

SCIENTIFIC REPORTS



OPEN

The known genetic loci for telomere length may be involved in the modification of telomeres length after birth

Received: 08 September 2016

Accepted: 11 November 2016

Published: 08 December 2016

Qiao Weng^{1,2,4,*}, Jiangbo Du^{2,3,*}, Fei Yu^{2,3,*}, Tongtong Huang³, Mengxi Chen³, Hong Lv³, Hongxia Ma³, Zhibin Hu^{2,3}, Guangfu Jin^{2,3}, Yali Hu^{1,4} & Hongbing Shen^{2,3}

Telomere length varies considerably among individuals. It is highly heritable and decreases with ageing or ageing related diseases. Recently, genome-wide association studies (GWAS) have identified several genetic loci associated with telomere length in adults. However, it is unclear whether these loci represent the genetic basis of telomere length or determine the individual susceptibility to shortening during growth process. Using DNA extracted from peripheral and cord blood of 444 mother-newborn pairs from a Chinese population, we measured relative telomere length (RTL) and genotyped eight known telomere length related variants that were initially identified in populations of European descent. We observed the T allele of rs10936599 and the T allele of rs2736100 were normally associated with shorter RTL ($P = 0.041$ and 0.046 , respectively) in maternal samples. Furthermore, the Weighted genetic score (WGS) of eight variants was significantly associated with RTL in maternal samples ($R^2 = 0.012$, $P = 0.025$). However, we didn't detect any significant associations for any individual variant or the combined WGS with RTL in newborns. These findings didn't support the hypothesis that telomere length related loci may affect telomere length at birth, and we suggested that these loci may play a role in telomere length modification during life course.

Telomeres are tandem repeats of TTAGGG nucleotides at the ends of eukaryotic chromosomes and crucial in protecting the chromosomes from deterioration and rearrangement¹. During normal somatic cell divisions in human, telomeres are progressively attrited due to the 'problem of linear chromosome' (incomplete replication at 3' end of chromosomes)², eventually reaching a critical length that leads to cell senescence³. Telomeres can be lengthened usually by the activation of telomerase reverse transcriptase (TERT)⁴ or rarely through the ALT (alternative lengthening of telomeres) pathway⁵. Telomere length has been extensively implicated with the risk of cardiovascular disease⁶, metabolic disease⁷, chronic obstructive pulmonary disease (COPD)^{8,9}, malignant tumor¹⁰, and infection¹¹. Therefore, telomere shortening is a biomarker for biologic aging as well as development and progression of disease¹².

Telomere length exhibits considerable inter-individual variability. Intra-uterine variables including genetic and other factors during pregnancy determine the telomere length of individuals at birth, and external environmental factors advance or slow down the attrition of telomere after birth¹³. Genetic determinants of telomere length have been widely investigated. Twins studies indicate that heritable factors may contribute up to 80% of the inter-individual variation of telomere length^{14,15}. Quantitative trait linkage studies have mapped several loci for telomere length^{16–18}. Recently, genetic variants at chromosomes 2p16.2 (*ACYP2*), 3q26 (*TERC*), 5p15.33 (*TERT*), 4q32.2 (*NAF1*), 10q24.33 (*OBFC1*), 19p12 (*ZNF208*) and 20q13.3 (*RTEL1*) have been identified to be associated with telomere length in three genome-wide association studies (GWAS) of European descent^{19–22}. Thereafter, the

¹Drum Tower Clinical Medical College, Nanjing Medical University, Nanjing 210008, China. ²State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing 211166, China. ³Department of Epidemiology and Biostatistics, School of Public Health, Nanjing Medical University, Nanjing 211166, China. ⁴Department of Obstetrics and Gynecology, Nanjing Drum Tower Hospital, Affiliated to Nanjing University Medical School, Nanjing 210008, China. *These authors contributed equally to this work. Correspondence and requests for materials should be addressed to G.J. (email: guangfujin@njmu.edu.cn) or Y.H. (email: glyyhuyali@163.com) or H.S. (email: hbshen@njmu.edu.cn)

association of 5p15.33 (*TERT*) with telomere length was also replicated in Chinese populations^{23,24}. However, all of these studies evaluated the association between genetic variants and telomere length in adult subjects, which represents both telomere length at birth and telomere attrition after birth. Therefore, it is unclear whether these identified loci directly determine the telomere length in the foetal period or influence the shortening of telomere in growth process.

