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Distribution of Telomere Length in the Cord Blood of Chinese Newborns

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Authors' contributions

This work was carried out in collaboration between all authors. Authors ECT, MPH and GSHY designed the study, authors TM and EEPK selected the subjects, collected the cord blood samples and the data on maternal age, birth weight and gestational age. Authors SNL, ZY and DZ did the TRF assay, author ECT did the analyses, author SNL wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: We studied the variability in telomere length in cord blood collected from newborns of different birth weights and gestational ages.
Study Design: Prospective cohort study.
Place and Duration of Study: Samples were collected from KK Women's and Children's Hospital between March 2011 and March 2012 and the terminal restriction fragment assays (TRF) were performed at the Department of Physiology, National University of Singapore.
Methodology: Cord blood samples were prospectively collected in EDTA or heparin tubes for deliveries from Chinese parents. TRF assays were performed on genomic DNA extracted from whole blood. Data was collected for birth weight, gestational age, and maternal age. Variance analyses of telomere lengths and correlation coefficients were calculated using Statistical Package for the Social Sciences (SPSS).

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Results: The birth weight of the samples collected ranged from 0.61 kg to 5.18 kg with gestation age from 196 to 288 days. TRF results from 184 samples (96 males, 88 females) showed that there was a wide range from 6.6 kbp to 19.2 kbp. The mean TRF length was 12.64 kb (males: 12.33 kb ± 2.50; females: 12.99 kb ± 2.35). There was no statistically significant correlation of TRF with birth weight, gestation age or maternal age. There was highly significant correlation of birth weight with gestational age (*P*=0.00).
Conclusion: Our results showed no correlation of either gestational age or birth weight with telomere length as measured by TRF assay.

Keywords: Birth weight; Chinese; gestational age; maternal age; telomere length.

1. INTRODUCTION

Telomeres are specialised nucleoprotein structures made up of tandem repeats of hexamers. They act as a cap to protect chromosome ends from degradation and fusion with other chromosome ends. Telomere repeats provide a mechanism for DNA replication at the ends of chromosomes and are essential for chromosomal stability. As telomeres undergo progressive shortening with every replication, the length is frequently used as a marker for cell division and proliferative potential [1-3].

In men, short telomeres have been associated with higher risk of cardiovascular and metabolic disorders, dementia, emphysema, depression, and cancer [4-8]. Cells with critically truncated telomeres exhibit chromosomal rearrangements which eventually lead to malignancies or apoptosis. Mice with shorter telomeres have increased incidence of tumour formation [9,10]. Hence telomere length is also a marker for organismal fitness and risk for certain diseases.

Telomere length is an inherited trait. There is inter-individual variability even when adjusted for age [11,12]. However, it is also modifiable by environmental factors. For its association with both inherited disorders and diseases with both genetic and environmental influences, it is not clear whether the disease predisposition is due to the inherited shorter telomere length, or that the shorter telomere length is a consequence of the disease. There is no longitudinal data on telomere length in such patients.

Combined epidemiologic and clinical studies have shown that intrauterine environment affects foetal growth and development and also subsequently impacts adult health disease and survival. This is due to the fact that foetal life is associated which rapid cell division and an insult or injury during this period can have significant long-term consequences on postnatal tissue or organ function [13]. There is a significant relationship between low birth weight and later development of cardiovascular disease and impaired glucose tolerance (IGTT) in adult life [14]. Besides cardiovascular and metabolic diseases, those born with very low or low birth weight (below 2500 grams) are also more at risk for cognitive impairment, behavioural problems and higher risk of hepatoblastoma[15,16] As the spectrum of diseases overlaps with those associated with short telomeres, it would be interesting to find out whether the low weight births already have shorter telomeres at birth due to intrauterine stress.

There is no large scale study on telomere length in newborns. There is also no data on telomere length for children from our population. In this study, we investigated the telomere

length of newborns from Chinese parents in a public hospital in Singapore. Our data will provide some insight into the range of telomere length at birth for children with different birth weight and gestational ages for the Asian population.

