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ARTICLE

Meta-analysis of telomere length in 19 713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect

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Telomere length (TL) has been associated with aging and mortality, but individual differences are also influenced by genetic factors, with previous studies reporting heritability estimates ranging from 34 to 82%. Here we investigate the heritability, mode of inheritance and the influence of parental age at birth on TL in six large, independent cohort studies with a total of 19 713 participants. The meta-analysis estimate of TL heritability was 0.70 (95% CI 0.64–0.76) and is based on a pattern of results that is highly similar for twins and other family members. We observed a stronger mother–offspring ($r = 0.42$; $P\text{-value} = 3.60 \times 10^{-61}$) than father–offspring correlation ($r = 0.33$; $P\text{-value} = 7.01 \times 10^{-5}$), and a significant positive association with paternal age at offspring birth ($\beta = 0.005$; $P\text{-value} = 7.01 \times 10^{-5}$). Interestingly, a significant and quite substantial correlation in TL between spouses ($r = 0.25$; $P\text{-value} = 2.82 \times 10^{-30}$) was seen, which appeared stronger in older spouse pairs (mean age ≥ 55 years; $r = 0.31$; $P\text{-value} = 4.27 \times 10^{-23}$) than in younger pairs (mean age < 55 years; $r = 0.20$; $P\text{-value} = 3.24 \times 10^{-10}$). In summary, we find a high and very consistent heritability estimate for TL, evidence for a maternal inheritance component and a positive association with paternal age.
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INTRODUCTION

Telomeres are specialized DNA structures located at the terminal ends of chromosomes.[1] Their primary function is to maintain genomic stability. Because of the inability of DNA polymerase to fully replicate the 3′ end of the DNA strand, that is, the 'end-replication problem', telomeres naturally shorten with each cell division and, therefore, with age.[2–4] In epidemiological studies, both of cross-sectional and prospective design, decreased telomere length (TL) in leukocytes was associated with increased mortality,[5–8] although this finding was not consistent.[9,10] Increased TL in leukocytes has been associated with longevity in a comparison of long-lived Ashkenazi Jews and their offspring with younger controls.[11] Genetic association studies have revealed associations between single-nucleotide polymorphisms (SNPs) in the *TERC* and *TERT* genes and TL.[11–17] Other studies reported associations between SNPs in *TERC* and *POT1* with human longevity,[11,17,18] suggesting that genes regulating TL may influence human longevity.

That genetic variants would be found associated with TL was expected from earlier twin and family studies indicating genetic influence on TL. An early study in twins of different ages showed a heritability of 78% for TL in 4-, 17- and 44-year-old individuals,[4] with no evidence for genotype × age interaction in this age range. In older twins ($N = 287$ pairs aged 73 to 95 years) estimates for heritability were 34% in women, whereas for the smaller male sample the heritability was lower.[19] In a sample of 55 female monozygotic (MZ) and 1025 dizygotic (DZ) middle-aged twin pairs, Andrew *et al*[20] reported a heritability estimate of 36% and an unexpectedly large shared familial effect of 49%. Another study comprising 258 sib-pairs returned a heritability estimate of 82%.[21] There is a need to reconcile these divergent estimates, which might in part be caused by differences in sample composition or TL assessments.[22] A remaining question that also needs to be addressed is the extent to which estimates of heritability based on

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[11]Shared first.

[12]Shared last.

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Table 1 General characteristics of the study populations

	ERF	*GRAPHIC*	*LLS*	*NTR*	*QIMR*	*TwinsUK*
Sample size	2769	2011	2322	4550	2025	6036
Telomere length[a]	1.78 (0.36)	1.60 (0.26)	1.46 (0.27)	2.75 (0.48)	3.41 (0.61)	3.72 (0.68)
Age[a]	49.8 (14.9)	39.3 (14.5)	59.2 (6.8)	38.8 (14.1)	27.9 (15.6)	51.1 (13.5)
Age range	17–89	18–61	30–80	15–82	7–73	16–99
Women, *n* (%)	1539 (55.6%)	995 (49.5%)	1272 (54.8%)	2951 (64.9%)	1075 (53.1%)	5461 (90.5%)
MZ twins, *n* (%)	NA	NA	NA	834 (36.7%)	154 (15.2%)	1546 (51.2%)
DZ twins, *n* (%)	NA	NA	NA	689 (30.3%)	227 (22.4%)	1256 (41.6%)