Herein, we designed a study including 444 mother-newborn pairs in a Chinese population, to compare the associations of the identified loci with telomere length between maternal peripheral blood and cord blood of newborns.

Results

A total of 444 pregnant women were enrolled into our study. Table 1 shows the characteristics of pregnant women and newborns. The age at current pregnancy of women were ranging from 19 to 42 years, and 80.86% were in the 25–35 age group. Few children were born before 37 weeks of gestation ($n = 45$, 10.14%) or with a birth weight $< 2,500$ g ($n = 35$, 7.88%) (Table 1). No statistically significant correlation was observed between RTL of maternal and cord blood (Fig. 1A). The overall RTL of maternal blood was significantly shorter (mean: 0.309) than of cord blood (mean: 0.354, $P < 0.001$), and this consistent trend was observed in all subgroups although not all the subgroups reached the statistically significant level (Fig. 1B, Table 1).

Genotyping call rates of all the selected genetic variants were higher than 95%, and the observed genotype frequencies for these variants were in Hardy-Weinberg equilibrium ($P > 0.00625$) among both the maternal or cord blood samples (Supplementary Table 1). We evaluated the association between genetic variants and telomere length among mother or newborns. In maternal samples, we found that the T allele of rs10936599 and the T allele of rs2736100 were nominally associated with short RTL ($P = 0.041$ and 0.046 , respectively), but none of the variants were significant after Bonferroni correction. Both of the associations were consistent with that reported in populations of European descent. No significant associations were observed between the other genetic variants and RTL in maternal samples. However, we did not find significant association between the genotypes of these eight genetic variants and RTL in cord blood (Table 2).

We further calculated WGS to analyze the cumulative effect of eight loci on telomere length. As expected, we observed significant correlation between maternal WGS and RTL ($R^2 = 0.012$, $P = 0.025$, Fig. 2A). However, there were no association between cord blood WGS and RTL ($R^2 = 0.000$, $P = 0.716$, Fig. 2B).

Discussion

In our study, we observed that rs10936599 and rs2736100 related to telomere length in Europeans were also associated with maternal telomere length in Chinese. Rs10936599 and rs2736100 were located in *TERC* (telomerase RNA component) locus on 3q26 and *TERT* (telomerase reverse transcriptase) locus on 5p15, respectively. *TERC* encode the RNA component, and *TERT* encode the catalytic subunit of telomerase reverse transcriptase, both the two genes are key components of telomerase. Although the other 6 variants were not significantly associated with telomere length of maternal, 4 of these variants were in the same association direction with those observed in populations of European descent. The sample size may be the main limitation to fully detect the modest effect of individual variant on telomere length.

In previous study, genetic variants associated with telomere length were discovered and replicated in adults, which, however, was believed to explain a fraction of heritability of telomere length. If it is true, we supposed that the association between genetic variants and RTL in cord blood may be stronger than that in maternal blood, because the confounding factors among postnatal exposure can be reduced by using the cord blood sample to detect the genetic association. However, it is out of our expectation that we did not observe any association between genetic variants and RTL in cord blood either in the single variant analysis or WGS analysis. These findings suggest that the known telomere length related variants may not directly affect the telomere length in the foetal period or at birth of individuals, but influence the maintaining of telomere homeostasis or the resistance to the risky external stimulus in the growth process of individuals.

The heritability of telomere length has been firstly proved in a twin study about twenty years ago¹⁴. However, the mode of its inheritance was still unclear. A terminal restriction fragment (TRF) based study has firstly proposed that X-linked inheritance of telomere length is a probable genetic pattern²⁵, because significant associations of telomere length were observed between mother-daughter, mother-son, and father-daughter, but not between father-son. In contrast, a positive linkage between paternal age and telomere length of offspring was revealed in another study²⁶. More interestingly, two following studies reported a significant association between fathers and offspring but no significant association between mothers and children^{27,28}, suggesting a paternal inheritance mode of telomere length. In the current study, we did not find a significant association between telomere length of maternal blood and cord blood, which was in accordance with the previous findings and confirmed the potential paternal inheritance pattern telomere length. All of these evidences point to a gene imprinting mechanism in telomere length regulation, rather than the X chromosome genetic inheritance.

