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Starvation May Change the Type of Paternal but Not Maternal Inheritance of the Telomere Length Throughout Generations: A Retrospective Cohort Study

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ABSTRACT

Our aim was to evaluate the effect of starvation on the paternal and maternal inheritance of the leucocyte telomere length (LTL) in three birth cohorts: before, during, and after the Chuvashian famine of 1922–1923. This retrospective cohort study comprised native Chuvash men (n= 678) and women (n=647) born between 1909–1980. Data were gathered during three expeditions: 1994, 1999, 2002, enabling us to treat age and birth year as independent variables. LTL was measured by a quantitative polymerase chain reaction technique. A significant difference in LTL values ($\chi^2_{d.f=2}$=79.04, p<0.0001) was observed between the sexes. In a pedigree-based variance component analysis, ~67.4% of the LTL variation was explained by an additive genetic component. In the entire sample, a significant correlation was observed between the LTL of the parents and offsprings. Fathers born between 1924–1928 demonstrated a significantly stronger LTL correlation with their offsprings. The LTL correlation between mothers and offspring in this group and between parents and offspring in those born after 1928 did not differ from the entire population. We believe that the increased correlation between the LTL in the father-offspring pairs born after starvation in Chuvashia can be explained by differences in the processes of oogenesis and spermatogenesis in humans.

Key words: *cohort study, famine, inheritance, starvation, telomeres*

Introduction

Telomeres are special nucleoprotein complexes consisting of a repeated TTAGGG sequence located at the ends of chromosomes, shortening with each mitotic cycle. It has been suggested that there is a strong connection between telomere dynamics and the processes that determine one's life span[1]. Evidence has been collected showing that telomere length is substantially heritable and at the same time, that environmental/lifestyle factors have been associated with changes in telomere length over time[2].

A few epidemiologic studies have addressed the effects of starvation on the maintenance of telomere length with controversial results. The Dutch Famine Birth Cohort study revealed no association between antenatal exposure to famine and the shortening of telomeres in peripheral blood leukocytes in individuals aged 68 years old[3]. However, this association has been observed in a study that addressed leucocyte telomere length (LTL) in individuals who experienced starvation during the siege of Leningrad in 1941–1944[4]. A possible explanation for this contradiction is that starvation during the siege of Leningrad was much more severe and lasted far longer than the Dutch famine[5,6]. Nevertheless, the question of whether starvation affects LTL warrants additional research studies[7]. The current work evaluated LTL in a Chuvash population-based sample comprised of survivors of the mass famine of 1922–1923 and their descendants.

In a previous study published by our group[8], we reported that the decrease in LTL with age was significant only in males ($\chi^2_{d.f=1}$=8.39, p=0.004). This difference in the LTL age dependency between men and women was significant

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($\chi^2_{2d.f=2}$=79.04, p=6.86*10–18). Furthermore, the authors were unable to provide direct evidence for leukocyte telomere shortening in famine survivors. The comparative analysis of LTL in the survivors and their descendants suggests that such an effect did take place. The study also implied that mass famine might be associated with telomere shortening in male descendants of famine survivors[8]. Moreover, the data as to the mode of inheritance and differences in parental impact are contradictory. Several studies have concluded that there is a stronger maternal rather than paternal inheritance, in contrast to other studies which have found no significant difference between mother-offspring and father-offspring telomere length regression.

Chuvashia is a rural area located in the mid-Volga region of Russia. A mass famine began in January 1922 in many rural regions of Russia, including Chuvashia. In late March 1922, ~90% of the total population were starving, going to the extreme of eating corpses and dead animals[9]. By the end of April 1923 and into late 1923, the famine ended[9]. This information and the fact that the rural Chuvash population is generally characterized by low mobility[10] justified our speculation that most rural Chuvashians who lived in the 1990s and the early 2000s were either individuals who survived the famine or their descendants.

The aim of this study was to evaluate the effect of starvation on the paternal and maternal inheritance of telomere length in three Chuvash birth cohorts born before, during, and after the starvation period.

