is references allel). Conversely, the A allele observed in diabetic group only (30%), again with statistical significance(OR:26.55295% CI; 1.540 - 457.810). These data are summarized in Table 3 and visualized in Figure 2.

Table 3. The percentage, allele frequency, and genotypes of the TERT gene for the locus (rs2736100) in the patient group.

Genotype	Patients No. (30)		Control No. (15)		*P* value	OR	95% CI
	No.	Freq (%)	No.	Freq (%)			
GG	16	53.33	15	100		Ref.	-
AG	10	33.33	0	0	≤ 0.01**	19.727	1.063 - 365.978
AA	4	1.34	0	0		8.454	0.419 - 170.311
Allele	**No.**	**Freq (%)**	**No.**	**Freq (%)**	***P* value**	**OR**	**95% CI**
G	42	70	30	100		Ref.	-
A	18	30	0	0	≤ 0.01*	26.552	1.540 - 457.810

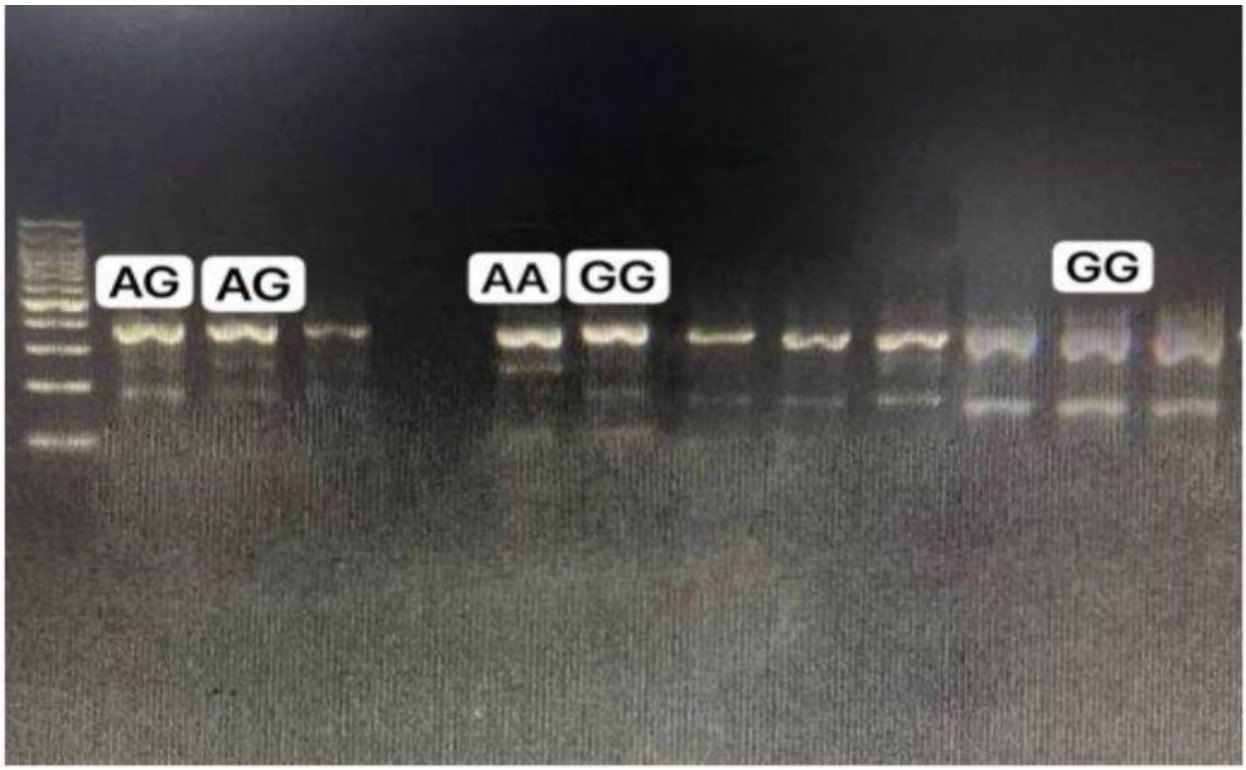

Figure 2. Gel electrophoresis showing TERT (rs2736100) polymorphism analysed for type 2 diabetic patients on 2% agarose gel.