In our study, we found that RTL of cord blood was 15% longer than that of maternal blood. But we did not observe a reverse association between age and RTL in pregnant women. One of the possible explanations is the narrow age span of our participants. The range of age at current pregnancy in our study is 19 to 42 and the majority was 25 to 35 years old. Moreover, there were mounting evidences indicating that gradual loss of telomeric repeat sequences with aging is not linear; the velocity of telomere attrition is more rapid during childhood and adolescence, remaining relatively stable in adulthood, and thereafter is followed by a gradual loss of telomere repeats at old age^{3,25,26,29,30}. In addition, only 32 pregnant women were older than 35, so the small sample size in this subgroup may cause some deviation as the data might be not stable enough. This reason may lead to the unexpected phenomenon. The above reasons may dilute the adverse effects of ageing on telomere length in our study.

Variables	No. (%)	RTL of maternal blood	RTL of cord blood	P ^a
Age at current pregnancy (Years)				
<25	53(11.94)	0.320 ± 0.091	0.358 ± 0.095	0.052
25~35	359(80.86)	0.305 ± 0.080	0.354 ± 0.106	0.000
≥35	32(7.21)	0.327 ± 0.105	0.343 ± 0.087	0.534
P ^b		0.042	0.260	
Season of delivery				
March–May	153(34.46)	0.309 ± 0.077	0.358 ± 0.102	0.000
June–August	165(37.16)	0.315 ± 0.087	0.353 ± 0.118	0.001
September–November	93(20.95)	0.296 ± 0.080	0.350 ± 0.081	0.000
December–February	33(7.43)	0.314 ± 0.097	0.350 ± 0.086	0.124
P ^b		0.350	0.947	
Gestational age (weeks)				
<37	45(10.14)	0.310 ± 0.074	0.369 ± 0.119	0.010
≥37	399(89.86)	0.308 ± 0.084	0.352 ± 0.101	0.000
P ^b		0.897	0.294	
Birth weight (g)				
<2,500	35(7.88)	0.318 ± 0.090	0.372 ± 0.135	0.069
≥2500	409(92.12)	0.308 ± 0.083	0.352 ± 0.100	0.000
P ^b		0.492	0.281	
Mode of delivery				
Vaginal	363(81.76)	0.309 ± 0.085	0.353 ± 0.102	0.000
Cesarean section	81(18.24)	0.308 ± 0.078	0.358 ± 0.112	0.002
P ^b		0.905	0.685	
Sex of newborns				
Boy	226(50.90)	0.306 ± 0.083	0.347 ± 0.103	0.000
Girl	218(49.10)	0.311 ± 0.083	0.361 ± 0.104	0.000
P ^b		0.579	0.133	

Table 1. Selected characteristics of pregnant women and newborns and distributions of relative telomere length (RTL) between maternal blood and cord blood. ^aP value for paired t-test that was used to compare the differences between mother–newborn pairs for RTL. ^bP value for one-way anova or t-test that was employed to examine the differences of RTL between subgroups divided by selected characteristics.

Many studies have reported that telomere length in adult women were significantly longer than that in men^{16,23,25,31–33}. Recently, Benetos *et al.* indicated that the sex difference in telomere length is largely determined in utero, based on the study of telomere length dynamics in adult same-sex twins and opposite-sex twins. This intra-uterine effect was attributed to the intrauterine sex hormonal environment¹³. In our study, although we observed that the RTL in female newborns was 4% longer than that in male newborns, but there was no significant difference. It could be due to the limited sample size. Therefore, the potential effect of the intra-uterine environment on the sex difference in telomere length is an interesting and noteworthy issue.

In our study, no difference was found in newborn RTL as a function of maternal age, birth weight, and gestational age in our study. Part of our findings can be supported by the following evidences. De Meyer *et al.* found that paternal age was a vital determinant for newborn RTL while maternal age was not independently related to newborn RTL³⁴. Researchers also have indicated that there were no difference between the RTL of preterm neonates and full-term newborns³⁵. In addition, several studies observed that higher birth weight was associated with longer RTL^{36,37}, but which were inconsistent with our findings. Possible reason is that intra-uterine variables that affect newborn RTL are extremely complex, maternal psychosocial stress³⁸, maternal estriol concentrations³⁹, maternal Folate Concentrations⁴⁰ and undetected factors might play an important role in affecting newborn RTL and disturbed the correlation between birth weight and RTL. Besides, it is the first time that the relationship between newborn RTL and mode of delivery had been evaluated and there seemed to be no significant association in our current study. However, more well-designed studies are still needed to explore the relationship between maternal conditions and newborn RTL.