2. MATERIALS AND METHODS

2.1 Cord Blood Samples

The study protocol was approved by the Sing Health Institutional Review Board which oversees all research activities in the hospital. Deliveries involving Chinese parents were identified and the cord blood was collected in both heparin and EDTA tubes. Data on gender, birth weight, gestational age and maternal age were also collected. All newborns were singleton births, free of major congenital birth defects and not suspected of chromosomal disorders.

2.2 DNA Extraction

Genomic DNA was extracted from whole blood using DNeasy Blood and Tissue Kit (QIAGEN, Valencia, CA, USA) according to manufacturer's protocol. The quality and quantity of extracted DNA was assessed by optical density measurement at 260nm and 280nm using the NanoDrop 1000 Spectrophotometer (Fisher, Wilmington, DE, USA).

2.3 Telomere Restriction Fragment (TRF) Assay

The TRF length analysis assay was performed using the Telo-TAGGG Length Assay Kit (Roche Applied Science, Mannheim, Germany). Extracted pure genomic DNA (1.5 µg/sample) was digested with FastDigest® restriction enzymes, *Hin*f1 and *Rsa*1 (Fermentas, Burlington, Ontario, Canada), for 10 minutes at 37ºC. Digested DNA fragments were fractionated by gel electrophoresis in a 0.8% agarose at 60 V for four hours. The gel was then washed in hydrochloric solution (0.25 M HCl), denaturation solution (0.4 M NaOH) and neutralisation solution (1 M Tris 7.4, 5 M NaCl). The DNA fragments in the gel were transferred to the Nytran® positively-charged nylon membrane (Sigma-Aldrich, St. Louis, MO, USA) overnight. Subsequently, DNA is cross-linked onto the membrane by ultraviolet light (Stratagene, Santa Clara, CA, USA), hybridized with Digoxgenin (DIG)-labelled telomere probe at 42ºC for three hours and washed with a series of anti-DIG alkaline phosphatase washing solutions. The membrane was incubated with avidin-conjugated horseradish peroxidase for five minutes, followed by horseradish peroxidase substrate solution, tetramethylbenzidine, for five minutes. Visualization of the DNA fragments were detected on X-ray films (Kodak, Rochester, NY, USA). The chemiluminescent signals were scanned by the Kodak Gel imaging system and analyzed by the Kodak imaging software for quantitative measurements. The mean TRF length for each lane was estimated as the weighted average of the optical density as described in the TeloTAGG kit. The DIG Molecular Weight Marker from the kit was included in every gel as size markers.

2.4 Statistical Analysis

Relationships between continuous variables were assessed with Pearson or Spearman correlation. Partial correlations were also used to control for interaction between variables. All analysis was done using SPSS 19. Statistical significance was set at $P< 0.05$.

3. RESULTS

The demographic variables of the study population by gender and TRF results are presented in Table 1.

Table 1. Distribution of variables in the study samples

Group	Males (n=96)		Females (n=88)		*P*
	Mean ± SD	Range	Mean ± SD	Range	
Birth weight (g)	3233 ± 525	610 – 5184	3226 ± 401	2200 – 4298	.921
Gestational age (days)	266.09 ± 11.10	196 – 280	267.89 ± 7.52	252 – 288	.205
Maternal age (years)	32.86 ± 4.90	18 – 42	32.32 ± 5.28	17 – 47	.843
TRF (kb)	12.32 ± 2.50	6.63 – 19.21	12.99 ± 2.35	8.19 – 18.66	.065