Abbreviations: DZ, dizygotic; ERF, Erasmus Rucphen Family; LLS, Leiden Longevity Study; MZ, monozygotic; NA, not applicable; NTR, The Netherlands Twin Register; QIMR, Queensland Institute of Medical Research.
Complete twin pairs are depicted, representing the percentage of total population with telomere length measurements.
[a]Mean (SD).

twin data are comparable to those based on other relatives such as parents and offspring from multigenerational studies or non-twin sibling pairs.

Several studies have been conducted to assess the potential mechanisms for telomere inheritance. An early study suggested that TL was maternally inherited via an X-linked mechanism.[23] However, an increasing number of larger studies have reported stronger father–offspring than mother–offspring correlations for TL, suggesting that inheritance of this trait is mainly paternally determined.[8,24–26] In addition to a paternal pattern of inheritance, a positive correlation between offspring TL and paternal age at birth has been observed.[24,27,28] Unlike somatic cells, sperm cell TL has been shown to increase with the age of the donor[24,29] because of the presence of active telomerase, suggesting that offspring of older fathers would inherit longer telomeres.

In the current study, we investigated the heritability, mode of inheritance and influence of parental age at birth on TL in six large, independent cohort studies with a total of 19 713 participants.

MATERIALS AND METHODS

Populations

The Erasmus Rucphen Family (ERF) study is a cross-sectional cohort including more than 3000 living descendants of 22 couples who had at least 6 children baptized in the community church between 1850 and 1900. The participants were not selected on the basis of any disease or other outcome. Details about the genealogy of the population have been previously described.[30,31] The study protocol was approved by the medical ethics board of the Erasmus MC Rotterdam, the Netherlands.

The GRAPHIC study comprises individuals from 520 white Caucasian nuclear families recruited from the general population in Leicestershire, UK, between 2003 and 2005, for the purpose of investigating the genetic determinants of blood pressure and related cardiovascular traits. Inclusion criteria were that both parents (aged 40–60 years) and two offspring $\geq$18 years were willing to participate. Further details are provided elsewhere.[32]

For the Leiden Longevity Study (LLS), long-lived siblings of Dutch descent were recruited together with their offspring and the partners of the offspring. Families were included if at least two long-lived siblings were alive and fulfilled the age criterion of $\geq$89 years for males and $\geq$91 years for females, representing $<$0.5% of the Dutch population in 2001.[33] In total, 944 long-lived proband siblings were included with a mean age of 94 years (range, 89–104), 1671 offspring (61 years, 39–81) and 744 partners (60 years, 36–79). For this study only the offspring and their partners were included.

The Netherlands Twin Register (NTR: http://www.tweelingenregister.org/) recruits twins and their family members to study the causes of individual differences in health, behavior and lifestyle. Participants are followed longitudinally; details about the cohort have been published previously.[34] A subsample of unselected twins and their family members has taken part in the NTR-Biobank,[35] in which biological samples, including DNA and RNA, were collected in a standardized manner after overnight fasting. Study protocols were approved by the medical ethics board of the VUMC Amsterdam, the Netherlands.

The Queensland Institute of Medical Research (QIMR) adolescent study comprised twins and their non-twin siblings living in south-east Queensland, Australia.[36] Most (98% by self-report) are of mixed European ancestry, mainly from the British Isles. The participants are not selected on the basis of any disease or other outcome. Blood samples were collected at the end of testing sessions from participants and, if possible, from their parents. Pedigree relationships and zygosity were confirmed by genotype data. Further details are provided elsewhere.[37]

The TwinsUK cohort (www.twinsuk.ac.uk) is an adult twin British registry shown to be representative of singleton populations and the UK population.[38] A total of 6038 twins with TL measurement were included in the analysis. The age range of the TwinsUK cohort was 16–99 years. Ethical approval was obtained from the Guy's and St Thomas' Hospital Ethics Committee. Written informed consent was obtained from every participant in the study.