Material and Methods

Design

A retrospective cohort study. The exposure was the mass famine of 1922–1923 occurring in Chuvashia (part of the Povolzhye famine). The outcome was age-adjusted separately for males and females' LTL.

Sample

The sampled cohort comprised native Chuvash men (n = 678) and women (n= 647) born between 1909–1980 and resided in small villages in the Chuvash Republic of the Russian Federation. Participation was consensual, and the subjects signed an informed consent form. The entire project was approved by the Ethics Committee of Tel-Aviv University, Tel Aviv, Israel. Data were gathered during three expeditions undertaken in 1994, 1999, and 2002 (Figure 1)[11,12] and retrieved from 1325 individuals belonging to 410 nuclear families. This method enabled us to treat age and birth year as independent variables (i.e., after adjustment for age, we were able to analyze how the LTL correlated with a birth year during 1909–1980)[8].

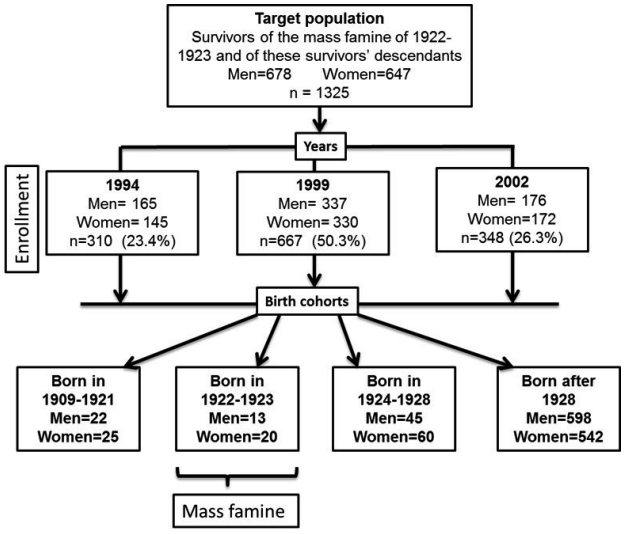

Fig 1. Studied population.

In order to examine the famine's influence on the LTL, we arbitrarily divided the sample into three groups: (1) individuals born between 1909–1923, i.e., before the famine and, hence, exposed to the famine during childhood (children ranging from 1 to 13 years of age), and individuals born during the famine; (2) individuals born between 1924–1928, i.e., after the famine. The parents of these individuals were exposed to the famine during their reproductive ages; (3) individuals born after 1928 (Table 1).

Telomere length evaluation

The DNA of peripheral blood leukocytes measured the telomere length using a quantitative polymerase chain reaction technique. DNA was prepared from peripheral blood lymphocytes as described elsewhere[13]. Telomere length was measured using a quantitative polymerase chain reaction (qPCR)-based technique[14]. Testings were performed at the DNA Analysis Laboratory, Hebrew University of Jerusalem, Israel. A detailed description of the method has been published in our previous study[8,15].

Statistical analysis

Statistical analysis was performed using the STATISTICA 7.1 software program (www.statsoft.com). Descriptive statistics characterized the study sample, and Pearson's partial correlation with age- and sex adjustment investigated the correlation between LTL in different family members. The likelihood ratio test was used to build the best fitting most parsimonious (MP) models of age and LTL dependence. The MP model was selected using the maximum likelihood ratio test amongst the linear, polynomial, and multi-interval age-fitting models, as implemented by the MAN statistical package. By using this model, the LTL phenotypes were adjusted for age separately in males and females. The standardized resid-

TABLE 1

LTL IN MEN AND WOMEN IN DIFFERENT BIRTH COHORTS[1]

Group	Cohort	Sex: n	LTLas ±SE	P-men*
1	Individuals who were born in 1909-1923	Men: 35	0.29 ± 0.23	----
		Women: 45	0.09 ± 0.23	
2	Individuals who were born in 1924-1928	Men: 45	-0.39 ± 0.14	=0.007 compared with group 1
		Women: 60	0.06 ± 0.13	
3	Individuals who were born after 1928	Men: 598	0.01 ± 0.04	**=0.166 compared with group 1**
		Women: 542	0.00 ± 0.04	=0.007 compared with group 2

[1] p-values were determined by the Student's t-test with Bonferroni correction; significance was set at p≤0.0125.