Table(4) showed the genetic analysis of 28 sample focusing on 1364 neucletide location on TERT gene(rs2736100). The study investigate three genotypes(homozygous GG, heterozygous GT and mutant homozygous TT). The GT genotype were more frequent with 46% (12/26) followed by GG with 42%(11/26) while the TT were the less frequent with 11%(3/26).

Based on allele frequency, G allele (normal) were more frequent with 65%(34/52) than T(mutant) with 35%(18/52). This particular variant, rs2736100, is an intron variant, meaning it is located outside of the gene's coding area. Introns are thought to have important regulatory roles in gene expression, especially in RNA splicing. A shift in nitrogenous bases, as in this transition-like substitution, can impact gene stability or regulation. The functional classification of this variant is that of an intron variant, which is a form of transition point mutation where the nitrogenous base thymine (T) is used instead of guanine (G).

Table 4. Mutation screening in *TERT* gene.

Sample No.	SNP ID	Gene	Consequence	Nucleotide Location	Status (G>T)	Type	Chromosome
K1	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant	
K2	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant	
K3	**rs2736100**	*TERT*	Intron Variant	1364			
K4	**rs2736100**	*TERT*	Intron Variant	1364	TT	Transition> Homozygous mutant	
K5	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant	
K6	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant	
K7	**rs2736100**	*TERT*	Intron Variant	1364	TT	Transition> Homozygous mutant	
K8	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild	
K9	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant	
K10	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition>	

K11	**rs2736100**	*TERT*	Intron Variant	1364	GT	Heterozygous mutant Transition> Heterozygous mutant
K12	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K13	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant
K14	**rs2736100**	*TERT*	Intron Variant	1364	TT	Transition> Homozygous mutant
K15	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant
K16	**rs2736100**	*TERT*	Intron Variant	1364		
K17	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K18	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K19	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant
K20	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K21	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K22	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K23	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K24	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K25	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant
K26	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild
K27	**rs2736100**	*TERT*	Intron Variant	1364	GT	Transition> Heterozygous mutant
K28	**rs2736100**	*TERT*	Intron Variant	1364	GG	Homozygous Wild

Genotype	**Frequency**
GG	11/26(42%)
GT	12/26(46%)
TT	3/26(11%)
Allele	**Frequency**
G	34/52(65%)
T	18/52(35%)

Association of TRET(rs2736100) gene with Disease

Meta-analysis for associations of TRET(rs2736100) with diseases included 77 studies. These studies included a variety of cancers of which the majority ($n = 6$) involved studies on lung cancer ($n = 2$), Basa cell carcinoma (n=1), Prostate cancer(n=1) and colorectal cancer ($n = 1$). The majority of studies reported a positive association with the G allele of rs2736100. However, One of the included studies reported a negative association with the G allele, this included idiopathic pulmonary pathway. In the meta-analysis of studies, the pooled effect size was significant with a pooled OR [95% CI: 1.07–1.31] and shows that the G allele is a risk allele for cancer disease.

Table 5. Association of TRET(rs2736100) gene with Disease.

Study/Year	Population	Disease / Trait	Risk Allele	Odds Ratio (95% CI)	p-Value	Notes
McKay et al., (12)	European (GWAS)	Lung adenocarcinoma	G	1.22 (1.15–1.29)	2×10^{-10}	One of first TERT-CLPTM1L cancer-risk loci identified