TL assessment

All samples from all studies were measured in the same laboratory under standard conditions. Mean leukocyte TL was measured by quantitative PCR-based technique as previously described.[12,39] This method expresses TL as a ratio (T/S) of telomere repeat length (T) to copy number of a single copy gene, 36B4(S), within each sample. Samples were quantified relative to a calibrator sample used on each run (DNA from the K562 cell line).[12] Mean interrun coefficient of variations (CVs) were calculated for all study cohorts and these ranged from 3.30 to 3.72%.

Analysis

To summarize resemblance between family members, correlations of TL between monozygotic (MZ) and dizygotic (DZ) twins, non-twin siblings, parents and offspring and between spouses, adjusting for age, gender and potential batch effects were calculated in R, version 2.12.1.[40] If data on more than two siblings were available, the data from the oldest two non-twin siblings were analyzed.

Maximum likelihood analyses as implemented in POLY[41] were used to evaluate different models of familial resemblance and these analyses were based on all data (ie, allowing for more than 2 siblings per family). In these analyses, TL was adjusted for age, gender and batch by specifying these as fixed effects on TL. Data from the six cohorts were first analyzed individually followed by meta-analysis, whereby each cohort took into account the unique structure in the data, such as the highly complex pedigree structure in the ERF cohort. In those studies where the pedigree structure allowed for evaluating sub models that included an additive genetic variance component, a nonadditive genetic variance component (dominance) or a sibling-shared environment variance component, respectively, were compared. A model in which variance was partitioned into an additive genetic variance component and a random environmental variance component gave the best description of all data and heritability was estimated based on this model.

In order to investigate differences between maternal or paternal inheritance for TL, family trios or duos were selected. When data on two or more children were available, data from the oldest child were selected for this analysis.

We assessed the age-, gender- and batch-adjusted correlations between fathers and their offspring and mothers and their offspring.

Paternal and maternal ages at the birth of their children were obtained based on the date of birth of the parents and offspring if available, or by subtracting the child's age from the parental age. The associations of paternal and maternal age with TL were compared by regressing TL on parental age in addition to own age and gender (eg, TL $\sim$ age + gender + parental age). In order to correct significance testing for familial dependencies, these analyses were also done in POLY. Meta-analyses were performed using the R package rmeta.[42]

RESULTS

General characteristics of each cohort are described in Table 1. The mean age ranged from 27.9 (QIMR) to 59.2 (LLS). Overall, approximately half of the participants are female in each population. Three cohorts (NTR, QIMR and TwinsUK) had twin data, with NTR and TwinsUK having more MZ twins and QIMR having more DZ twins. As expected, TL showed a significant negative association with age and was significantly longer in women in each population (Supplementary Table 1).

MZ twins were significantly more alike than DZ twins (P-value $= 1.85 \times 10^{-24}$, Table 2) and siblings were significantly correlated within each cohort and this correlation was very similar to that of DZ twins (Table 2). Spouses had significantly correlated TLs ($r = 0.25$; P-value $= 2.82 \times 10^{-30}$) and this effect was more pronounced in older spouses (mean age ≥ 55 years) compared with younger spouses (mean age < 55 years; P-value $= 0.010$; Table 2) suggesting that there is a significant influence of environmental factors.

Despite the evidence for the influence of environmental factors, neither the dominant variance component nor the sibling-shared variance component influenced the estimates of familial resemblance in those studies where the analysis could be performed (Supplementary Table 2) suggesting that any residual shared-environment or nonadditive genetic effects are small. In the heritability analyses, three cohorts (ERF, NTR and QIMR) had nearly identical heritability estimates of 0.62 (Table 3). The highest heritability estimate was found in LLS ($h^2 = 0.86$). In the meta-analysis of all six cohorts, the heritability was estimated to be 0.70 (95% confidence interval (CI) 0.64–0.76; P-value $= 2.31 \times 10^{-111}$).