LTL- leucocyte telomere length, LTLas age- and sex-adjusted standardized leucocyte telomere length, SE - standard error

*No significant differences in telomere length were observed in women of the tested groups.

uals (LTLas) were used for further analyses. Two regression models (one and two-interval linear models) estimated the association between the LTLas and birth year. Familial correlations of LTLas, r_{sp} for spouses (r_{sp}), parent-offspring (r_{po}), and siblings (r_{sib}) were estimated by the MAN program. Based on these estimates, the maximal heritability of LTL (H^2) was calculated by applying the following equation: $[H^2 = (r_{sib} + r_{po})(1 + r_{sp})/(1 + r_{sp} + 2r_{sp}r_{po})]$. The statistical comparison of the LTLas between birth cohorts in our sample was performed by the Student's t-test with Bonferroni correction. The two-tailed level of significance of differences was set at 0.0125.

To estimate the extent of the familial and possible genetic influences on the LTL levels, we performed a pedigree-based variance decomposition analysis using the MAN-7 statistical package[16]. This program finds the best fitting and MP model of trait variability, produces maximum likelihood estimates of genetic and various common family environment components and corresponding standard errors based on pedigree data. This method also allows the total phenotypic variation of the studied trait (V_{PH}) to be partitioned into several components, according to the contributing factors: the additive genetic component (V_{AD}), the spouse environment component (V_{SP}), the common household environment component (V_{HS}), and the shared sibling environment (V_{SB}), specific for siblings raised together. The unexplained residual influences component was defined as V_{RS}.

In our previous study[8], we estimated family correlations and the heritability of the LTL of the same sample. Familial correlations were found to be significant for all categories of family members (parent-offspring: r=0.331; P=0.000282, n=1120), including a weak significant correlation between spouses. The heritability of the LTL in the tested cohort was ~0.63. It should be mentioned that due to the familial structure of our sample, the above correlation estimates, and in particular, the p-values, may be biased. Therefore, at this stage of analysis, the confounding effects of gender and age on the variation of each studied variable were simultaneously estimated with variance components, using multiple regression functions.

Results

The mean age for the men was 47.90±0.66, and for the women, 47.9±0.67 years old. Body mass index in men was 23.19±3.23 and in women 25.15±4.90 kg/m^2. There was a strong sex difference in LTL values ($\chi^2_{2d.f=2}$=79.04, p<0.0001) between the men (0.997±0.177) and women (0.917±0.148). To estimate the contribution of genetic, familial, and environmental factors to LTL variance, we performed a pedigree-based variance component analysis (Table 2). The general (unrestricted) model was compared with the MP model and each of the two restricted models (RM). A significance of age and birth-year effects (LRT=10.94, p=0.001, and LRT=8.18, p=0.004, respectively) was found. The estimated σ_{AD}^2 implies that ~67.4% of the LTL variation may be explained by an additive genetic component. Parameters σ_{HS}^2 σ_{SB}^2, β_{1f}, β_{2f} were restricted to zero in the MP model, since household component and sib effects, as well as effects of age and birthdate on telomere length in women, were non-significant. No significant sibling cross-correlation was found, whereas the spouses' common environment was ~10.7%. The effects of age and birth year in men (β_{1m} and β_{2m}) were substantial (LTL declined with increased age). Convincing evidence exists to suggest that telomere length in humans is highly heritable. However, the literature reporting on LTL provides conflicting results on the mode of LTL inheritance, i.e., is offspring LTL more strongly correlated with maternal or paternal LTL[17–21].

