Genetic architecture and heritability of early-life telomere length in a wild passerine

Michael Pepke[1], Thomas Kvalnes[2], Sarah Lundregan[3], Winnie Boner[4], Pat Monaghan[4], Bernt-Erik Sæther[2], Henrik Jensen[2], and Thor Harald Ringsby[2]

[1]Norges teknisk-naturvitenskapelige universitet
[2]Norwegian University of Science and Technology
[3]Norges Teknisk Naturvitenskapelige Universitet Institutt for biologi
[4]Glasgow University

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Abstract

Early-life telomere length (TL) is associated with fitness in a range of organisms. Little is known about the genetic basis of variation in TL in wild animal populations, but to understand the evolutionary and ecological significance of TL it is important to quantify the relative importance of genetic and environmental variation in TL. In this study, we measured TL in 2746 house sparrow nestlings sampled across 20 years and used an animal model to show that there is a small heritable component of early-life TL (h2=0.04), but with a strong component of maternal inheritance. Variation in TL among individuals was mainly driven by environmental (year) variance, but also brood and parental effects. We did not find evidence for a negative genetic correlation underlying the observed negative phenotypic correlation between TL and structural body size. Thus, TL may evolve independently of body size and the negative phenotypic correlation is likely to be caused by non-genetic environmental effects. We further used genome-wide association analysis to identify genomic regions associated with TL variation. We identified several putative genes underlying TL variation; these have been inferred to be involved in oxidative stress, cellular growth, skeletal development, cell differentiation and tumorigenesis in other species. Together, our results show that TL is a lowly heritable, polygenic trait which is strongly affected by environmental conditions in a free-living bird.

INTRODUCTION

Telomeres are nucleoprotein structures that cap the ends of linear chromosomes in most eukaryotes (Blackburn, 1991). Understanding the causes of individual variation in telomere length (TL) is important because this trait has been shown to predict variation in survival or lifespan within and among species (Joeng, Song, Lee, & Lee, 2004; Bize, Criscuolo, Metcalfe, Nasir, & Monaghan, 2009; Monaghan, 2010; Heidinger et al., 2012; Tricola et al., 2018; Wilbourn et al., 2018; Pepke & Eisenberg, 2021) and individual fitness in wild animals (Eastwood et al., 2019). Telomeres shorten through life in many organisms (Dantzer & Fletcher, 2015) due to cell division, oxidative stress, and other factors (Jennings, Ozanne, & Hales, 2000; Reichert & Stier, 2017), which can ultimately result in telomere dysfunction, genome instability, and cell death (Nassour et al., 2019) and organismal senescence (Herbig, Ferreira, Condel, Carey, & Sedivy, 2006). Individual TLs may act as biomarkers or sensors of exposure to intrinsic and extrinsic stressors (Houben, Moonen, van Schooten, & Hageman, 2008), and hence reflect individual condition (Rollings et al., 2017), but the physiological mechanisms underlying the ontogenetic variation in TL is not well known (Monaghan, 2014; Erten & Kokko, 2020). Several studies have investigated the potential of telomere dynamics (i.e. individual differences in TL and telomere loss rate) in mediating life-history trade-offs both across (Dantzer & Fletcher, 2015; Pepke & Eisenberg, 2020) and within relatively long-lived species (Monaghan, 2010; Spurgin et al., 2018). However, despite being an ecologically important trait in many species (Wilbourn et al., 2018),

knowledge about the genetic architecture of TL or its adaptive potential in wild populations remains scarce (Dugdale & Richardson, 2018).

Quantifying the additive genetic variance of a trait is required to understand mechanisms driving adaptive evolution, i.e. the response to selection on a trait (Lande, 1979; Ellegren & Sheldon, 2008; Kruuk, Slate, & Wilson, 2008). However, the magnitude of the heritability and mode of inheritance of TL is not well-known in populations of wild animals, and few general patterns have been described (Horn et al., 2011; Dugdale & Richardson, 2018; Bauch, Boonekamp, Korsten, Mulder, & Verhulst, 2019). Utilizing long-term pedigree data, individual variation in early-life TL can be decomposed into various genetic and environmental sources of variation through a type of mixed-effect model ('animal model'), which takes all relationships from the pedigree into account (Kruuk, 2004; Wilson et al., 2010). Estimates of TL heritabilities from studies using animal models (reviewed in Dugdale & Richardson, 2018) have varied considerably across bird species from h^2 =0 (n =177, in wild white-throated dippers, *Cinclus cinclus* , Becker et al., 2015) toh^2 =0.99 (n =125, in captive zebra finches, *Taeniopygia guttata* , Atema et al., 2015). While most studies are characterized by relatively small sample sizes, recent long-term studies on Seychelles warblers (*Acrocephalus sechellensis* , n =1317, h^2 =0.03-0.08, Sparks et al., 2021) and common terns (*Sterna hirundo* ,n =387, h^2 =0.46-0.63, Vedder et al., 2021) also revealed contrasting estimates of TL heritabilities. Epidemiological studies of humans have documented consistently high TL heritabilities, ranging from h^2 =0.34-0.82 (Broer et al., 2013). In humans, some studies reported strong paternal inheritance (e.g. Njajou et al., 2007) or maternal inheritance (e.g. Broer et al., 2013) or that there were no differences in parental mode of inheritance (e.g. Eisenberg, 2014). In birds, several studies have documented maternal effects on offspring telomere dynamics (Horn et al., 2011; Asghar, Bensch, Tarka, Hansson, & Hasselquist, 2015; Reichert et al., 2015; Heidinger et al., 2016), or effects of parental age at conception on offspring TL (Eisenberg & Kuzawa, 2018). Reichert et al. (2015) found a significant correlation between mother-offspring TL measured at 10 days of age in king penguins (*Aptenodytes patagonicus*), but not when TL was measured at later ages (>70 days). This may be because post-natal telomere loss rate is strongly influenced by individual environmental circumstances (Wilbourn et al., 2018; Chatelain, Drobniak, & Szulkin, 2020) and does not always correlate strongly with chronological age (Boonekamp, Simons, Hemerik, & Verhulst, 2013; Boonekamp, Mulder, Salomons, Dijkstra, & Verhulst, 2014).

Telomeres shorten during growth and a negative phenotypic correlation between TL and body size has been documented within several species (Monaghan & Ozanne, 2018). This may indicate that there is a negative genetic correlation between TL and size, which could act as an evolutionary constraint on the response of TL to selection on body size and contribute to the trade-off between growth and lifespan (Metcalfe & Monaghan, 2003; Roff & Fairbairn, 2012). Thus, quantifying the genetic correlation between TL and size enables us to determine whether TL can evolve independently of body size. Pepke et al. (2021, *submitted*) showed that artificial directional selection on body size affected TL in the opposite direction. However, it is not known if there is a genetic correlation between the two traits, in which case selection acting on TL will affect body size. It is also possible that the negative phenotypic correlation between TL and size has no genetic basis but is shaped by environmental (co)variances (Hadfield, 2008; Kruuk et al., 2008).