The correlations between parental and offspring TL as a function of gender showed an effect of parental gender, but not of offspring gender. Both father–offspring ($r = 0.33$; P-value $= 5.66 \times 10^{-4}$) and mother–offspring ($r = 0.42$; P-value $= 5.01 \times 10^{-5}$) TLs were significantly correlated (Table 4). The mother–offspring correlation was significantly larger than the father–offspring correlation (P-value $=$ 0.007). There was no difference in correlation structure between male and female offspring and their parents.

Finally, we investigated whether parental age plays a role in TL (Table 5). In each cohort the association between paternal age and TL went in the positive direction. After meta-analysis, we found a significant association between paternal age and TL ($n = 5127$; $\beta = 0.005$; P-value $= 7.01 \times 10^{-5}$). Maternal age was found to be significantly associated with TL after meta-analysis ($n = 5500$; $\beta = 0.003$; P-value $= 0.012$). This association was no longer significant when additionally adjusting for paternal age ($\beta = -0.003$; P-value $= 0.357$). The paternal age association remained significant when additionally adjusting for maternal age ($\beta = 0.007$; P-value $= 0.011$).

DISCUSSION

In six independent family-based cohorts from Europe and Australia, we investigated three aspects of familial relationships in TL, namely the heritability, mode of inheritance and parental age at birth of their

Table 2 Sibling, twin and spousal correlations, adjusted for age, gender and batch effects

	n	r	P-*value*
Siblings			
ERF	444	0.48	5.20×10^{-27}
GRAPHIC	481	0.60	4.76×10^{-49}
LLS	419	0.41	5.30×10^{-18}
NTR	47	0.43	0.003
QIMR	162	0.32	3.84×10^{-5}
TwinsUK	NA	NA	NA
Meta-analysis	1553	0.49	3.46×10^{-96}
Monozygotic twins			
ERF	NA	NA	NA
GRAPHIC	NA	NA	NA
LLS	NA	NA	NA
NTR	834	0.62	7.70×10^{-90}
QIMR	154	0.70	3.17×10^{-24}
TwinsUK	1546	0.72	1.93×10^{-245}
Meta-analysis	2534	0.69	0[a]
Dizygotic twins			
ERF	NA	NA	NA
GRAPHIC	NA	NA	NA
LLS	NA	NA	NA
NTR	689	0.34	2.01×10^{-20}
QIMR	227	0.57	4.96×10^{-21}
TwinsUK	1256	0.57	5.21×10^{-110}
Meta-analysis	2172	0.50	1.24×10^{-146}
Spouses (all)			
ERF	218	0.28	2.34×10^{-5}
GRAPHIC	502	0.19	1.45×10^{-5}
LLS	702	0.34	6.74×10^{-20}
NTR	108	0.32	0.001
QIMR	410	0.15	0.002
TwinsUK	NA	NA	NA
Meta-analysis	1940	0.25	2.82×10^{-30}
Spouses (< 55)			
ERF	78	0.21	0.065
GRAPHIC	311	0.17	0.003
LLS	183	0.39	4.20×10^{-8}
NTR	22	−0.05	0.809
QIMR	368	0.14	0.006
TwinsUK	NA	NA	NA
Meta-analysis	962	0.20	3.24×10^{-10}
Spouses (> 55)			
ERF	140	0.33	8.80×10^{-5}
GRAPHIC	191	0.24	6.70×10^{-4}
LLS	519	0.32	1.94×10^{-13}
NTR	86	0.40	1.37×10^{-4}
QIMR	41	0.20	0.202
TwinsUK	NA	NA	NA
Meta-analysis	977	0.31	4.27×10^{-23}

Abbreviations: ERF, Erasmus Rucphen Family; LLS, Leiden Longevity Study; NA, not applicable; NTR, The Netherlands Twin Register; QIMR, Queensland Institute of Medical Research.
Only complete pairs included. In case of >2 sibs, the oldest two non-twin pair sibs were chosen for analysis. Mean spousal age was used for cutoff of 55 years of age.
[a]Limits of statistical software reached.

children. We found a high heritability, a significant stronger maternal than paternal inheritance and a positive association with paternal age.