In the present study, we investigated LTL correlations between parent-child pairs. Parent-child correlations of LTL are presented in Table 3. After analyzing the entire population, we observed a highly significant correlation between parent's and offspring's LTL, independent of the sex (father-son: r=0.345, p=0.0005, n=293; father-daughter: r=0.277, P=0.0007, n=242; mother-son: r=0.369; p=0.0005, n=320; mother-daughter: r=0.318, p=0.0006, n=264). No statistically significant differences between the correlation coefficients (i.e., R-values) were observed. Concurrently, in the 1924–1928 group, the LTL correlation between fathers and offspring was found to be sig-

TABLE 2

VARIANCE COMPONENT ANALYSIS OF GENETIC, ENVIRONMENTAL, AGE, AND BIRTH YEAR EFFECTS OF TELOMERE LENGTH

	Model			
Parameter	General	MP (Value±SE)	RM by age	RM by birth year
σ_{AD}^2	0.608	0.674±0.080	0.679	0.678
σ_{SP}^2	0.092	0.107±0.026	0.105	0.106
σ_{HS}^2	0.029	(F) 0	(F) 0	(F) 0
σ_{SB}^2	0.006	(F) 0	(F) 0	(F) 0
σ_{RS}^2	0.254	0.208±0.071	0.213	0.212
β_{1m}	-0.764	-0.816±0.246	(F) 0	-0.118
β_{1f}	0.140	(F) 0	(F) 0	(F) 0
β_{2m}	-0.652	-0.705±0.246	0.103	(F) 0
β_{2f}	0.139	(F) 0	(F) 0	(F) 0
LH	-1735.77	-1735.98	-1741.45	-1740.07

The additive genetic effect σ_{AD}^2, environmental - spousal (σ_{SP}^2), sib (σ_{SB}^2), household (σ_{HS}^2) and residual (σ_{RS}^2) effects, as well as β_{1m} and β_{1f} which are sex-specific age effects (m (male) and f (female)) and β_{2m} and β_{2f} are sex-specific birth year effects.

SE is the standard error of the parameter's value, χ^2df =1 is the likelihood (LH) ratio test, which compared most parsimonious (MP) models with a corresponding restricted model (RM).

TABLE 3

PARENTAL-CHILD CORRELATIONS OF LTL

Relatives	Parent's birth year	Number of pairs	LTL	
			R	P
Father-Son	Total sample	293	0.345	0.0005
	1909-1923	42	0.290	0.0649
	1924-1928	41	0.543	0.0009
	After 1928	210	0.286	0.0007
Father-Daughter	Total sample	242	0.277	0.0007
	1909-1923	23	0.355	0.0967
	1924-1928	28	0.604	0.0009
	After 1928	191	0.178	0.0149
Mother-Son	Total sample	320	0.369	0.0005
	1909-1923	38	0.308	0.0622
	1924-1928	58	0.240	0.0731
	After 1928	224	0.432	0.0004
Mother-Daughter	Total sample	264	0.318	0.0006
	1909-1923	23	0.441	0.0379
	1924-1928	47	0.286	0.0536
	After 1928	194	0.345	0.0006

nificantly stronger (father-son: r=0.543, p=0.0009, n=41; father-daughter: r=0.604, p=0.0009 n=28), whereas, the LTL correlation between mothers and offspring (mother-son: r=0.240, p=0.0731, n=58; mother-daughter: r=0.286, p=0.0536, n=47), did not significantly differ from that observed in the entire population. Furthermore, in the group born after 1928, the LTL correlations between parents and offspring did not significantly differ from those observed in the entire population (father-son: r=0.286, p=0.0007, n=210; father-daughter: r=0.178, p=0.0149, n=191; mother-son: r=0.432; p=0.0004, n=224; mother-daughter: r=0.345 p=0.0006, n=194).