TL is a complex phenotypic trait (Aviv, 2012; Hansen et al., 2016) expect to be polygenic, i.e. affected by small effects of many genes (Hill, 2010; Dugdale & Richardson, 2018). Accordingly, numerous genome-wide association studies (GWAS), which tests associations of single-nucleotide polymorphisms (SNPs) with specific traits, have identified several loci correlated with TL in humans that map to genes involved in telomere and telomerase maintenance, DNA damage repair, cancer biology, and several nucleotide metabolism pathways (e.g. Vasa-Nicotera et al., 2005; Andrew et al., 2006; Codd et al., 2010; Levy et al., 2010; Mirabello et al., 2010; Jones et al., 2012; Mangino et al., 2012; Soerensen et al., 2012; Codd et al., 2013; Deelen et al., 2013; Liu et al., 2014; Mangino et al., 2015; Ojha et al., 2016; Delgado et al., 2018; Zeiger et al., 2018; Coutts et al., 2019; Nersisyan et al., 2019; Li et al., 2020). None of the GWA studies in humans specifically tested the marker associations of early-life TL, which pose a challenge to the interpretation of the results, as TL shortens through life in humans (Blackburn, Epel, & Lin, 2015) and genes may have different impacts at various life stages. Furthermore, large sample sizes and dense sampling of genetic loci is

needed to ensure high power in GWA studies (Mackay, Stone, & Ayroles, 2009) and resolve any pleiotropic effects (Prescott et al., 2011). The genes influencing TL in humans that were identified through GWAS only explain a small proportion of the inter-individual variation in TL (<2 %, Aviv, 2012; Codd et al., 2013; Fyhrquist, Saijonmaa, & Strandberg, 2013). One GWAS on TL of a non-human species (dairy cattle, *Bos taurus*) was recently performed (Ilska-Warner et al., 2019) supporting the polygenic nature of early-life TL. However, domesticated species in captivity may display TL dynamics that are not representative for natural populations (Eisenberg, 2011; Pepke & Eisenberg, 2021). There is a paucity of GWAS on TL performed in natural populations.

In this study, we aim to provide novel insights into the genetic architecture of TL and the evolutionary mechanisms by which natural selection can alter telomere ecology using data from a passerine bird. We sampled TL of most individuals (n =2746) born within 20 cohorts in two natural insular populations of wild house sparrows (*Passer domesticus*) at about the same age (11 days), in addition to individuals at the same age in two insular populations that underwent artificial selection on body size for 4 consecutive years (n =569, Kvalnes et al., 2017; Pepke et al., 2021, *submitted*). First, we estimate the phenotypic correlations between TL and tarsus length (as a proxy for body size, Araya-Ajoy et al., 2019) in house sparrow nestlings. Second, we test for effects of parental age on offspring TL. Third, we estimate heritability, environmental variances, and parental effects on early-life TL, and test for genetic correlations between TL, body size, and body condition in the natural populations (primary analyses). We then use similar analyses in the artificially selected populations to validate our results from the primary analyses. Finally, we use high-density genome-wide Single Nucleotide Polymorphism (SNP) genotype data (Lundregan et al., 2018) in a GWAS to identify genetic regions and potential candidate genes underlying variation in early-life TL within wild house sparrows (up to$n$ =383).

MATERIALS AND METHODS

Study populations and data collection

The study was performed in four insular house sparrow populations off the coast of northern Norway (Fig. S1.1 in Appendix S1). The study periods differed between the populations with data from Hestmannøy (66°33'N, 12°50'E) in the years 1994-2013, Træna (Husøy island, 66°30'N, 12°05'E) in the years 2004-2013, and Leka (65°06'N, 11°38'E) and Vega (65°40'N, 11°55'E) both in the years 2002-2006. Hestmannøy and Træna were unmanipulated natural populations and are included in the primary analyses. The populations of Leka and Vega underwent artificial size selection (see Kvalnes et al., 2017; Pepke et al., 2021,*submitted*) and were analyzed separately in a set of secondary analyses as replications of the primary analyses. All four islands are characterized by heathland, mountains, and sparse forest. The sparrows live closely associated with humans and within the study area they are found mainly on dairy farms (Hestmannøy, Vega and Leka), where they have access to food and shelter all year, or in gardens and residential areas (Træna), where they may be more exposed to weather conditions (Araya-Ajoy et al., 2019). Natural nests inside barns or artificial nest boxes were visited at least every 9$^{\text{th}}$ day during the breeding season (May-August) to sample fledglings (5-14 days old, with a median of 11 days). All individuals were ringed using a unique combination of a metal ring and three plastic color rings. Fledged juvenile sparrows and unmarked adults were captured using mist nets during the summer and autumn (September-October). These procedures ensured that approximately 90% of all adult birds were marked on all islands during the study period (Jensen, Steinsland, Ringsby, & Sæther, 2008; Kvalnes et al., 2017). For most fledglings, we measured tarsometatarsus (tarsus) length using digital slide calipers to nearest 0.01 mm and body mass to nearest 0.1 g with a Pesola spring balance (see details in Appendix S1). For 234 nestlings, no nestling morphological measurements were available. Following Schulte-Hostedde, Zinner, Millar, and Hickling (2005) nestling body condition was calculated as the residuals of a linear regression of mass on tarsus length (both $\log_{10}$-transformed). To avoid collinearity in models where both nestling age and tarsus length were included as covariates, we age-corrected tarsus length by using the residuals from a regression of tarsus length on age and age squared (to account for the diminishing increase in tarsus length with age). A blood sample (25 µL) was collected from all individuals, which was stored in 96% ethanol at room temperature in the field and subsequently at -20°C in the laboratory until DNA

extraction.

Molecular sexing and pedigree construction

DNA extraction is described in Appendix S1. Sex of most fledglings (n =2641) was determined using amplification of the CHD-gene located on the avian sex chromosomes as described in Griffiths, Double, Orr, and Dawson (1998). 21 individuals were sexed exclusively based on their phenotype as adults and 84 nestlings could not be sexed. We used individual genotypes on 13 polymorphic microsatellite markers scored using the GeneMapper 4.0 software (Applied Biosystems) to assign parentage in CERVUS 3.0 (Kalinowski, Taper, & Marshall, 2007), as detailed in Rønning et al. (2016). Briefly, for each nestling, CERVUS calculates a LOD-score (log-likelihood ratio) for all putative parents, which is compared to the critical values generated by the simulated parentage analyses, resulting in a 95% parentage assignment confidence. Nestlings within the same clutch were assumed to have the same mother. Nestlings with missing (unassigned) parents were assigned dummy parents, assuming that nestlings within the same clutch were full siblings and thus had the same (unassigned) parents. The dummy parents were included in the pedigree as founders. We calculated individual inbreeding coefficients (F) based on the microsatellite pedigree using the R package 'pedigree' (Coster, 2012). Pedigrees were ordered using the R package 'MasterBayes' (Hadfield, Richardson, & Burke, 2006) and pruned to only contain informative individuals. The pruned pedigrees included 4118 individuals (3093 maternities and 3130 paternities) in the natural populations, and 1057 individuals in artificially selected populations. Maximum pedigree depth was 13 generations, the number of equivalent complete generations (the sum of the proportion of known ancestors across all generations, Wellmann, 2021) was 1.510, and mean pairwise relatedness was 0.003.