The advantages and limitations of the current study should be addressed. The major advantage is that we systematically investigated the association between telomere length and genetic variants in mother–newborn pairs and this design may help to clarify inheritance mechanism of telomere length. Nevertheless, there still existed a lot of deficiencies. Firstly, we did not get the blood samples of the husbands of the pregnant women. So we could not further evaluate the association between RTL of father–newborn pairs, which is crucial for the clearly illustrating of the inheritance pattern of telomere length. Secondly, our current analysis lack of the information about maternal lifestyle (smoking status, alcohol consumption, physical activity, etc) and maternal health condition (obesity, hypertension, etc), which were very important and should be taken into our further study. At last, we

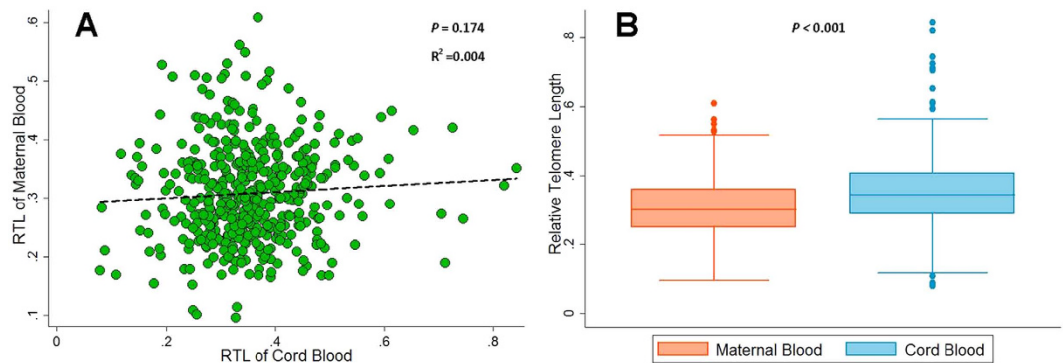


Figure 1. (A) Correlation between relative telomere length (RTL) of maternal blood and cord blood ($R^2 = 0.004$, $P = 0.174$); (B) Comparison of relative telomere length (RTL) means between maternal blood and cord blood ($P < 0.001$).

Locus [reference]	Chr.	Associated gene	Reported effect allele ^a	Alternative allele	Maternal genotype and RTL ^b			Cord genotype and RTL ^b		
					EAF ^c	β	P	EAF	β	P
rs10936599 ¹⁹	3q26.2	<i>TERC</i>	T	C	0.574	-0.0119	0.041	0.566	-0.0017	0.819
rs11125529 ¹⁹	2p16.2	<i>ACYP2</i>	C	A	0.811	0.0019	0.792	0.825	-0.0012	0.892
rs2736100 ¹⁹	5p15.33	<i>TERT</i>	T	G	0.570	-0.0110	0.046	0.594	0.0052	0.470
rs2736108 ²²	5p15.33	<i>TERT</i>	G	A	0.684	-0.0080	0.176	0.722	-0.0020	0.799
rs4387287 ²¹	10q24.33	<i>OBFC1</i>	C	A	0.840	-0.0027	0.725	0.847	-0.0010	0.920
rs755017 ¹⁹	20q13.33	<i>RTEL1</i>	A	G	0.590	-0.0017	0.779	0.573	0.0023	0.736
rs7675998 ¹⁹	4q32.2	<i>NAF1</i>	A	G	0.155	-0.0054	0.493	0.159	-0.0005	0.958
rs8105767 ¹⁹	19p12	<i>ZNF208</i>	A	G	0.711	0.0061	0.307	0.719	-0.0002	0.978

Table 2. Regression analysis of reported telomere length related loci with relative telomere length (RTL) among pregnant women and newborn. ^aThe reported effect allele associated with short telomeres in populations of European descent. ^bDerived from generalized linear models. The reference homozygotes, heterozygotes and effect homozygotes were encoded as 0, 1 and 2, respectively. ^cEAF: Effective allele frequency.

used the “Power and Sample Size Calculation software” to evaluate statistic power. We controlled type I error rate to be 0.05 and other relevant parameters derived from our current data: slope of the line obtained by regressing RTL against genotype ranges from 0.0002 to 0.012, the standard deviation of the regression errors ranges from 0.082 to 0.1 and the standard deviation of genotype ranges from 0.51 to 0.74. As a result, the statistic power ranges from 5% to 54% based on 444 participants. Statistical power might be improved with larger sample size, while the limited sample size might constrain our capacity to find the positive correlation. Therefore, further studies based on trio samples with large sample size may facilitate to evaluate our findings.

