Newborn Telomere genetics association with parental telomerase gene polymorphism

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ABSTRACT

BACKGROUND

Telomeres, the marker for cellular senescence, are involved in the stability of chromosomes. The telomere length (TL) is maintained by two major genes of telomerase enzyme known as TERT (Telomerase reverse transcriptase) and TERC (telomerase reverse component). Several genome-wide association studies (GWAS) have highlighted novel genetic polymorphisms of these two genes. This study aimed to find the association between parental TL and Single nucleotide polymorphism (SNP) of telomerase genes (TERC and TERT) with newborn telomere genetics.

MATERIALS AND METHODS

In this cross-sectional study, blood samples (n=612) were collected from 204 families (mother-father-newborn triad) and TL was determined with the help of (T/S) ratio using qPCR. Sanger sequencing was performed to identify SNP in TERC and TERT genes and sequences were analysed with the help of Mega X software. The *SHEsis* software (available online) was used for the association between parents-newborn alleles. The Statistical Package for Social Sciences (SPSS) version 24 was used for data analysis. The $p < 0.05$ was considered statistically significant.

RESULTS

The allelic distribution of TERC (rs10936599) and TERT (rs2736100) genes showed the C allele was predominant in the triad. The only C allele of the TERT gene (Odds ratio: 2.44, X^2: 4.82, P=0.028) was found 2 times more odds of having an effect from mothers on newborns. The genotypic comparison among parents and newborns in both genes highlighted longer TL (2.02$\pm$0.96, P=0.00, 2.07$\pm$0.89, P=0.006, respectively) in newborns than in parents. Moreover, TT(TERC) and AA(TERT) genotypes had significantly longer TL (p=0.00, 0.006).

CONCLUSION

The study provides new insight into the association between the SNPs of the TERC (rs10936599) and TERT gene (rs2736100) and Telomere length (TL) among the mother-father-newborn triad.

The newborn had longer TL compared to the parents', highlighting the in-utero reprogramming of telomeres.

KEYWORDS: Telomere, Telomerase, TERC, TERT, Polymorphism, Gene

INTRODUCTION

Telomerase, a telomere maintenance enzyme prevents telomere (a biological marker of the aging) erosion. It is mostly present in cancer cells, adult stem cells, and proliferating cells including human T cells and B cells, but they are not present in somatic cells (1). Additionally, telomerase has been linked to studies that show it can prevent oxidative damage in a variety of non-dividing cells, including cardiac myocytes and neurons (2, 3). Nevertheless, telomere lengthening by telomerase occurs during the S phase of the cell cycle as a result of interactions between many proteins and genes (4). Telomeres have hexameric repeats (TTAGGG) and are extremely conserved. The length of the telomere is greatest at birth and subsequently decreases with each cell division, acting as a mitotic clock and undergoing senescence or triggering apoptosis (5). Leukocyte telomere length (LTL) has been used as a common marker for assessing disease risk in all cells. (6).

The two genes of telomerase, TERC(Telomerase reverse component), also known as TERRA (telomeric repeat-containing RNA), is a noncoding RNA that is 451 nucleotides long and located on chromosome 3q26 (lncRNA). Most normal human cells express it, indicating that it may play additional roles in the body, such as speeding up the release of inflammatory cytokines (7). On chromosome 5p15.3, the other gene, TERT (Telomerase reverse transcriptase) is located, which is a 42 kilobases catalytic subunit of telomerase. It has 16 exons and 15 introns. TERC serves as a TERT template and adds GGTTAG repeats to chromosomal ends and together, the two genes form the telomerase complex (8).

The telomere variation or genetic inheritance pattern may be shown by the single nucleotide polymorphisms (SNPs) in the TERC and TERT genes. In this regard, it has been discovered that telomere molecular lifespan may be affected by the reprogramming of neonatal TL in utero (9). Numerous genome-wide association studies (GWAS) on TERC and TERT serve as effective tools

to highlight the novel findings of genetic variation linked to a variety of common diseases and features as well as the genetic basis of complex disorders (10-15).

This study may help in the identification of genetic changes that cause comorbidity, mortality, or aging in parents and their newborns. Telomere length at birth can be a marker for inherited genetics that have been modified, and its decrease and polymorphism can be used to predict the likelihood of developing various diseases both at birth and in later life. Therefore, this study aimed to associate parental genetics and telomere length with the polymorphisms of TERC and TERT in the parents-newborn (triad).