Telomere length measurements

Relative erythrocyte telomere lengths (TL) of 2746 nestlings from Hestmannoy and Traena were successfully measured using the real-time quantitative polymerase chain reaction (qPCR) amplification method by Cawthon (2002) with modifications by Criscuolo et al. (2009). Primer sequences, PCR assay setup and thermal profiles followed Pepke et al. (2021, *submitted*) and are detailed in Appendix S1. Briefly, this method measures the ratio of telomere sequence relative to the amount of a non-variable gene (GAPDH) and a reference sample. The reference sample consisted of pooled DNA from 6 individuals, which was also included as a 2-fold serial dilution (40-2.5 ng/well) on all plates to produce a standard curve, in addition to a non-target control sample (all in triplicates). Samples were randomized and run on 2x127 96-well plates (telomere and GAPDH assays, respectively). The qPCR data was analyzed using the qBASE software (Hellemans, Mortier, De Paepe, Speleman, & Vandesompele, 2007), which computes relative TL as the ratio (T/S) of the telomere repeat copy number (T) to a single copy gene number (S) similar to Cawthon (2002). In qBASE the T/S ratio is calculated as calibrated normalized relative quantities (CNRQ) that control for differences in amplification efficiency between plates and for inter-run variation by including three inter-run calibrators from the standard curve. All individual plate efficiencies were within 100+-10% (mean telomere assay efficiency was 97.5+-3.9%, and 97.6+-4.2% for GAPDH assays). The average of the reference sample cycle thresholds (Ct) across all plates were 10.54+-0.03 S.D. and 21.53+-0.02 S.D. for telomere and GAPDH assays, respectively. Thus, while reproducibility of TL measurements within the reference sample of the same DNA sample extract is high, we performed DNA re-extraction of the same blood samples for 25 individuals to test TL consistency across DNA extractions (Appendix S1). The re-extractions were run on different plates and the TL estimates of these samples remained highly correlated (R^2=0.75, Fig. S1.2). For these individuals, the average of the TL measurements was used in subsequent analyses. All reactions for the primary analyses (from the populations on Hestmannoy and Traena) were performed by the same person (MLP). MLP and WB generated the secondary dataset (n =569 on 2x21 plates, from the populations on Leka and Vega) as described in Pepke et al. (2021, *submitted*). The primary and secondary datasets used different reference samples and are therefore not combined in the analyses.

Statistical analyses

The correlation between tarsus length and telomere length

We first tested the phenotypic correlation between TL and tarsus length (as a proxy for body size) within 2462 house sparrow nestlings from Hestmannoy and Traena. TL (response variable) was $\log_{10}$-transformed and linear mixed-effects models (LMMs) were fitted with a Gaussian error distribution (R package '*lme4* ', Bates, Machler, Bolker, & Walker, 2015). Sex differences in TL are known for house sparrows (Pepke et al., 2021,*submitted*). Thus, models included sex, (continuous) fledgling age at sampling, hatch day (ordinal date mean centered across years), and island identity as fixed effects. We fitted random intercepts for brood identity and year to account for the non-independence of nestlings from the same brood and year. Because our study populations are known to be affected by inbreeding depression (Niskanen et al., 2020), we included the inbreeding coefficient (F) as a fixed effect (Reid & Keller, 2010). We then compared models with and without (age-standardized) tarsus length using Akaike's information criterion corrected for small sample sizes ($AICc$, Akaike, 1973; Hurvich & Tsai, 1989), and Akaike weights (w) and evidence ratios (ER) to determine the relative fit of models given the data (Burnham & Anderson, 2002). Models were validated visually by diagnostic plots and model parameters are from models refitted with restricted maximum likelihood (REML). Estimates and 95% confidence intervals (CI) are reported.

Parental age effects on offspring telomere length

We tested whether maternal age at conception (MAC [mean 1.8+-1.1 S.D. years, range 1-7 years], n =373 mothers with n =1967 offspring) or paternal age at conception (PAC [mean 2.1+-1.2 S.D. years, range 1-8 years], n =388 fathers with n =1927 offspring) predicted TL in offspring from Hestmannoy and Traena. We applied within-subject centering (van de Pol & Wright, 2009) to separate within-parental age effects (e.g. senescence) from between-parental age effects (e.g. selective disappearance), by including both the mean parental age at conception and the deviation from the mean parental age for each parent as fixed effects in two LMMs (for fathers and mothers, respectively) explaining variation in offspring TL ($\log_{10}$-transformed). Both models included island identity and sampling age as fixed effects, and random intercepts for year and either maternal identity or paternal identity.

Heritabilities and genetic correlation of telomere length, tarsus length, and body condition

We used a multivariate Bayesian animal model (Kruuk, 2004; Hadfield, 2019) fitted with Markov chain Monte Carlo (MCMC) to estimate heritability and genetic correlations of early-life TL, age-standardized tarsus length and body condition in the two natural island populations (Hestmannoy and Traena, n =2662) and the two manipulated island populations (Leka & Vega, n =569) that underwent artificial size selection. TL was $\log_{10}$-transformed and all traits were fitted with a Gaussian error distribution using the R package 'MCMCglmm' (Hadfield, 2010). Models included sex, fledgling age at sampling, island identity, and inbreeding coefficient (F) as fixed effects (Wilson, 2008), which were fitted such that different regression slopes were estimated for each trait (Hadfield, 2019). To estimate variance components, random intercepts were included for individual identity ('animal', V_A), brood identity (V_B) nested under mother identity, father (V_F) and mother identity (V_M), and birth year (cohort effects, V_Y). Parental effects include those influences on offspring TL that are repeatable across the lifetime of the mother or father (Kruuk & Hadfield, 2007), while brood identity accounts for other common environmental effects (McAdam, Garant, & Wilson, 2014). House sparrows are multi-brooded laying up to 3 clutches in a season and may breed in multiple years, with an average of 3.6+-1.3 S.D. fledglings per brood in this study. They are socially monogamous, but extra-pair paternity occurs at rates of 14-18 % in wild populations (Ockendon, Griffith, & Burke, 2009; Hsu, Schroeder, Winney, Burke, & Nakagawa, 2014). Using genetic pedigrees, extra-pair paternity can be seen as natural cross-fostering experiments that improve statistical power to separate genetic and environmental variance components (Kruuk & Hadfield, 2007). Random effects were specified with 3x3 covariance matrices to estimate the variances and covariances between the effects for each trait.

We also ran univariate models of TL, tarsus length and body condition including the same fixed and random effects as in the multivariate model (Appendix S2). For comparison with previous studies (e.g. Asghar et al., 2015), we tested whether maternal TL and/or paternal TL predicted offspring TL using two LMMs (parent-offspring regressions, Appendix S2). Furthermore, we included maternal (V_{DAM}) and paternal (V_{SIRE}) genetic effects (e.g. Wolf & Wade, 2016) in a multivariate animal model to quantify these effects

while accounting for the environmental variances specified above (Appendix S2). To test for sex-specific heritabilities (e.g. Jensen et al., 2003; Olsson et al., 2011), we ran a bivariate animal model of TL in females and males as two different phenotypic traits with a genetic correlation between them (Appendix S2).

We used inverse-Wishart priors for random effects and residual variances in the multivariate model (V=I_3 and nu=3, Hadfield, 2019). We re-ran analyses with other relevant priors (parameter expanded) to verify that results were not too sensitive to the choice of prior. The MCMC chain was run for 2,000,000 iterations, sampling every 500 iterations after a burn-in of 5% (100,000 iterations). Mixing and stationarity of the MCMC chain was checked visually and using Heidelberger and Welch's convergence test (Heidelberger & Welch, 1983) implemented in the 'coda' package (Plummer, Best, Cowles, & Vines, 2006). All autocorrelation values were <0.1 and effective sample sizes were >3,000. The narrow-sense heritability was calculated as the posterior mode of the proportion of phenotypic variance explained by additive genetic variance (Wilson et al., 2010):$h^2 = \frac{V_A}{(V_A+V_B+V_F+V_M+V_R+V_Y)}$, where V_R is the residual variance. Estimates are provided as their posterior mode with 95% highest posterior density intervals (HPD). All analyses were performed in R version 3.6.3 (R Core Team, 2020).