In summary, our study did not support the hypothesis that telomere length related loci identified in European may affect telomere length at birth in Chinese, and we suggested that these loci may play an important role in telomere length modification during life course.

Materials and Methods

Study participants. Subjects of current study were enrolled from Nanjing Drum Tower Hospital in Nanjing, Jiangsu province of eastern China. During the recruitment period from April 2014 to April 2015, a total 444 singleton pregnant women were included in our study. Detailed information on maternal characteristics, birth weight, gestational age, infant sex, and mode of delivery was obtained from maternity records. Gestational age (completed weeks) was calculated based on last menstrual period or ultrasound-based estimated date of conception. Venous blood samples of mother were collected from 444 pregnant women before or during the delivery period. Paired umbilical cord blood samples were collected immediately after birth from the cord vein of newborns and locally stored at -20°C . Samples were then shipped on dry ice to the study laboratories and genomic DNA was extracted from peripheral blood of mothers and cord vein blood of newborns. This study was approved by the ethics committees of Nanjing Medical University and Nanjing Drum Tower Hospitals and all experiments were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participating women.

Measurement of relative telomere length. Based on a modified quantitative polymerase chain reaction (qPCR) protocol²³, we measured telomere length using ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). Firstly, the reference DNA (pooled from 5 adults’ samples) was used to draw a standard curve with concentrations ranging from 0.25 to 8 ng/ μL , and linear correlation between input DNAs and Ct value

results should be re-detected; (3) Only those variants with call rate higher than 95% can be selected in further analysis. The genotyping results were determined by using the SDS 2.3 Allelic Discrimination Software (Applied Biosystems).

Calculation of genetic scores. In order to assess the combined effect of the eight telomere length related genetic variants, Weighted genetic score (WGS)⁴² was calculated based on the genotypes of those variants. For each individual, WGS was calculated by multiplying the number of risk alleles by the telomere length associated beta (β_j), which was derived from the regression analysis of telomere length and genotype in the current study. For each SNP, we appointed the longer telomere length related allele as risk allele. To calculate WGS for the i -th subject, the following formula was used:

$$WGS_i = \sum_1^j x_{ij} \beta_j$$

In this formula, x_{ij} is the number risk alleles for the j -th variant in the i -th subject ($x_{ij} = 0, 1$ or 2) and β_j is the coefficient or weight for the j -th variant.

Statistical analysis. RTL from our data was similar to normal distribution. Paired t-test was used to compare the differences between mother-newborn pairs for RTL. One-way anova or t-test was employed to examine the differences of RTL between subgroups divided by selected characteristics. Generalized linear models (GLMs) were used to conduct tests for correlation between RTL and genotype of genetic variants, WGS, and other continuous variables. Bonferroni correction was used for multiple testing during the genetic association analysis and Hardy-Weinberg equilibrium analysis and the significance level was defined at 0.00625 (0.05/8 tests). A P -value less than 0.05 was considered statistically significant unless specifically notified. General analyses were performed with Stata version 9.2 (StataCorp LP).