There was no significant deviation from normality for all the variables. There was no statistically significant difference in maternal age, birth weight and gestational age between male and female births. There was a wide range for mean TRF length with the longest almost three times that of the shortest. There was also a trend for shorter telomeres in males compared to telomeres in females although the difference did not reach statistical significance. The shortest mean TRF length was a male with birth weight of 3.73 kilogram (kg), gestational age of 273 days and the mother was 23 years old. The longest mean TRF length was of a male with birth weight of 2.89 kg, gestational age of 259 days and the mother was 42 years old. Mean TRF length of the youngest birth at 196 days and birth weight of 0.61 kg was 9.26 kilobases (kb). The heaviest birth of 5.18 kg was a male with gestational age of 266 days and the mother was 31 years old. His mean TRF length was 15.15 kb. The heaviest female birth was 4.298 g (gestational age 273 days and 26-year old mother) with mean TRF length of 11.73 kb. A representative TRF blot from whole blood DNA of nine samples is shown in Fig. 1.

There was significant inverse correlation between maternal age and gestational age (Pearson's r = –0.161, P = 0.029) with older mothers giving birth earlier. There was also highly significant correlation between higher birth weights and older gestational ages (Pearson's r = 0.385, P< 0.00). There was no statistically significant correlation of mean TRF length with birth weight or gestational age, even after controlling for maternal age. And there was no independent correlation of mean TRF length with either birth weights or gestational ages even after controlling for the other variable.

There were 143 mothers who were older than 30 years. For this group there was statistically significant correlation between maternal age and mean TRF length of the newborns (Pearson's r = 0.190, P = 0.023), with older mothers giving birth to newborns with longer telomeres. Similar to the whole sample set, there was again statistically significant correlation between higher birth weight and older gestational age (r = 0.417, P< 0.00).

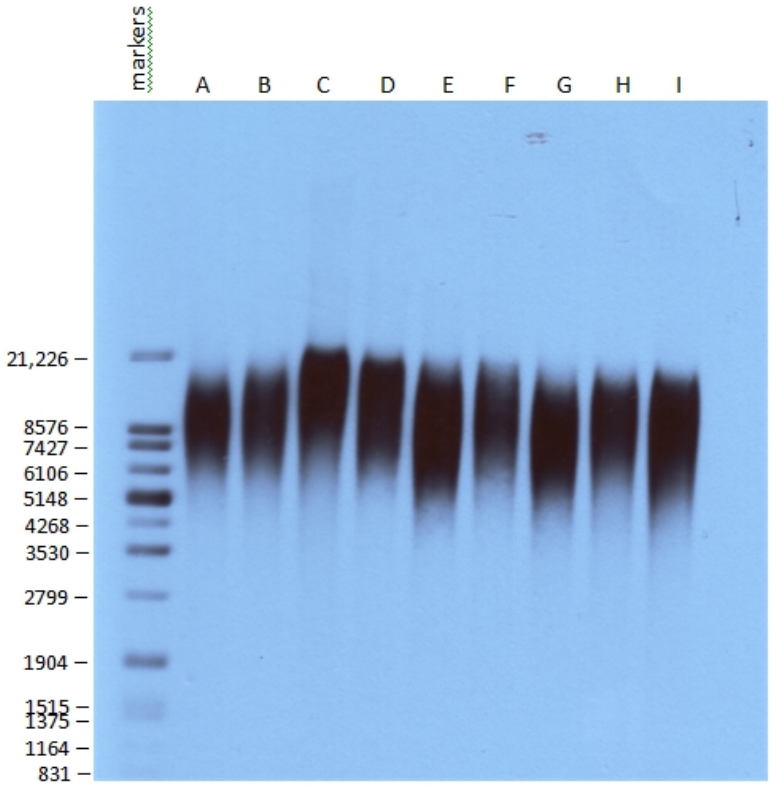

Fig.1. A blot used for TRF measurements

First lane on the left is the DIGmolecular weight markers with the sizes in basepairs, lanes (A) to (I) are cord blood samples.