SNP genotype data and association analyses

Nestlings that survived to adulthood (recruited) on Hestmannoy and Traena were genotyped on a high-density 200K SNP array (detailed in Lundregan et al., 2018) with median distances between SNPs shorter than 5,000 bp. SNPs were originally identified from whole-genome re-sequencing of 33 individual house sparrows which were mapped to the house sparrow reference genome (Elgvin et al., 2017). DNA was extracted as described in Hagen et al. (2013), separately from telomere analyses. Data preparation and quality checks were performed using the 'GenABEL' package (GenABEL project developers, 2013). We removed SNPs or individuals for which there was more than 5% missing data, the minor allele frequency (MAF) was less than 1%, or pairwise identity-by-state (IBS) was more than 95%. After quality control, the genomic relationship matrix (GRM) was computed based on 180,650 [180,666] autosomal markers in 373 [383] individuals (142 [145] males and 137 [142] females from Hestmannoy and 47 [48] males and 47 [48] females from Traena) with numbers in brackets showing sample sizes when individuals with missing tarsus length measurements are included. We then performed two GWA analyses by fitting LMMs for the variation in TL using the package 'RepeatABEL' (Ronnegard et al., 2016): The first model included age-standardized tarsus length as a covariate, and the second model did not. Both models included sex, age, hatch day (mean centered), F , and island identity as fixed effects, and brood identity, year, and the GRM fitted as random effects. Finally, we determined if SNPs significantly associated with TL were within 100 kb of any gene within the annotated house sparrow genome, because this is the distance that linkage disequilibrium decays to background levels in this species (Elgvin et al., 2017; Hagen et al., 2020).

RESULTS

The correlation betweentarsus length and telomere length

The model that included tarsus length was the highest ranked model for explaining variation in TL (w_1=0.78,$ER_{\ 1}=w_1/w_2$ =3.55, model without tarsus length: $[?]_2AICc$ =2.5). Thus, there was a negative association between tarsus length and TL ($\beta_{\tau\alpha\rho\sigma\upsilon\varsigma\ \lambda\epsilon\nu\gamma\tau\eta}$ =-0.004±0.002, CI=[-0.007, -0.000], n =2462, Fig. 1 and Table 1), such that larger nestlings generally had slightly shorter early-life telomeres.

Parental age effects on offspring telomere length

There was no evidence for associations between offspring TL and MAC ($\beta_{[;]MA^{\backprime}}$ =0.004±0.004, CI=[-0.005, 0.013],$\beta_{\mu\epsilon\alpha\nu\ MA^{\backprime}}$ =0.002±0.005, CI=[-0.008, 0.012], Fig. S2.1a,c) or PAC ($\beta_{[;]\Pi A^{\backprime}}$ =0.000±0.003, CI=[-0.005, 0.006], $\beta_{\mu\epsilon\alpha\nu\ \Pi A^{\backprime}}$ =0.002±0.005, CI=[-0.007, 0.012], Fig. S2.1b,d).

Heritabilities and genetic correlations of telomere length, tarsus length, and body condition

We found non-zero additive genetic variances (V_A) for TL (V_A =0.009, HPD=[0.008, 0.010]), tarsus length (V_A =0.190, HPD=[0.116, 0.315]) and body condition (V_A =0.006, HPD=[0.005, 0.006]) in the natural po-

pulations (Table 2, Fig. 3). The main component contributing to variance in TL was between-year differences (V_Y , explaining 70% of the variance), while maternal (V_M , 8%), paternal (V_F , 7%), and brood variances (V_B , 6%) also explained considerable proportions of the total phenotypic variance (Fig. 3). Combined, these environmental effects captured 91% of the phenotypic variance in TL. For tarsus length and condition, the main variance components were among different broods (38%) and among years (77%), respectively (Table 2, Fig. 3). The heritabilities were h^2 =0.042 for TL (HPD=[0.024, 0.064]), h^2 =0.076 (HPD=[0.045, 0.123]) for tarsus length, andh^2 =0.028 (HPD=[0.016, 0.0.043]) for body condition. The heritability estimates were of the same magnitude in the univariate animal models (Table S2.1). There was no evidence for a genetic correlation between TL and tarsus length (r_A =-0.017, HPD=[-0.120, 0.091]) or between TL and condition (r_A =-0.010, HPD=[-0.079, 0.060]).

Parent-offspring regressions showed a large maternal inheritance component in TL ($h^2{}_{maternal}$ =0.45±0.16, CI=[0.136, 0.758]), but no paternal inheritance (Fig. S2.2). Including parental genetic effects in a multivariate animal model confirmed slightly higher maternal ($h^2{}_{maternal}$ =0.078, HPD=[0.042, 0.104]) than paternal heritability of TL ($h^2{}_{paternal}$ =0.070, HPD=[0.038, 0.094], Table S2.2). We found no evidence of differences in sex-specific heritabilities of TL (Table S2.3).

In the analyses of the artificially selected populations (Leka and Vega, Table S2.4) we found comparable heritability estimates for TL (h^2 =0.035, HPD=[0.008, 0.084]) and body condition (h^2 =0.019, HPD=[0.004, 0.050]), and a slightly higher estimate for tarsus length (h^2 =0.114, HPD=[0.045, 0.247]). Similarly, there was no evidence for genetic correlations between TL and tarsus (r_A =-0.027, HPD=[-0.224, 0.181]) or between TL and body condition (r_A =-0.006, HPD=[-0.130, 0.134], Table S2.4).

GWA analyses

Six SNPs showed evidence for an association with early-life TL (Table 3, Fig. 4), with a Bonferroni corrected threshold (nominal P<0.05 and P[?]2.77x10^{-7} at the genome-wide P-value threshold) and a genomic inflation factor λ=1.0476±0.0002 (Fig. S2.3). Seven SNPs that showed weak evidence for an association with TL (nominal 0.05<P<0.10) are also shown in Table 3. Using the annotated house sparrow genome, a total of sixteen genes on four chromosomes were found to be located within proximity (±100 kb) of four of the six top SNPs (Table 4). Among five of the seven SNPs with weak evidence for an association with TL we identified 10 genes within ±100 kb on three chromosomes (Table S2.5).

SNPa429690 is located on chromosome 2 within the Aquaporin-1 (AQP1) gene, which encodes the AQP1 water channel membrane protein. The AQP1 protein is abundant in erythrocytes (where TL is measured) and important in regulating body water transport and balance (Nielsen et al., 2002), but also in a range of other physiological functions including cell migration, wound healing, fat metabolism and oxidative stress (Saadoun, Papadopoulos, Hara-Chikuma, & Verkman, 2005; Verkman, Anderson, & Papadopoulos, 2014). The same SNP is located 39 kb from the growth hormone-releasing hormone receptor (GHRHR), which controls body growth (Mullis, 2005), and has been associated with telomerase activity (Banks et al., 2010), lifespan (Soerensen et al., 2012) and the progression of several types of cancer (Chu et al., 2016; Schally et al., 2018; Villanova et al., 2019). Humans with over-expression of growth hormones and consequently insulin-like growth factor 1 (IGF-1) have shorter telomeres (Aulinas et al., 2013; Deelen et al., 2013; Matsumoto et al., 2015; Monaghan & Ozanne, 2018). SNPa17235 was close (11 kb) to FRMD4B (FERM domain-containing protein 4B), which is involved in epithelial cell polarity that is important in tissue morphogenesis (Ikenouchi & Umeda, 2010). This SNP was also near other genes related to cell proliferation (UBA3 and TMF1), skeletal muscle organization (LMOD3) and oxidative stress (ARL6IP5, see Table 4). SNPa108592 was in the vicinity (43-84 kb) of several genes on chromosome 15 linked to cell proliferation, ubiquitination and immune response (Table 4). SNPa450086 was 76 kb from OXR1 (oxidation resistance protein 1) that regulates expression of several antioxidant enzymes (Volkert, Elliott, & Housman, 2000).