References

- Blackburn, E. H. Telomeres and telomerase: the means to the end (Nobel lecture). *Angew Chem Int Ed Engl* **49**, 7405–7421, doi: 10.1002/anie.201002387 (2010).
- Olovnikov, A. M. Principle of marginotomy in template synthesis of polynucleotides. *Doklady Akademii nauk SSSR* **201**, 1496–1499 (1971).
- Frenck, R. W. Jr., Blackburn, E. H. & Shannon, K. M. The rate of telomere sequence loss in human leukocytes varies with age. *Proc Natl Acad Sci USA* **95**, 5607–5610 (1998).
- Blackburn, E. H., Greider, C. W. & Szostak, J. W. Telomeres and telomerase: the path from maize, Tetrahymena and yeast to human cancer and aging. *Nature medicine* **12**, 1133–1138, doi: 10.1038/nm1006-1133 (2006).
- Cesare, A. J. & Reddel, R. R. Alternative lengthening of telomeres: models, mechanisms and implications. *Nature reviews. Genetics* **11**, 319–330, doi: 10.1038/nrg2763 (2010).
- Serrano, A. L. & Andres, V. Telomeres and cardiovascular disease: does size matter? *Circ Res* **94**, 575–584 (2004).
- Valdes, A. M. *et al.* Obesity, cigarette smoking, and telomere length in women. *Lancet* **366**, 662–664, doi: 10.1016/S0140-6736(05)66630-5 (2005).
- Shapiro, S. D. Merging personalized medicine and biology of aging in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **184**, 864–866, doi: 10.1164/rccm.201108-1486ED (2011).
- Lee, J. *et al.* The relationship between telomere length and mortality in chronic obstructive pulmonary disease (COPD). *PLoS One* **7**, e35567 (2012).
- Wentzensen, I. M., Mirabello, L., Pfeiffer, R. M. & Savage, S. A. The association of telomere length and cancer: a meta-analysis. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **20**, 1238–1250, doi: 10.1158/1055-9965.EPI-11-0005 (2011).
- Bestilny, L. J., Gill, M. J., Mody, C. H. & Riabowol, K. T. Accelerated replicative senescence of the peripheral immune system induced by HIV infection. *AIDS* **14**, 771–780 (2000).
- Bojesen, S. E. Telomeres and human health. *Journal of internal medicine* **274**, 399–413, doi: 10.1111/joim.12083 (2013).
- Benetos, A. *et al.* Sex difference in leukocyte telomere length is ablated in opposite-sex co-twins. *Int J Epidemiol* **43**, 1799–1805 (2014).
- Slagboom, P. E., Droog, S. & Boomsma, D. I. Genetic determination of telomere size in humans: a twin study of three age groups. *American journal of human genetics* **55**, 876–882 (1994).
- Graakjaer, J. *et al.* The relative lengths of individual telomeres are defined in the zygote and strictly maintained during life. *Aging cell* **3**, 97–102, doi: 10.1111/j.1474-9728.2004.00093.x (2004).
- Vasa-Nicotera, M. *et al.* Mapping of a major locus that determines telomere length in humans. *Am J Hum Genet* **76**, 147–151 (2005).
- Andrew, T. *et al.* Mapping genetic loci that determine leukocyte telomere length in a large sample of unselected female sibling pairs. *Am J Hum Genet* **78**, 480–486 (2006).
- Mangino, M. *et al.* A regulatory SNP of the BICD1 gene contributes to telomere length variation in humans. *Hum Mol Genet* **17**, 2518–2523 (2008).
- Codd, V. *et al.* Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet* **45**, 422–427, doi: 10.1038/ng.2722 (2013).
- Codd, V. *et al.* Common variants near TERC are associated with mean telomere length. *Nat Genet* **42**, 197–199 (2010).
- Levy, D. *et al.* Genome-wide association identifies OBFC1 as a locus involved in human leukocyte telomere biology. *Proc Natl Acad Sci USA* **107**, 9293–9298 (2010).
- Bojesen, S. E. *et al.* Multiple independent variants at the TERT locus are associated with telomere length and risks of breast and ovarian cancer. *Nat Genet* **45**, 371–384, doi: 10.1038/ng.2722 (2013).
- Du, J. *et al.* Telomere length, genetic variants and gastric cancer risk in a Chinese population. *Carcinogenesis* **36**, 963–970, doi: 10.1093/carcin/bgv075 (2015).
- Liu, Y. *et al.* A genome-wide association study identifies a locus on TERT for mean telomere length in Han Chinese. *PLoS One* **9**, e85043 (2014).
- Nawrot, T. S., Staessen, J. A., Gardner, J. P. & Aviv, A. Telomere length and possible link to X chromosome. *Lancet* **363**, 507–510 (2004).
- Unryn, B. M., Cook, L. S. & Riabowol, K. T. Paternal age is positively linked to telomere length of children. *Aging Cell* **4**, 97–101 (2005).