MATERIALS AND METHODS

From September 2021 to June 2022, n=612 samples were collected from 204 families (parents-newborn triad) from Ziauddin Hospitals. The Ziauddin University Ethics Review Committee (Ref No. 3950721SFBC) gave their approval for this cross-sectional study. The study included women aged 18 to 35 with gestational ages greater than 35 weeks (based on ultrasound data) and their husbands, who were aged 18 to 45. After receiving both parents' explicit written informed consent, all samples were taken. The Performa was used to record demographic information, laboratory results, and parents' medical histories. Following birth, the parents' venous blood (5ml) and umbilical venous cord blood (5ml) were drawn into ethylenediaminetetraacetic acid (EDTA) tubes and stored at 4°C. According to company protocol, DNA was extracted from the blood using a Qiagen DNA Blood Mini Kit (catalog number 51306, Germany) and stored at -80 °C.

Following Cawthon et al., multiplex protocol, the leukocyte telomere length (LTL) was used for telomere length quantification by qPCR (16). The reference DNA (a pool of four healthy males and females) was used in each run of the experimental sample qPCR to create the standard curve. The experimental DNA was then quantified of the mother, father, and cord (the newborn). The software(AriaMx System Software version 17.1) was used to collect data, and the thermal cycler (Agilent, USA) was configured following the recommendations (16). In all responses, good linearity (R^2.0.99) was maintained.

Following qPCR, the samples were sequenced by sanger sequencing. The following set of primers, created by primer 3 software, was used to conventionally amplify the gene loci (544 base pairs(TERC) and 617 base pairs(TERT)). The following served as the primer for the TERC and TERTgenes;Forward:5'AAGCGTCAGGTTTTGCTGTG3;Reverse:5'TTGCTGTGAAGACTAC TGACTAG3';Forward:5′CTCGGAGCCTCATCCTTTGT3';Reverse:5'TCTCAGGCATCTTG ACACCC3'(Synbio Tech, USA). According to the manufacturer's instructions, the PCR was carried out using DreamTaq master mix (catalog number: K0181, Thermo Scientific, USA). For PCR product purification, Thermofischer's ExoSap-IT PCR Product Cleanup kit (catalog no. 78200, USA) was utilized. SeqStudio Genetic Analyzer used the Big Dye Terminator v.3.1 Sequencing Kit (Catalog No. 4337456, Thermofischer, USA) to analyze the sequence (Thermofisher Scientific, USA). Data analysis used the samples with SNPs that passed the Quality Control process.

STATISTICAL ANALYSIS

Data analysis was done using Statistical Package for Social Sciences version 24 (SPSS 24). Different TERC and TERT gene SNPs were found in the targeted region using the 1000 genome project. The analysis of sequencing data and identification of minor alleles was performed using the Mega x software. The genotype and allele frequency distribution were examined using the online *SHEsis* software (http://analysis.bio-x.cn/myAnalysis.php). To determine differences between allele groups and telomere length(TL), the Kruskal-Wallis test was applied. The $p < 0.05$ was considered statistically significant.

RESULTS

A total of n=612 participants: mother-father-newborn triad was recruited in the study. The distribution of allele frequency(Table 1) of the targeted SNPs of telomerase genes TERC (rs rs10936599) and TERT (rs2736100) had the highest frequency of the C allele in the triad. The minor allele T/T of TERC gene was less frequent in the participants whereas, A/A genotype of TERT gene was not found in mothers.

Table 1: Distribution of the allele frequencies of TERC and TERT gene

Variant	**rs10936599**		**rs2736100**	
Gene	**TERC**		**TERT**	
Polymorphism	**T/C**		**C/A**	
Allele distribution	**C**	**T**	**C**	**A**
Mother	39(65)	21(35)	42(65)	22(34)
Father	36(6)	24(4)	45(70)	19(29)
Newborn*	46(71)	18(28)	56(82)	12(17)

*Two samples with twin babies

The *SHEsis* software analysis for TERC gene polymorphic allele(C/T) distribution when mother-newborn and father-newborn were compared, did not show significant results (P<0.40, 0.162) with Odd ratio(OR) 1.37 and 1.70 respectively(Table 2). The other TERT gene comparison among mother-newborn had significant results (p<0.028) with OR:2.4 and X^2: 4.82, highlighting the 2 odds of having the effect on newborns than fathers (OR: 1.97, p<0.10)(Table 2).