Among the SNPs with weak evidence for an association with TL, SNPa34968 was close (11 kb) to the ZBED1 (zinc finger BED domain-containing protein 1) gene that is involved in cell proliferation and DNA replication (Ohshima, Takahashi, & Hirose, 2003; Hansen, Traynor, Ditzel, & Gjerstorff, 2018), and may also regulate

telomere length in*Drosophila* flies (Silva-Sousa, Varela, & Casacuberta, 2013). Expression of the SCN4A gene (68 kb from SNPa491204) has previously been correlated with TL in human stem cells (Wang et al., 2017). SNPa491204 was also near (49 kb) the growth hormone gene GH (which is linked to TL as described above, see also Pauliny, Devlin, Johnsson, & Blomqvist, 2015) and WNT9B (40 kb) of the Wnt/β-catenin signaling pathway, which is modulated by telomerase (Park et al., 2009). SNPi16410 was closest to SHCBP1 (70 kb) and CDCA4 (76 kb), which are both involved in cell proliferation and probably apoptosis (Wang et al., 2008; Asano et al., 2014; Xu, Wu, Li, Huang, & Zhu, 2018; Zou et al., 2019). SHCBP1 is upregulated by growth factor stimulation (Schmandt, Liu, & McGlade, 1999). CDCA4 is likely involved in the regulation of hematopoietic stem cells from where erythrocytes (reflecting TL) are derived (Abdullah, Jing, Spassov, Nachtman, & Jurecic, 2001).

Searching beyond the ±100 kb limits, the top marker, SNPa223513, was found closest (106 kb) to the SAMD5 (sterile alpha motif domain-containing protein 5) gene, which function is unknown, but may play a role in tumorigenesis (Sa, Lee, Hong, Kong, & Nam, 2017), cancer cell proliferation (Matsuo et al., 2014) or tumor suppression in the cytoplasm (Yagai et al., 2017). SNPa108592 is 263 kb from LRRC43 (leucine-rich repeat-containing protein 43) that belongs to a class of poorly known proteins often associated with innate immunity (Ng & Xavier, 2011). Members of the LRRC superfamily have previously been associated with TL variation in humans (Codd et al., 2010). The same SNP is 363 kb from ZCCHC8 (zinc finger CCHC domain-containing protein 8) that is required for telomerase functioning (Gable et al., 2019).

When not controlling for the effect of tarsus length on TL, the same six top SNPs were identified as in the analysis above including tarsus length (Table S2.6). In addition, SNPa208275 was associated with TL and found 47 kb from FGFR2 encoding a tyrosine-protein kinase that is a receptor for fibroblast growth factors that regulates several aspects of cell proliferation and bone morphogenesis (Table S2.7, Katoh, 2009).

DISCUSSION

The evolutionary response to selection on telomere length depends on the additive genetic variance of TL and the strength and sign of any genetic correlations with other traits under selection. Dugdale and Richardson (2018) criticized past quantitative genetic studies of TL on the main grounds that 1) they applied basic regression analyses that did not consider environmental effects impacting TL and as a consequence of that, additive genetic effects may have been overestimated in previous studies; 2) TL changes with age, complicating the fact that parents and offspring are often sampled at different ages; and 3) sample sizes were too small to provide enough power to separate genetic and environmental effects using animal models. Here, we have accommodated this critique by 1) using mixed-effect animal models to partition genetic and environmental effects; 2) measuring early-life TL in both offspring and parents at the same time point in life (as around 11 days old fledglings); and 3) collect TL data from more than 3300 individuals across 4 populations, which represent a considerably larger sample size than those of previous wild animal studies.

We found that around 4% of the variation in early-life TL in house sparrows at the end of the nestling growth period was determined by additive genetic variation. The relatively small additive genetic variance and large year variance in early-life TL appears to be in accordance with the effects of relative growth and weather conditions on TL in similar sparrow populations (Pepke et al., 2021,*submitted*). Similarly small but significant heritabilities of TL have been reported using animal models for e.g. nestling collared flycatchers, *Ficedula albicollis*(h^2 =0.09, Voillemot et al., 2012), Seychelles warblers (h^2 =0.03-0.08, Sparks et al., 2021) and adult greater mouse-eared bats, *Myotis myotis*(h^2 =0.01-0.06, Foley et al., 2020), in which TL correlates with several weather variables. These studies also documented considerable year effects on TL (Foley et al., 2020; Sparks et al., 2021) similar to studies finding no heritability of TL in white-throated dippers (Becker et al., 2015) and European badgers (*Meles meles* , van Lieshout et al., 2021). In comparison, studies based on parent-offspring regression have often found higher TL heritabilities in e.g. king penguins (h^2 =0.2, Reichert et al., 2015), jackdaws (*Coloeus monedula* ,h^2 =0.72, Bauch et al., 2019), and sand lizards (*Lacerta agilis* , h^2 =0.5-1.2, Olsson et al., 2011). The heritability of TL in house sparrows is comparable to that of many life-history traits and considerably lower than many morphological traits (e.g. Mousseau & Roff, 1987; Visscher, Hill, & Wray, 2008), which may suggest that TL is under strong selection in the wild (Voillemot et al., 2012)

or that there are considerable non-additive genetic or environmental influences on early-life TL. Curiously, Pepke et al. (2021, *submitted*) reported indications of weak non-linear or negative associations between TL and various measures of fitness (survival and reproductive success) in house sparrows, suggesting that the environmentally pliant TL dynamics of these relatively fast-lived birds may be very different from several other bird species (reviewed in Wilbourn et al., 2018). In other species, positive associations between early-life TL and survival have been documented (Wilbourn et al., 2018), which may translate into an increased lifetime reproductive success (Eastwood et al., 2019; Sudyka, 2019; Bichet et al., 2020).