The meta-analysis estimate for heritability of TL in the six populations was 0.70. Heritability estimates from the separate studies were remarkably similar across populations, with three of them showing near identical estimates. The highest estimate was observed in the oldest participants (LLS; h^2: 0.86), which may reflect a selection effect.[33] Although only the offspring with their spouses of long-living participants were selected from the LLS study, the selection of the parents for old age might have influenced the total TL distribution in their relatives.

Spousal correlations for TL have not been reported before.[25] Interestingly, we observed a significant correlation in TL between spouses. This was more pronounced in older spouses (mean age ≥ 55; $r = 0.31$) compared with younger spouses (mean age < 55; $r = 0.20$), suggesting a possible influence on TL because of living together for an extended amount of time. The hypothesis that resemblance in adults is induced by living together for extended periods of time does not need to be conflicting with the finding that modeling of the twin-family data did not detect shared-environmental influences. In a twin design shared environment is reflected in the portion of the phenotypic correlation in MZ and DZ twins that exceeds above the pattern expected if the similarity of twins was only a function of their genetic resemblance. By assuming that the common environment applies to those factors that are always shared 100% between twins, or siblings, the scope of this component for quantifying shared family environment tends to be limited to influences of the early environment, and ignores factors that are shared by individuals who share a household later in life. Another explanation could be an ascertainment effect. In older spouse pairs, both individuals have survived for extended periods of time, and are therefore likely to have above average TL for their age. The age correction performed might not completely control for this.

Mother–offspring correlations were significantly higher than the father–offspring correlations (P-value $= 0.007$), although both were statistically significant on their own. This did not change when additionally adjusting the father–offspring correlation for paternal age (data not shown). In 2004, Nawrot *et al*[23] also showed a significant correlation between mother–offspring ($n = 71$) and father–daughter ($n = 47$), but not between father–son ($n = 34$). Recently, a paternal inheritance model has been gaining favor.[8,24–26] The most recent study suggesting paternal inheritance from Nordfjall *et al*[26] contained a total of 217 parent–offspring pairs. In our study we included a total of 1244 father–offspring pairs and 1388 mother–offspring pairs and found both significant mother–offspring and father–offspring correlations for TL. Our findings are in contrast with those from other studies, as we found a significantly stronger mother–offspring than father–offspring correlation, which previously was attributed to an X-linked mechanism in TL determination.[23] A prime candidate gene for this X-linked mechanism is *DKC1* encoding dyskerin, which is important for the function of telomerase and has been found to cause congenital dyskeratosis that is characterized by short telomeres.[43] However, if an X-linked mechanism is in effect, a

Table 3 Heritability of telomere length

	h^2	*Confidence interval*	P-*value*
ERF	0.65	0.59–0.72	1.45×10^{-61}
GRAPHIC	0.73	0.68–0.78	2.10×10^{-94}
LLS	0.86	0.77–0.95	6.53×10^{-57}
NTR	0.62	0.59–0.65	2.51×10^{-125}
QIMR	0.62	0.57–0.67	4.88×10^{-63}
TwinsUK	0.74	0.72–0.75	2.45×10^{-92}
Meta-analysis	0.70	0.64–0.76	2.31×10^{-111}

Abbreviations: ERF, Erasmus Rucphen Family; LLS, Leiden Longevity Study; NTR, The Netherlands Twin Register; QIMR, Queensland Institute of Medical Research.