TABLE 4

PARENTAL-OFFSPRING CORRELATIONS OF LTL

Relatives	Parent's birth year	Number of pairs	LTL	
			R	P
Father-offspring	Total sample	535	0.313	0.0004
	1909-1923	65	0.307	0.0134
	1924-1928	69	0.570	0.0006
	After 1928	401	0.232	0.0006
Mother- offspring	Total sample	584	0.349	0.0003
	1909-1923	61	0.348	0.0078
	1924-1928	105	0.263	0.0082
	After 1928	418	0.396	0.0003

Parent-offspring correlations are presented in Table 4. As can be seen, father-offspring and mother-offspring correlations in groups born in 1909–1923 and born after 1928 scarcely differ (r=0.307 vs. r=0.232 in father-offspring, and r=0.348 vs. r=0.396 in mother-offspring). However, the group born in 1924–1928 was significantly different. In this group, father-offspring correlations were significantly higher (r=0.570) and mother-offspring correlations significantly lower (r=0.263) than in other groups.

Discussion

In our previous study, we estimated family correlations and the heritability of LTL. Familial correlations were significant for all categories of a family member, albeit a weak significant correlation was observed between spouses. The heritability of LTL in the tested cohort was estimated at 0.63. Previous research has suggested a strong correlation between telomere dynamics and the processes determining human aging and lifespan. Telomeres, the genetic key to longevity, are nucleoprotein complexes located at the ends of chromosomes, which shorten with every chromosome replication cycle. The replication machinery is unable to copy the ends of the DNA.

Globally, there is still widespread hunger and malnutrition. This study, while demonstrating that starvation has the potential to shorten telomere length, raises several questions. Does starvation exert a stronger effect on telomere length in the reproductive cells of adults (parents) than in the leukocytes of children? Is starvation-induced telomere shortening a sex-dependent phenomenon? Our research team is currently considering conducting experimental in vivo studies to answer these and other questions.

In our opinion, the increased correlation between telomere lengths in father-offspring pairs and the low correlation in mother-offspring pairs in subjects born after the famine in Chuvashia can be explained by the differences in the processes of oogenesis and spermatogenesis in humans. It is known that telomere shortening, as well as the activity of the telomerase enzyme, which lengthens telomeres both in germ cells and in somatic cells at the early stages of embryo formation, transpires during DNA replication. Replication occurs at the interphase of the cell cycle before the cell enters the division process. However, the process of meiotic division, the main component of the gametogenesis process in mammals, and humans, in particular, significantly differs in males and females[22,23]. Unlike spermatogenesis (which begins at puberty and continues during the reproductive period), there is a long pause in oogenesis after the first-order oocyte enters the prophase of the first meiotic division in the woman's ovaries during the embryonic period[23]. The process of telomere shortening during DNA replication in the interphase for future oocytes occurs during the embryonic period of a woman, which is at least fifteen years before fertilization. In other words, by the time of fertilization, the process of DNA replication (and telomere shortening) for future oocytes has been ceased. On the contrary, in the gonads of sexually mature men in spermatogonia before meiosis, the process of DNA replication continues constantly, and first-order spermatocytes are formed. Accordingly, the shortening of sperm telomeres occurs shortly (72–74 days) before fertilization. Therefore, we believe that the long-term nutritional deficiency experienced by males who have undergone prolonged malnutrition affects not only their somatic but also their generative cells. Thus, in contrast to oocytes, spermatocytes can be exposed to stress more quickly and be more responsive to food shortages. The proof of this hypothesis will require laboratory mammal experiments as to the effects of hunger on telomere length in sperm and oocytes.

Aiken et al.[24] examined the influence of a suboptimal grandmaternal diet on the reproductive potential of granddaughters in the absence of any further dietary manipulations in the daughters using a rat low-protein diet model. The authors reported that exposure to a low-protein grandmaternal diet to the granddaughters' ovaries led to a decreased ovarian reserve and an increased intra-abdominal fat mass accompanied by an accelerated accumulation of oxidative stress and mtDNA

copy number instability. Ovarian telomere length declined more rapidly in the exposed granddaughters, indicating accelerated aging in the reproductive tract.