A considerable proportion of the phenotypic variance in TL could be attributed to brood and parental effects (Fig. 3). However, we did not find evidence that parental effects were transmitted through a parental age at conception effect (Fig. S2.1). Paternal age effects, which has been observed in several other species (Eisenberg & Kuzawa, 2018), may not manifest in these house sparrows because the mean age at reproduction was low (around 2 years). Parent-offspring regressions (Fig. S2.2) and parental genetic effects models (Table S2.2) suggested a stronger component of maternal heritability of TL, which is similar to the inheritance pattern found in several bird species (Horn et al., 2011; Asghar et al., 2015; Becker et al., 2015; Reichert et al., 2015) and some studies on humans (Broer et al., 2013). Maternal effects on offspring TL are expected to be strongest in early-life (Wolf, Brodie Iii, Cheverud, Moore, & Wade, 1998) and could act through e.g. yolk-deposited components in the egg (Criscuolo, Torres, Zahn, & Williams, 2020; Stier et al., 2020a) or post-laying through maternal care behavior (e.g., incubation and feeding rate, Stier, Metcalfe, & Monaghan, 2020b; Viblanc et al., 2020). Since TL is a heritable trait, a positive maternal effect on offspring TL may be expected to increase the expected rate of adaptive evolution of TL (Wolf et al., 1998; Rasanen & Kruuk, 2007). Parental and environmental effects documented in other studies (Monaghan & Metcalfe, 2019) suggest that some of the variation in TL may be inherited through epigenetic carry-over effects (Bauch et al., 2019; Eisenberg, 2019) that are not resolved by comparing early-life TLs. Thus, such effects may be more important in shaping nestling TL loss, rather than early-life TL (Heidinger et al., 2016). However, TL maintenance are at present not well known within house sparrows (Vangorder-Braid et al., 2021).

There was evidence for additive genetic variance in the tarsus length of sparrow nestlings, but the heritability estimate (h^2 =0.076, Table 2) was considerably smaller than those of adult house sparrows in a larger sample of populations in the same area (Jensen et al., 2008; Araya-Ajoy et al., 2019) and other avian species (Merila & Sheldon, 2001). However, there was a large brood effect on nestling tarsus length suggesting common environmental effects within broods (e.g. Potti & Merino, 1994). For instance, variation in clutch size, seasonal differences in food availability, weather conditions (Ringsby, Saether, Tufto, Jensen, & Solberg, 2002), and provisioning rates by parents (Ringsby, Berge, Saether, & Jensen, 2009) may induce intra-clutch competition and variation in the degree to which nestlings are able to achieve their adult tarsus lengths at fledging (Naef-Daenzer & Keller, 1999; Metcalfe & Monaghan, 2001). Furthermore, measurement error is probably higher for the incompletely ossified nestling tarsi, which are covered by a soft fleshy skin tissue that contributes to the measured length.

Individuals with shorter tarsi (a proxy for structural size, Araya-Ajoy et al., 2019) were found to have longer telomeres, although the effect of tarsus length on TL was small and there was considerable variation in TL for a given size (Fig. 1). This confirms previous observations of a prevailing negative correlation between body size and TL within house sparrows (Ringsby et al., 2015; Pepke et al., 2021, *submitted*) and other species (Monaghan & Ozanne, 2018). We did not find evidence for a significant negative genetic correlation between TL and tarsus length (Table 2). Instead, the negative phenotypic association between TL and tarsus length may be induced by common environmental effects that affects both traits in opposite directions. The lack of a genetic correlation between TL, tarsus length or body condition could also be attributed to selection acting simultaneously on some correlated, unmeasured trait (Merila, Sheldon, & Kruuk, 2001). Both with and without controlling for the effect of tarsus length on TL, our GWAS on TL identified several genes involved in skeletal development, cellular growth and differentiation that may regulate body growth or size (e.g. GHRHR, Tmem120b, LMOD3, GH, POU1F1, SHCBP1, and FGFR2, Table 4, S2.5, and S2.7), which could, however, suggest some genetic basis of the negative correlation between TL and size. For instance, several growth factors were downregulated in telomerase deficient mouse bone marrow stromal stem cells

(Saeed & Iqtedar, 2015) suggesting that short telomeres or telomere loss could also be a constraint on proliferation potential. Thus, because several of the genes that may regulate TL during early development appear to also be involved in cell proliferation or morphogenesis, such genes may have co-evolved.

None of the genes highlighted in our analysis have previously been linked to TL in GWA studies (reviewed in the introduction). However, the*Drosophila* orthologue of ZBED1 (dDREF) has been linked to telomere maintenance in *Drosophila* flies (Tue et al., 2017), but telomere biology in this taxon is very different from most other eukaryotes and does not involve telomerase (Casacuberta, 2017). Yet, the dDREF/ZBED1 is important for cell proliferation in both*Drosophila* (Matsukage, Hirose, Yoo, & Yamaguchi, 2008), bats (*Rhinolophus ferrumequinum* , Xiao et al., 2016) and human cancer cells (Jiang et al., 2018, but see Hansen et al., 2018). Several of the identified candidate genes (ZBED1, AQP1, SHCBP1, CDCA4, ARL6IP5, UBA3, RNF34, RHOF, ANAPC5, and FGFR2) are involved in cell proliferation and apoptosis during which TL and telomerase activity invariably play an important role (Greider, 1998; Masutomi et al., 2003). The RHOF gene product functions cooperatively with CDC42 and Rac to organize the actin cytoskeleton (Ellis & Mellor, 2000). While the latter complex participates in the control of telomerase activity in human cancer cells (Yeh, Pan, & Wang, 2005), any direct link between RHOF and TL remains unexplored. CDC42 is activated by FGD4 (Chen et al., 2004), which was found within a major locus affecting TL in humans (Vasa-Nicotera et al., 2005). SNPa108592 was found near several genes involved in cell proliferation, differentiation, immune response, and ubiquitination (Table 4). Ubiquitination regulates several shelterin components and telomerase activity (Peuscher & Jacobs, 2012; Yalcin, Selenz, & Jacobs, 2017). The closest gene, ORAI1 (43 kb), the keeper of the gates of calcium ions (Homer, 1924), is crucial for lymphocyte activation and immune response (Feske et al., 2006). Although not linked to ORAI1 mutations, calcium ion levels can modulate telomerase activity (reviewed in Farfariello, Iamshanova, Germain, Fliniaux, & Prevarskaya, 2015).

We identified a particularly interesting gene associated with TL, AQP1. The AQP1 channel not only conducts water across cell membranes, but also hydrogen peroxide, a major reactive oxygen species (ROS, Tamma et al., 2018), and nitric oxide (Herrera, Hong Nancy, & Garvin Jeffrey, 2006), which is an important regulator of oxidative stress (Pierini & Bryan, 2015) and a weak oxidant itself (Radi, 2018). Furthermore, increased availability of nitric oxide may activate telomerase and thereby prevent replicative senescence (in endothelial cells, Vasa, Breitschopf, Zeiher Andreas, & Dimmeler, 2000). Enhanced oxidative stress associated with endothelial cell senescence may also be mediated by AQP1-regulated nitric oxide flow (Tamma et al., 2018; Chen et al., 2020). In AQP1 knocked-out erythrocytes (where TL was measured) cell lifespan was shortened (Mathai et al., 1996) and angiogenesis is inhibited in AQP1 knocked-out chicken embryos (Camerino et al., 2006) and mice (Saadoun et al., 2005). Telomeres are particularly sensitive to ROS and shorten due to oxidative stress during growth (von Zglinicki, 2002; Reichert & Stier, 2017). For instance, Kim, Noguera, Morales, and Velando (2011) found a negative genetic correlation between growth and resistance to oxidative stress in yellow-legged gull (*Larus michahellis*) chicks, which could be mediated by TL (see also Smith, Nager, & Costantini, 2016). Another candidate gene, OXR1, 76 kb from SNPa450086, has a well-described antioxidant function (Volkert et al., 2000; Oliver et al., 2011) and is upregulated in senescent human cells (Zhang et al., 2018). Knockdown of OXR1 increases ROS production and ultimately induces apoptosis (Oliver et al., 2011; Zhang et al., 2018), which could be due to telomere crisis.