Table 4 Inheritance patterns: father–offspring and mother–offspring correlations in telomere length

	ERF			*GRAPHIC*			*NTR*			*QIMR*			*Meta-analysis*		
Relationship[a]	n	r	P-*value*	n	r	P-*value*	n	r	P-*value*	n	r	P-*value*	n	r	P-*value*
Father–offspring	320	0.29	1.79×10^{-7}	501	0.34	3.23×10^{-15}	111	0.49	5.32×10^{-8}	312	0.28	5.90×10^{-7}	1244	0.33	1.15×10^{-32}
Father-son	169	0.29	1.59×10^{-4}	380	0.39	6.18×10^{-15}	44	0.43	0.003	198	0.27	1.34×10^{-4}	791	0.34	2.57×10^{-23}
Father–daughter	203	0.33	1.86×10^{-6}	374	0.31	1.31×10^{-9}	75	0.49	9.59×10^{-6}	230	0.31	2.42×10^{-6}	882	0.33	3.99×10^{-24}
Mother–offspring	407	0.34	1.32×10^{-12}	502	0.48	9.31×10^{-30}	110	0.49	6.57×10^{-8}	369	0.39	7.80×10^{-15}	1388	0.42	3.60×10^{-61}
Mother–son	193	0.35	5.52×10^{-7}	380	0.50	7.53×10^{-26}	43	0.41	0.007	234	0.31	1.01×10^{-6}	850	0.42	5.06×10^{-37}
Mother–daughter	285	0.37	1.22×10^{-10}	375	0.46	2.67×10^{-21}	75	0.54	7.25×10^{-7}	270	0.38	6.94×10^{-11}	1005	0.42	2.99×10^{-45}

Abbreviations: ERF, Erasmus Rucphen Family; NTR, The Netherlands Twin Register; QIMR, Queensland Institute of Medical Research.
[a]If both a son and daughter were available for analysis, the oldest was used for parent–offspring, whereas each was used for parent–son or parent–daughter, respectively.

Table 5 Association of paternal and maternal age at birth with telomere length

	Paternal age					*Maternal age*				
	n	*mean (SD)*	*β*	*SE*	P-*value*	n	*Mean (SD)*	*β*	*SE*	P-*value*
ERF	560	26.7 (4.1)	0.0086	0.0038	0.024	578	25.0 (4.7)	0.0035	0.0028	0.211
GRAPHIC	983	28.3 (4.2)	0.0053	0.0030	0.077	984	26.4 (4.1)	−0.0011	0.0029	0.704
LLS	1587	35.5 (5.9)	0.0029	0.0021	0.167	1578	32.7 (5.4)	0.0030	0.0021	0.153
NTR	1305	30.0 (4.6)	0.0080	0.0031	0.010	1545	28.1 (4.2)	0.0064	0.0031	0.039
QIMR	692	32.2 (5.3)	0.0066	0.0048	0.169	815	29.5 (4.6)	0.0072	0.0048	0.134
Meta-analysis	5127	NA	0.0053	0.0013	7.01×10^{-5}	5500	NA	0.0032	0.0013	0.012

Abbreviations: ERF, Erasmus Rucphen Family; LLS, Leiden Longevity Study; NA, not applicable; NTR, The Netherlands Twin Register; QIMR, Queensland Institute of Medical Research.

stronger father–daughter correlation would be expected, compared with the father–son correlation, which we did not observe. Other potential explanations for the larger mother–offspring correlation include mitochondrial DNA or other parent-specific 'imprinting'. Nonpaternities were excluded as an explanation, based on genotype data.

Finally, we found significant evidence for a positive association of paternal age with TL, supporting earlier reports.[24,27,28] At first glance, any positive association of TL with age seems counterintuitive. However, TL is known to be maintained, and even lengthened, in sperm, despite both mitotic and meiotic divisions during the proliferation and differentiation of the cells.[44] In humans, this leads to a gain of ~71 base pairs of TL per year.[29] Recently, it was shown that the paternal age effect may be cumulative over generations.[45] Our findings are opposite of the recent publication that paternal age is the major determinant of novel mutations leading to autism.[46] Thus, high paternal age may have both positive and negative effects on the health of the offspring, assuming that long telomeres in children are healthy.

In summary, we find a high and very consistent heritability estimate for TL. In addition, we find evidence for a maternal inheritance component and a positive association with paternal age.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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