Broderick et al., (13)	UK	Colorectal cancer	G	1.07 (1.04–1.10)	2.49×10^{-5}	TERT polymorphism replicated in multiple GWAS
Rafnar et al., (14)	Icelandic	Basal-cell carcinoma	G	1.31 (1.19–1.44)	3×10^{-8}	Strongest signal at 5p15 region for BCC
Kote-Jarai et al., (15)	European	Prostate cancer	G	1.19 (1.12–1.26)	4×10^{-7}	Association with prostate cancer susceptibility
Matsubara et al., (16)	Japanese	Lung cancer	G	1.25 (1.10–1.42)	7×10^{-4}	Validated rs2736100 in Asian populations
Machiela et al., (17)	Multi-ethnic (14 cancers)	Pan-cancer risk	G	1.20 (avg.)	$< 10^{-8}$	Cross-cancer pleiotropy of TERT locus
Li et al., 2020, (18)	Asian meta-analysis	Idiopathic pulmonary fibrosis	T	0.81 (0.74–0.89)	< 0.001	Short-telomere-linked protective allele for IPF
Codd et al., 2021, (19)	Global cohort	Leukocyte telomere length	G	$\beta = +0.05$	3×10^{-30}	G allele associated with longer telomeres

Discussion

The correlation between type 2 diabetes mellitus and TERT gene polymorphism is the study's most significant finding. The catalytic subunit of telomerase is encoded by the TERT gene, which is found on chromosome 5p15.33 [20]. SNPs have been examined in the current investigation, including rs2736100 in the TERT promoter found in intron 2 of TERT in both healthy individuals and patients with type 2 diabetes mellitus [21]. Although there is mounting evidence linking short telomeres to type 2 diabetes mellitus (T2DM), the majority of research has been cross-sectional in nature, attempting to determine whether telomere attrition is caused by the metabolic abnormalities of T2DM or whether shorter telomeres increase the risk of T2DM [22]. Both situations are addressed by biological theories. According to Elks and Scott [23], short telomeres can cause early cell senescence, which lowers cell mass and impairs insulin secretion and glucose tolerance.

Subsequent research conducted by Adams and Boutwell [24] has demonstrated a correlation between the A allele and reduced blood cell telomere length, whereas the C allele is correlated with elongated telomeres. The duality in illness connection of the rs2736100 alleles may indicate a fundamentally distinct role of telomere biology in malignant versus non-cancerous disorders. This dichotomy emphasizes that therapeutic medicines affecting telomere length or telomerase activity must be employed judiciously, as both excessively long and short telomeres may result in disease [25].

The rs2736100 polymorphism, which is usually represented by an A > C substitution, has been extensively researched for its correlation with a number of cancer susceptibilities, such as lung, thyroid, colorectal, and hematologic malignancies, as well as some non-malignant conditions like idiopathic

pulmonary fibrosis [26]. According to functional investigations in study of Dratwa et al.,[27], this variation may modulate telomerase activity and contribute to cellular immortalization and genomic instability by influencing TERT expression through changed transcriptional regulation or chromatin accessibility. Tian et al., [28] revealed that major genetic determinant in the TERT–CLPTM1L locus, rs2736100 has been identified by genome-wide association studies (GWAS), highlighting its function as a pleiotropic marker across many illness characteristics. TERT expression and telomerase activity are influenced by the regulatory intronic variation rs2736100 (G>T). Longer telomeres and an increased risk of cancer are reliably linked to the G allele (often reported as "C" due to strand orientation). On the other hand, the T allele may make a person more vulnerable to degenerative illnesses like pulmonary fibrosis, but it also seems to be linked to shorter telomeres and a lower risk of several cancers. The variation exhibits pleiotropy, suggesting that depending on the tissue environment and telomere dynamics, different biological effects may occur [29].

According to Goswami's research [30], the TC genotype protects against type 2 diabetes. Cell division causes the loss of some telomeric DNA. Blackburn et al., [31] and Goglin et al. [32] found a link between TL and mortality rate, suggesting that telomeric length (TL) is a biomarker of biological aging. Because of the gradual shortening of telomeres that occurs with age, they are frequently called a "molecular clock of aging" [33], [34].

Conclusion

The polymorphism of telomerase reverse transcriptase(TERT) rs 2736100 variant are associated with the susceptibility of type2 diabetes mellitus. The only Mutant genotypes(TT and GT) were found in diabetes patients suggesting it role in disease predisposition. The T allele may consider a genetic risk factor for disease because it only found in diabetic patients. These findings imply that TERT gene variation may contribute to T2DM and that telomere preservation mechanisms may be linked to metabolic diseases.

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