Over-expression of AQP1 has been associated with several types of cancer (Verkman, Hara-Chikuma, & Papadopoulos, 2008), suppression of apoptosis (Yamazato et al., 2018) and may play an important role in tumor biology (Saadoun et al., 2005; Tomita et al., 2017). Other candidate genes including GHRHR, SAMD5, SHCBP1 (Tao et al., 2013), GH (Boguszewski & Boguszewski, 2019), and OXR1 (Yang et al., 2015) are also involved in tumorigenesis. Cancer prevalence is not well-studied in wildlife (Pesavento, Agnew, Keel, & Woolard, 2018), but tumors have been documented in house sparrows (Moller, Erritzoe, & Soler, 2017). Long telomeres or increased telomerase activity may increase the risk of acquiring an oncogenic mutation before cell proliferation ceases due to telomere crisis (Aviv, Anderson, & Shay, 2017; Pepke & Eisenberg, 2021). However, long telomeres also increase immune function required to combat cancers (Helby, Nordestgaard, Benfield, & Bojesen, 2017) and short telomeres can result in chromosomal instability leading to some types of cancer (Ma et al., 2011; Aviv et al., 2017). This TL paradox is not yet resolved (Eisenberg & Kuzawa,

2018). However, genes affecting both TL and cancer risk (Tacutu, Budovsky, Yanai, & Fraifeld, 2011; Jones et al., 2012) could underlie the antagonistic pleiotropy of trade-offs between long telomeres in early-life (with potential benefits to growth, reproduction, and other oxidative stress inducing processes) and later-life cancer mortality (Tian et al., 2018). For instance, Vedder et al. (2021) found a significant genetic correlation between TL and lifespan in wild common terns. Cancer is often viewed as a senescence-related pathology (Lemaitre et al., 2020). However, the absence of cancer in early-life should not lead us to conclude that a somatic and potentially fitness-related cost is not paid to maintain that status (Thomas et al., 2018).

We have shown that TL is a heritable, polygenic trait with considerable environmental variation and a maternal inheritance component in a wild passerine. It is, however, important that future studies attempt to confirm the candidate genes identified here as associated with TL in other wild populations. Even though the additive genetic component was small, selection on variation in TL may produce evolutionary change in TL over time in wild populations. The large component of variation in early-life TL caused by annual environmental stochasticity suggests that this will generate heterogeneity in TL among cohorts. Although we did not find a negative genetic correlation underlying the negative phenotypic correlation between TL and body size, we may hypothesize that selection for larger nestling size, which may enhance survival until recruitment (Ringsby, Saether, & Solberg, 1998), will be associated with selection for shorter early-life TL due to non-genetic mechanisms, which can ultimately influence lifespan or reproductive success.

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DATA ACCESSIBILITY

All data will be made available on Dryad or another open access channel upon acceptance of the manuscript. SNP genotype data is available on Dryad (https://doi.org/10.5061/dryad.hp758sn).

AUTHOR CONTRIBUTIONS

MLP measured telomeres, analyzed the data, and wrote the manuscript with comments from all authors. WB and PM advised telomere measurements. TK, HJ, THR, and SL advised statistical analyses. B-ES, THR, and HJ established the study system. THR, HJ, and TK contributed to the fieldwork.

TABLES AND FIGURES

Figure 1: The negative association between age-corrected tarsus length and telomere length ($\log_{10}$-transformed) in 2462 house sparrow nestlings with a regression line from a LMM shown in Table 1. The 95% confidence interval (grey) reflects only the fixed effects.

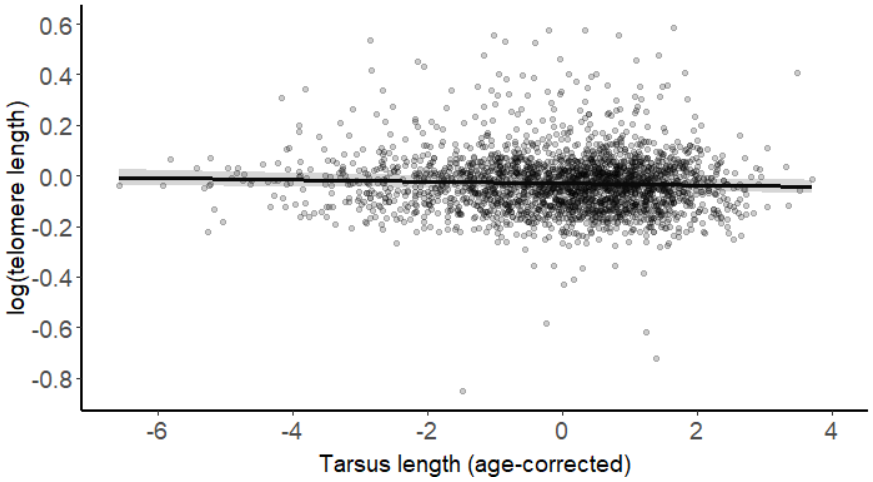

Table 1: Estimates, standard errors (SE), lower and upper 95% confidence intervals (CI) from a LMM of variation in telomere length (TL). The model included random intercepts for brood identity and year.

Response variable: $\log_{10}$(TL)	*Estimate*	SE
intercept	-0.012	0.020
tarsus length	*-0.004*	*0.002*
sex [female]	-0.005	0.004
island identity [Hestmannøy]	-0.002	0.007
age	-0.002	0.002
inbreeding coefficient (F)	*-0.194*	*0.096*
hatch day	-0.000	0.000
$\sigma^2_{\text{brood ID}}$ (n=948)	0.004	
σ^2_{year} (n=20)	0.002	
Marginal R^2 / Conditional R^2: 0.006 / 0.408	Marginal R^2 / Conditional R^2: 0.006 / 0.408	Marginal R^2 / Conditional R

Table 2: Mean posterior distribution estimates of a multivariate animal model of the co-variation of early-life telomere length, tarsus length, and body condition (n =2662) with fixed effects, variance components, and lower and upper 95% highest posterior density intervals (HPD). Abbreviations refer to: heritability h^2 , additive genetic variance V_A , brood variance V_B , maternal variance V_M , paternal variance V_F , year variance V_Y , residual variance V_R , and with identical subscripts for the co-variances (Cov) including the additive genetic correlation r_A .

Variable	$\log_{10}$(telomere length)	$\log_{10}$(telomere length)	$\log_{10}$(telomere length)	tarsus leng
Fixed effects	**Esti-mate**	**HPD Lower**	**HPD Upper**	**Esti-mat**
intercept	0.0214	-0.1799	0.2003	0.2115
sex [female]	-0.0036	-0.0137	0.0070	-0.0587
island identity [Hestmannøy]	0.0078	-0.0455	0.0470	0.0024
inbreeding coefficient (F)	-0.2434	-0.5632	0.1491	-0.9219
age	-0.0049	-0.0096	-0.0008	-0.0260
Variance components				
h^2	0.0424	0.0242	0.0641	0.0764
V_A	0.0092	0.0084	0.0103	0.1896

Variable	$\log_{10}$(telomere length)	$\log_{10}$(telomere length)	$\log_{10}$(telomere length)	tarsus leng
V_B	0.0117	0.0104	0.0135	0.9273
V_M	0.0144	0.0126	0.0170	0.1479
V_F	0.0135	0.0117	0.0155	0.1407
V_Y	0.1321	0.0747	0.2877	0.2199
V_R	0.0073	0.0066	0.0079	0.8165
Co-variances between TL and tarsus				
r_A	-0.0170	-0.1204	0.0914	
Cov_A	-0.0006	-0.0056	0.0038	
Cov_B	-0.0049	-0.0155	0.0068	
Cov_M	-0.0012	-0.0073	0.0056	
Cov_F	0.0005	-0.0057	0.0054	
Cov_Y	0.0004	-0.1041	0.1035	
Cov_R	-0.0043	-0.0099	0.0007	

Figure 3: Variance components for TL, tarsus length and body condition visualized as relative proportions of the total phenotypic variance. Abbreviations refer to: additive genetic variance V_A , brood variance V_B , maternal variance V_M , paternal variance V_F , year variance V_Y , and residual variance V_R .