4. DISCUSSION

Our data is in line with the higher incidence of earlier deliveries for older mothers [17] and the expected higher birth weight with older gestational age [18, 19]. Consistent with other studies, there is wide inter-individual variability in mean TRF length in newborns [20, 21]. Moreover, the huge variations in TRF length in newborns are as large as the variations observed in adults [22] . Hence the wide range of age-adjusted TRF length in adulthood could be attributed to strong genetic determinants that had exerted its effect *in utero*[23].

The previous largest study was from the United States in 2002 (Okuda et al) which found the mean TRF length to be 11.01 ± 0.058 kilobasepairs (kb) for cord blood [20], less than the average obtained in this study. Another study had even smaller range of 7.491 – 9.473 kb [24]. However, the sample size of that study is very small with only 26 newborns. One explanation could be that our study sample had a bigger range of birth weight (0.61 – 5.18 kg compared to 1.60 – 4.75 kg). Our average TRF length is closest to the 12.34 kb reported for 15 – 19 week old fetal tissues from 11 elective abortions [25]. One study reported even longer mean TRF length of 16.4 kb in 12 newborns [26]. Other studies had even smaller sample sizes of 10 or less [27-29]. A summary of previous studies on newborn telomere length is presented in Table 2.

Table 2 Summary of published newborn telomere length based on Southern blot analysis of mean telomere restriction fragment (TRF) length

Reference	Origin	Sample characteristics	Tissue studied	Birth weight	Gestational age (days)	Mean TRF (kb)± SD
Akkad et al. [30]	UK	38 AG[†]	whole blood	3497 ± 430	276.5 ± 9.1	10.36 ± 1.6
		34 SGA[†]		2342 ± 433	270.9 ± 13.3	10.33 ± 1.3
Allsopp et al. [27]	USA	10 full term	White blood cells	-	-	10.0 – 12.5^
Davy et al. [31]	USA	32 growth restricted	placenta	-	259 - 280	11.50*
		36 age-matched		-		11.25*
Frenck et al. [26]	USA	12	leucocytes	-	-	16.4 ± 1.2
Friedrich et al. [24]	Germany	11 full term	leucocytes	-	> 259	8.323 ± 0.50
		15 pre-term		6 VLBW, 7 LBW	< 259	8.512 ± 0.52
Okuda et al. [20]	USA	86 blacks	white blood cells	3120 ± 57	269.5 ± 1.47	10.98 ± 0.09
		48 whites		3413 ± 74	270.2 ± 1.61	10.92 ± 0.11
		29 hispanics		3282 ± 77	270.2 ± 2.03	11.25 ± 0.10
Pipes et al. [29]	USA	5	mononuclear cells	-	-	11.2 ± 0.93
Zeichner et al. [28]	USA	9[#]	mononuclear cells	-	-	10.08 ± 1.45

[†] AG: appropriately grown SGA: small for gestational age
^ Range estimated from bar graphs.
** Mean estimated from bar graphs.*
[#] Uninfected children born to HIV-positive mothers.

The shortest sample for the US study at 8.55 kb was longer than our shortest at 6.6 kb. As our samples were anonymously collected, we did not have any clinical data for this pregnancy which was a full-term birth with regard to pregnancy complications or prenatal stress experienced by the mother which could influence telomere length in the offspring [32]. While it was much shorter than the shortest of 8.55 kb in that study, the shortest in the study by Friedrich et al was 7.49 kb for a preterm newborn while Holmes et al had two out of five preterm infants with mean TRF length in the mid-7 kb range [24,33]. There were also 11 additional samples in our study with mean TRF length of < 9 kb. Hence the short mean TRF length for this infant could just be an extreme case of natural inter-individual variation. At the other end of the range, the longest mean TRF length in Okuda et al was only 13.32 kb whereas the longest in this study was 19.2 kb. One possibility for the longer mean TRF is that some of the subtelomeric restriction sites for the enzymes used in this assay might be polymorphic in our population, resulting in over-estimation and higher mean TRF length for those samples.