Table 2: Distribution of the allele frequencies of TERC and TERT gene in parents and newborn

Variable	**TERC(rs10936599)**				**TERT(rs2736100)**			
	Hazard Ratio /Odd Ratio	%95 CI	X^2	P value	Hazard Ratio /Odd Ratio	%95 CI	X^2	P value
Mother-Newborn	1.37	[0.643~ 2.943]	0.67	0.40	2.444	[1.088~5.4 9]	4.82	0.028*
Father-Newborn	1.70	[0.804~ 3.609]	1.94	0.162	1.97	[0.865~4.4 84]	2.65	0.102

The *Shesis* software analysis for TERC and TERT gene polymorphic allele. $X^{2:}$ Chi-square, CI: Confidence interval

The comparison of telomere length (T/S ratio) and TERC genotypes distribution had the longest TL(3.22±1.48) in newborns with T/T genotype(p=0.00)(Table 3). However, the C/T genotype was found most frequent in mother and father, whereas in newborns C/C was common.

The analysis of telomere length (T/S ratio) and TERT genotypes showed the longest TL(2.82±1.08) again in newborns with A/A genotype(p=0.006)(Table 3). The most frequent genotype in the mother and father was C/A and C/C with different TL (1.28±0.96, 0.99±0.45). Whereas, C/C was frequently found in newborns.

Table 3: Genotypic distribution and telomere length variation in mother, father and newborns

TERC GENE									
Mother				**Father**			**Newborn**		
Genotype n(%)		TL (Mean± SD)	P value	Genotype n(%)	TL (Mean ±SD)	P value	Genotype n(%)	TL (Mean±S D)	P value
C/T	15(50)	0.96± 0.65	0.30	16(53)	1.27 ±0.44	0.11	6(18)	1.65± 1.25	0.00**
C/C	12(40)	1.32± 0.87		10(33)	0.70 ±0.60		20(62)	2.02 ± 0.96	
T/T	3(10)	2.15± 2.05		4(13)	2.35± 1.39		6(18)	3.22± 1.48	
TERT GENE									
C/A	22(0.68)	1.28± 0.96	0.226	7(22)	1.42± 0.31	0.089	8(23)	1.20± 0.39	0.006**
C/C	10(0.31)	1.73± 1.12		19(59)	0.99 ±0.45		24(70)	2.07 ±0.89	
A/A	0(0)	0		6(19)	1.67± 2.03		2(6)	2.82± 1.08	

Krushkal Wallis test was applied to find mean difference among mother-father-newborn telomere genetics.

When the allele distribution was seen in the newborn gender, the T/T genotype of the TERC gene was not found in girls whereas it showed the longest TL in boys(p=0.024). Moreover, in the TERT gene, A/A genotype was absent in boys but had the longest TL in girls(p=0.30). C/C was seen with longer TL in both boys and girls(figure 1).