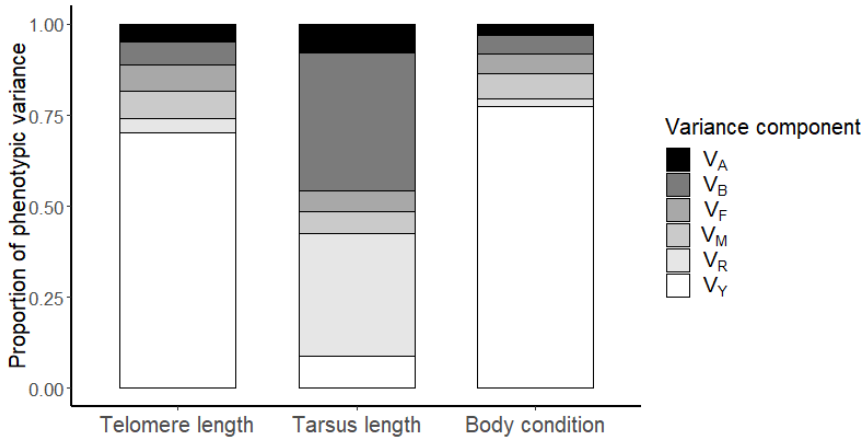

Figure 4: Manhattan plot showing genomic location plotted against -$\log_{10}$(P-value) of the GWA analysis results for early-life telomere length in house sparrows (n =373). The dotted line indicates the genome-wide significance threshold (corresponding to$p$ <0.05 divided by the number of tests n =180,650 SNPs) used to determine the top SNPs listed in Table 3.

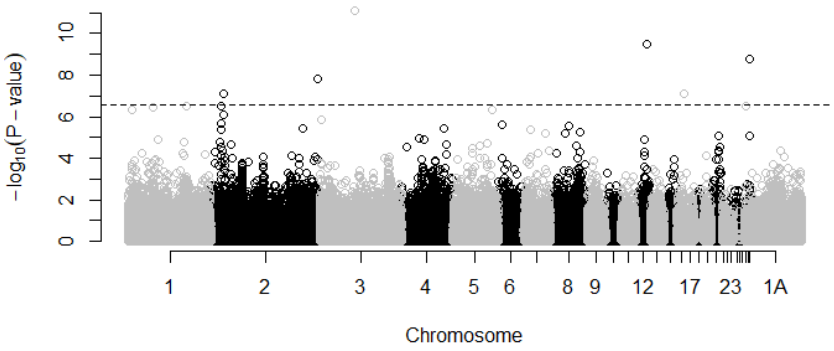

Table 3: Single nucleotide polymorphisms (SNPs) with evidence (italics, above the dashed line) or weak evidence for an association with early-life telomere length in house sparrows (n =373). Chromosome number, SNP position, reference allele A1, effect allele A2, estimated effect size (β) with standard error (SE), p-value, and Bonferroni adjusted p-value are shown.

SNP	Chro-mosome	Position	A1	A2	β	SE	p-value	adjuste p-value
SNPa223513	*3*	*46984591*	*T*	*C*	*0.5864*	*0.0857*	*8.00E-12*	*1.44E-06*
SNPa17235	*12*	*14959355*	*G*	*A*	*0.3051*	*0.0485*	*3.19E-10*	*5.76E-05*
SNPa500415	*30*	*133629*	*C*	*T*	*0.2866*	*0.0477*	*1.80E-09*	*0.0003*
SNPa429690	*2*	*145079103*	*G*	*A*	*0.3619*	*0.0640*	*1.56E-08*	*0.0028*
SNPa108592	*15*	*11173875*	*G*	*T*	*0.3426*	*0.0637*	*7.65E-08*	*0.0138*
SNPa450086	*2*	*17261563*	*G*	*T*	*0.3515*	*0.0656*	*8.40E-08*	*0.0152*
SNPa34968	1	78883614	C	T	0.2237	0.0436	2.92E-07	0.0527
SNPa491204	27	1191908	T	C	0.1386	0.0271	3.10E-07	0.0561
SNPa392732	2	13674493	A	G	0.5023	0.0984	3.29E-07	0.0594
SNPa374949	1	33502667	C	T	0.2189	0.0431	3.81E-07	0.0688
SNPa374964	1	33523052	G	A	0.2189	0.0431	3.81E-07	0.0688
SNPi16410	5	53016672	G	A	0.2206	0.0438	4.58E-07	0.0828
SNPa8679	1	5482366	T	C	0.2643	0.0525	4.85E-07	0.0876

Table 4: Genes found within ±100 kb of SNPs in Table 3 with evidence for an association with early-life telomere length house sparrows. Chromosome number, distance (in bp) between SNP and gene, general molecular or biological function or relevance to telomere biology are indicated with references. The list is sorted first by SNP p-value and then by gene distance.

Chr.	Gene	SNP	Distance	F
12	FRMD4B: FERM domain-containing protein 4B (*Homo sapiens*)	SNPa17235	11287	F
12	LMOD3: Leiomodin-3 (*Homo sapiens*)	SNPa17235	34383	S
12	ARL6IP5: PRA1 family protein 3 (*Gallus gallus*)	SNPa17235	42339	F
12	UBA3: NEDD8-activating enzyme E1 catalytic subunit (*Homo sapiens*)	SNPa17235	54117	C
12	TMF1: TATA element modulatory factor (*Homo sapiens*)	SNPa17235	67507	C
12	EOGT: EGF domain-specific O-linked N-acetylglucosamine transferase (*Gallus gallus*)	SNPa17235	86629	C
2	AQP1: Aquaporin-1 (*Sus scrofa*)	SNPa429690	0	V
2	GHRHR: Growth hormone-releasing hormone receptor (*Homo sapiens*)	SNPa429690	38572	F
15	ORAI1: Calcium release-activated calcium channel protein 1 (*Gallus gallus*)	SNPa108592	42546	F
15	morn3: MORN repeat-containing protein 3 (*Xenopus laevis*)	SNPa108592	53962	S
15	Kdm2b: Lysine-specific demethylase 2B (*Mus musculus*)	SNPa108592	61359	U
15	RNF34: E3 ubiquitin-protein ligase RNF34 (*Bos taurus*)	SNPa108592	71094	U
15	Tmem120b: Transmembrane protein 120B (*Mus musculus*)	SNPa108592	71684	F
15	RHOF: Rho-related GTP-binding protein RhoF (*Homo sapiens*)	SNPa108592	82475	C
15	ANAPC5: Anaphase-promoting complex subunit 5 (*Gallus gallus*)	SNPa108592	83811	C
2	OXR1: Oxidation resistance protein 1 (*Homo sapiens*)	SNPa450086	75676	C

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1: Notes on methods.

Appendix S2: Notes on results.