Entringer et al.[25] summarized the evidence from animal experiments and human observational studies. They suggested that adverse intrauterine conditions such as stress, poor nutrition, and obstetric complications are associated with shorter LTL in offspring or decreased telomerase activity at birth and/or in childhood and adulthood. In a previous study by Entringer et al. [26], the authors reported a positive association between maternal folate levels with offspring's LTL. Kim et al.[27] observed a positive association of newborn's LTL with maternal vitamin D levels during pregnancy. Accordingly, vitamin D and folate shortage in times of famine may be the reason for LTL shortening in the offspring.

It is generally known that telomerase activity also affects telomere length[28–30]. A decrease in telomerase activity as a result of stress is well-known. The first evidence of a link between prenatal exposure to stress in humans and subsequent, shorter telomere length in offsprings was published by Entringer et al.[31]. The authors found that exposure to stress in uterine life was associated with a shorter telomere length at a younger age. The same authors [32] found a significant independent linear effect of pregnancy-specific stress on neonatal telomere length in a later study. Similar findings were presented by Marchetto et al.[33], who found a significant negative association between maternal stress and telomere length in newborns. However, in a recent study [34], these patterns were not confirmed.

We believe that prolonged hunger is a stress factor at the somatic level and the psychological level. During the catastrophic famine, expectant mothers experienced severe stress, which may have led to a shortening of the telomeres of the somatic cells of their offspring during blastocyst formation and early embryogenesis.

Conclusions

Our previous study suggested that famine may result in telomere shortening. This study implies that famine may also affect the mode of LTL inheritance. Herein, we provide evidence that putative genetic factors involved in LTL regulation and environmental factors (famine) significantly contribute to the value of the paternal and maternal correlations.

We believe that the increased correlation between the LTL in the father-offspring pair and the low correlation in the mother-offspring pair in the subjects born after the starvation period in Chuvashia can be explained by the differences in the processes of oogenesis and spermatogenesis in humans, i.e., time interval, or a pause in the process of oogenesis, which reduces the possibility of influencing telomere length, oocyte stressors such as hunger, as well as the greater vulnerability of sperm to the effects of starvation.

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GLADOVANJE MOŽE PROMIJENITI NASLJEĐIVANJE DUŽINE TELOMERA PO OČEVOJ, ALI NE I PO MAJČINOJ LINIJI KROZ GENERACIJE: RETROSPEKTIVNA KOHORTNA STUDIJA

S A Ž E T A K

Naš je cilj bio procijeniti učinak gladovanja na nasljeđivanje po ocu i majci duljine telomera leukocita (LTL) u tri skupine ispitanika rođenih prije, tijekom i nakon gladi u Čuvašiji 1922-1923. Ova retrospektivna kohortna studija uključivala je domaće muškarce iz Čuvaša (n=678) i žene (n=647) rođene između 1909.-1980. Podaci su prikupljeni tijekom tri ekspedicije: 1994., 1999., 2002., što nam je omogućilo da dob i godinu rođenja tretiramo kao neovisne varijable. LTL je mjeren kvantitativnom tehnikom lančane reakcije polimerazom. Uočena je značajna razlika u vrijednostima LTL ($\chi^2_{d.f=2}$=79,04, p<0,0001) između spolova. U analizi komponente varijance na temelju pedigrea, ~67,4% LTL varijacije objašnjeno je aditivnom genetskom komponentom. U cijelom uzorku uočena je značajna korelacija između LTL roditelja i potomaka. Očevi rođeni između 1924.-1928. pokazali su znatno jaču LTL korelaciju sa svojim potomcima. LTL korelacija između majki i potomaka u ovoj skupini te između roditelja i potomaka kod rođenih nakon 1928. nije se razlikovala od cjelokupne populacije. Vjerujemo da se povećana korelacija između LTL-a u parovima otac-potomak rođenim nakon gladovanja u Čuvašiji može objasniti razlikama u procesima oogeneze i spermatogeneze u ljudi.