Okuda et al. also reported that telomere length results were similar for males and females [20]. While we found a trend towards shorter telomeres in males, it did not reach statistical significance. Nevertheless our result is consistent with other studies which showed that telomeres are longer in females compared to males of the same age for adults [34-36]. Our data showed that this difference might already be present at birth.

The present study is in line with two previous reports that there was no association between birth weight and mean TRF length in newborns, which had sample sizes of 72 and 68 [30,37]. However, another study reported significantly longer TRF length in “very low birth weight” pre-term compared to “low birth weight” newborns and this is based on a sampling size of 15 and 11 [24]. More studies involving larger sampling sizes are required to establish if impaired growth during intrauterine events is associated with higher telomere attrition. Postnatally, infants who were small at birth might undergo rapid growth and attain normal height and weight within a year. As telomerase activity is absent in many somatic tissues, it would be expected the telomeres in these cells would undergo more rapid attrition compared to normal birth wirght infants if the catch-up growth involved more replication and cell divisions. Longitudinal studies involving serial sampling over time during this period would be needed to ascertian if this is indeed the case.

A large proportion of small for gestational age (SGA) and intrauterine growth restriction (IUGR) cases are due to placenta insufficiency. Shorter telomeres have been reported for placental trophoblasts for pregnancies complicated by preeclampsia or intrauterine growth restriction [38,39]; while the expression of hTERT, the rate-limiting factor of telomerase activity was also found to be lower for the latter. Another group working on fetal growth retriction samples found similar results for placental telomere length and telomerase activity [31]. The reduced telomerase activity could explain the shorter telomeres found in the IUGR and FGR placentas but there was no corresponding decrease in telomere length for the FGR cord blood samples, leading them to conclude that the pathology is placental in origin. Future studies to assess levels of telomerase activity and telomere length in IUGR/FGR placentas (and fetal tissues if possible) at various stages of pregnancy would be needed to better understand the pathogenesis.

The known determinants of telomere length are genetic factors [12,40], age and gender [20,21,23,34,35,41-43]. Several findings lend support to the idea that paternal inheritance is the main genetic factor predicting telomere length, where higher paternal age is associated with longer newborn telomeres [41,44-46]. Nawrot et al. [35] further proposed the X-linked

inheritance of telomere length between fathers-daughters, mothers-sons, mothers-daughters and amongst siblings. In our study, the paternal age at the time of birth of the newborns were not recorded and hence we were unable to test if there was correlation between paternal age and the TRF length of their newborn daughters, or between mothers' age and newborn telomere length of their newborn sons after adjusting for paternal age and vice versa. We found no correlation of mother's age with the mean TRF length of their sons even after adjusting for gestational age or birth weight. Interestingly, for older mothers (> 30 years), a positive correlation was observed between maternal age and mean TRF length of their newborns. This was different from a previous study which found that paternal age but not maternal age at the time of birth is positively associated with telomere length [41]. However, a direct comparison cannot be made as the telomere length measurement was done when the subjects were aged 35-55 for that study and the observed difference could be due to different postnatal attrition rate.

Telomere length is known to be involved in aging and is associated with age-related diseases. Further research on telomere-telomerase maintenance *in utero* will lead to better understanding the factors which determine telomere length at birth. This will expand our knowledge on the impact of being born with relatively shorter telomeres and the risk of developing age-related chronic diseases associated with short telomeres.

4. CONCLUSION

To our knowledge, our study has the largest sampling size for telomere length in newborns, with 96 males and 88 females. In addition, our samples are more homogeneous in that all 184 are of Chinese ancestry. Our results showed a wide range of mean TRF length with no correlation with either gestational age or birth weight.

CONSENT

Written informed consent was obtained from women whose prenatal fetal ultrasound scan results indicated that there might be intra-uterine growth restriction. Remaining samples were collected anonymously from delivery suites with no identifier recorded.

ETHICAL APPROVAL

The study protocol was approved by the Sing Health Institutional Review Board (CIRB Ref: 2010/100/A).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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