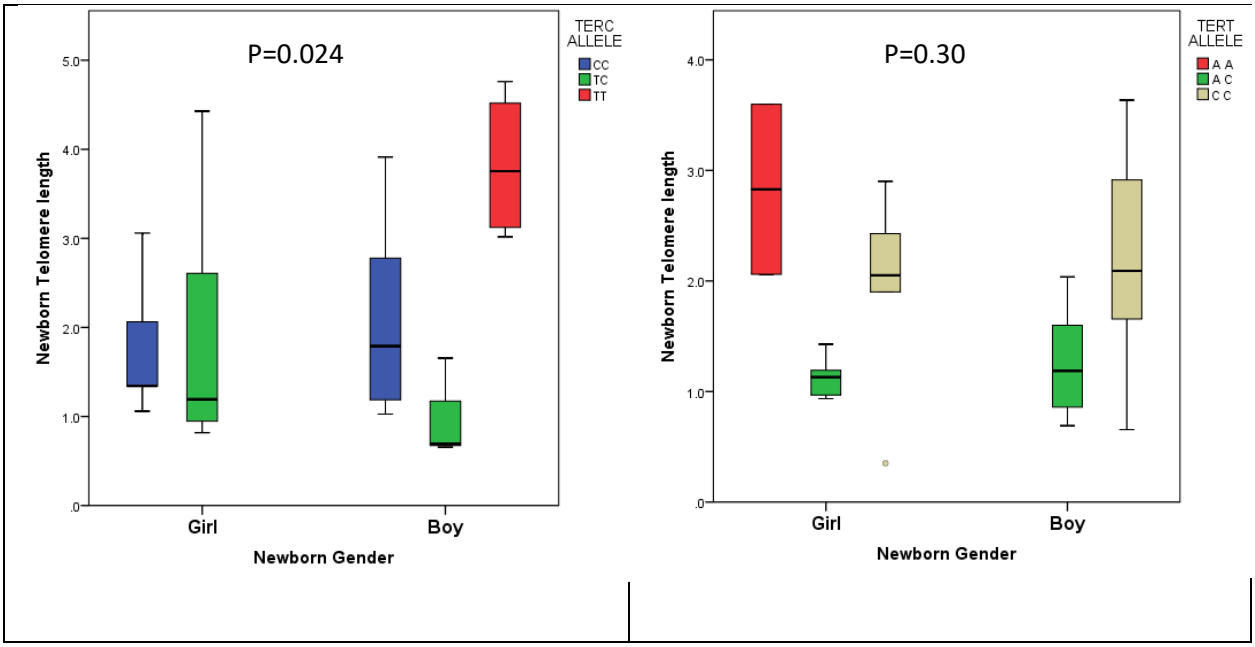

Figure 1: Allele distribution among newborn gender and genetic disparity with telomere length.

Krushkal Wallis test was applied to find mean difference among -newborn gender and telomere genetics.

DISCUSSION

This study is presented for the first time, data on telomere length and genetic variation in the mother-father-newborn triad. The polymorphism of TERC(rs10936599) (C/T) and TERT((rs2736100)(C/A) highlighted C/C as a major allele with shorter telomere length(TL) and T/T and A/A as minor allele with longer TL in the newborns. This was in accordance with a study in different populations of India, china and united kingdom which also reported major allele C of the variants(17-20). However, in a Chinese population, the TERT gene C allele was presented as a minor allele rather than A as seen in the Pakistani targeted population of this study(18).

Telomere integrity and maintenance are done by TERT and TERC, however, TERT encodes telomerase enzymes and plays a crucial role in their protection. It was pointed out by studies that the C allele (OR 1.16) is positively associated with cancer and longer telomere length, whereas, negatively associated with non-cancerous diseases (OR 0.81)(21,22). This emphasizes a longer telomere length in newborns vulnerability to diseases. The above studies were not in accordance with this study's findings, suggests that the gene locus with shorter C allele in triad, especially in newborns not prone to cancer development.

Telomeres have been extensively studied in an association of telomere length and its genes with the risk of different diseases like cardiovascular disease, upper respiratory track diseases in children, metabolic disease, chronic obstructive pulmonary disease (COPD and thalassemia (23-27) But data regarding the mother-father-newborn triad association with TL and TERC, TERT SNPs is not existing in the literature. In this study TERT SNPs were found associated with mothers and newborns but not with fathers, stressing the influence of mother genetics on newborns. However, other studies have correlated telomere length or telomerase gene TERC and TERT polymorphisms with age, and morbidity (28).

The underlying mechanism of decreased TL is due to the acute stress of reactive oxygen species due to multiple risk factors. As the age progresses, telomere erosion leads to an extremely short length which can cause apoptosis or senescence and overt to morbidity and mortality(28). Conversely, the mechanism that leads to cancer cells generation by upregulation of the TERT gene which makes the cells immortal due to uncontrolled cell division due to longer TL.(8)

TL is a marker of biological aging which maximizes at birth and reduces progressively with advancing age. In this study newborn, TL was observed longer than parents. The study results are supported by our prior study which confirmed longer newborn TL than mother, thus, emphasizing telomere length reprogramming during fetal life(9). A study illuminated it as a heritability factor and found a positive correlation ($\beta = 0.14$, $P = 1.99E{-}05$) between newborn and mother TL(29).

The strength of this study highlighted that maternal and paternal genetics and telomere length were explored along with newborn and targeting the role of mother genetics on telomere length. The identification of gene polymorphism and its association with TL and its genetics emphasized its importance in cellular fate.

Further studies on diseases and other risk factors can help in translating the telomere regulatory mechanism and disease progression identification.

CONCLUSION

The study found that the polymorphism of TERC (rs10936599) and TERT gene (rs2736100) genes of telomerase have major allele C, associated with smaller TL in parents-newborns of the targeted population. The longer TL is seen in minor alleles(T and A) in newborns than in parents highlighting the in-utero reprogramming of telomeres.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical statement

This was a cross-sectional study approved by the Ethics Review Committee (Ref No. 3950721SFBC) of Ziauddin University

Consent to participate

Written or verbal consent was taken from all the participants

Author Contributions

SF contributed to the study design, performed experiments, analyzed the data, and wrote the manuscript; SB gave the main concept of the study, supervised the whole research and revised the manuscript; RH contributed to data and sample collection; RA helped in study design, performing an experiment, data analysis and manuscript writing. OK helped in data and sample collection. All authors have read and agreed to the published version of the manuscript.

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