27. Nordfjall, K., Larefalk, A., Lindgren, P., Holmberg, D. & Roos, G. Telomere length and heredity: Indications of paternal inheritance. *Proc Natl Acad Sci USA* **102**, 16374–16378 (2005).
28. Njajou, O. T. *et al.* Telomere length is paternally inherited and is associated with parental lifespan. *Proc Natl Acad Sci USA* **104**, 12135–12139 (2007).
29. Brummendorf, T. H. *et al.* Telomere length dynamics in normal individuals and in patients with hematopoietic stem cell-associated disorders. *Ann N Y Acad Sci* **938**, 293–303; discussion 303–294 (2001).
30. Yamaguchi, H. *et al.* Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N Engl J Med* **352**, 1413–1424 (2005).
31. Fitzpatrick, A. L. *et al.* Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. *American journal of epidemiology* **165**, 14–21 (2007).
32. Brouillette, S., Singh, R. K., Thompson, J. R., Goodall, A. H. & Samani, N. J. White cell telomere length and risk of premature myocardial infarction. *Arterioscler Thromb Vasc Biol* **23**, 842–846 (2003).
33. Brouillette, S. W. *et al.* Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. *Lancet* **369**, 107–114 (2007).
34. De Meyer, T. *et al.* Paternal age at birth is an important determinant of offspring telomere length. *Human molecular genetics* **16**, 3097–3102, doi: 10.1093/hmg/ddm271 (2007).
35. Friedrich, U., Schwab, M., Griesse, E. U., Fritz, P. & Klotz, U. Telomeres in neonates: new insights in fetal hematopoiesis. *Pediatric research* **49**, 252–256, doi: 10.1203/00006450-200102000-00020 (2001).
36. Wojcicki, J. M. *et al.* Cord blood telomere length in Latino infants: relation with maternal education and infant sex. *Journal of perinatology: official journal of the California Perinatal Association* **36**, 235–241, doi: 10.1038/jp.2015.178 (2016).
37. Strohmaier, J. *et al.* Low Birth Weight in MZ Twins Discordant for Birth Weight is Associated with Shorter Telomere Length and lower IQ, but not Anxiety/Depression in Later Life. *Twin research and human genetics: the official journal of the International Society for Twin Studies* **18**, 198–209, doi: 10.1017/thg.2015.3 (2015).
38. Marchetto, N. M. *et al.* Prenatal stress and newborn telomere length. *American journal of obstetrics and gynecology* **215**, 94 e91–98, doi: 10.1016/j.ajog.2016.01.177 (2016).
39. Entringer, S. *et al.* Maternal estradiol concentrations in early gestation predict infant telomere length. *The Journal of clinical endocrinology and metabolism* **100**, 267–273, doi: 10.1210/jc.2014-2744 (2015).
40. Entringer, S. *et al.* Maternal Folate Concentration in Early Pregnancy and Newborn Telomere Length. *Annals of nutrition & metabolism* **66**, 202–208, doi: 10.1159/000381925 (2015).
41. Cawthon, R. M. Telomere measurement by quantitative PCR. *Nucleic Acids Res* **30**, e47 (2002).
42. Talmud, P. J. *et al.* Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. *BMJ* **340**, b4838, doi: 10.1136/bmj.b4838 (2010).

Acknowledgements

This study was supported in part by the National Key Research & Development Program (2016YFC1000204); the Key Program of National Natural Science Foundation of China (81230067); National Basic Research Program (973) (2013CB910304); National Natural Science Foundation of China (81373090, 81422042); Science Foundation for Distinguished Young Scholars in Jiangsu (BK20130042); Natural Science Foundation of Jiangsu Province (BK20161031); and Priority Academic Program for the Development of Jiangsu Higher Education Institutions (Public Health and Preventive Medicine). The authors would like to thank the participants and the supporting staff in this study.

Author Contributions

Obtained funding: H.S., G.J.; study concept and design: Q.W., J.D., G.J., Z.H.; critical revision of the manuscript for important intellectual content: all coauthors; statistically analysis: Q.W., J.D., F.Y.; Molecular analysis and technical support: J.D., T.H., H.M.; DNA samples preparing: F.Y., T.H., M.C., H.L.; subjects recruit and diagnostic evaluation: Q.W., Y.H.; Study supervision: H.S., Y.H., G.J.

Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Weng, Q. *et al.* The known genetic loci for telomere length may be involved in the modification of telomeres length after birth. *Sci. Rep.* **6**, 38729; doi: 10.1038/srep38729 (2016).

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>

© The Author(s) 2016