RESEARCH ARTICLE

Heritability of a skeletal biomarker of biological aging

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Abstract Changes in the skeletal system, which include age-related bone and joint remodeling, can potentially be used as a biomarker of biological aging. The aim of the present study was to investigate the extent and mode of inheritance of skeletal biomarker of biological aging—osseographic score (OSS), in a large sample of ethnically homogeneous pedigrees. The investigated cohort comprised 359 Chuvashian families and included 787 men aged 18–89 years (mean 46.9) and 723 women aged 18–90 years (mean 48.5). The TOSS - transformed OSS standardized in 5-year age groups for each sex, was analyzed as a BA index. We evaluated familial correlations and performed segregation analysis. Results of our study suggest the familial aggregations of TOSS variation in the Chuvashian pedigrees. In a segregation analysis we found a significant major gene (MG) effect in the individual's TOSS with a dominant most parsimonious model ($H^2 = 0.32$). Genetic factors (MG genotypes) explained 47% of the residual OSS variance after age adjustment and after including sex-genotype interaction, they explained 52% of the residual variance. Results of our study also indicated that the inherited difference in the skeletal aging pattern in men lies mostly in the rate of aging, but in women in the age of the onset of the period of visible skeletal changes.

Keywords Osseographic score · Skeletal aging · Chuvashia · Biological aging · Heritability

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Introduction

Biological age (BA) estimates the functional status of an individual in reference to his or her chronological peers on the basis of how well he or she functions in comparison with others of the same chronological age (Borkan and Norris 1986). Changes in the skeletal system, which include age-related bone and joint remodeling, can potentially be used as a biomarker of BA. Skeletal aging measures are strongly correlated with the status of the vital health systems (Gabriel et al. 1999; Kiel et al. 2001, Kadam et al. 2004, Kalichman et al. 2006b) and ultimately with survival rates (Johansson et al. 1998; Haara et al. 2003). The rate of degenerative changes in the skeleton may reflect an individual's biological resistance,

immunity, functional or health status in reference to his or her chronological age. Therefore, age-related skeletal changes can possibly be used as an index of BA.

Roentgenography is one of the common methods used to assess health status and age-related changes in bones and joints (Plato 1987; Plato et al. 1994). Previously, Kobyliansky et al. (1995) reported an osseographic scoring (OSS) system that uses hand radiographs to assess skeletal aging. OSS is a synthetic measure for assessing skeletal aging based on radiographic features of the hand, combining both osteoporotic and osteoarthritic changes of hand bones and joints. This system was originally suggested by Pavlovsky (1987) and has been used in BA evaluations in population studies (Kobyliansky et al.1995; Livshits et al. 1996; Pavlovsky and Kobyliansky 1997). Importantly, OSS has been shown to highly correlate with chronological age in adults of different ethnic groups (Karasik et al. 1999, Kalichman et al. 2002).

Accumulating research shows that single gene changes in yeast, worms, and rodents can significantly alter life span (Kenyon et al. 1993; Kaeberlein et al. 1999; Cheng et al. 2003; McBurney et al. 2003). The observation that the first-degree relatives of human centenarians are both disease resistant and have longer than average life spans implies a genetic component to human longevity (Perls et al. 2002; Atzmon et al. 2004). Current estimates based on twin studies indicate that the human life span is 25% heritable (McGue et al. 1993; Herskind et al. 1996; Gudmundsson et al. 2000; Perls et al. 2002). Genetic factors may also significantly contribute to interindividual differences in BA (Karasik et al. 2004, 2005). In variance component genetic analysis, performed in Karasik's study (2004), genetic factors explained 57% of the total variance of the BA index based on OSS measurements.

The aim of our study was to investigate the extent and mode of inheritance of a skeletal biomarker of biological aging (OSS) in a large sample of ethnically homogeneous pedigrees.

Materials and methods

Sample

The population sampled consisted of native Chuvashians residing in numerous small villages in the Chuvashia and Bashkartostan Autonomies of the Russian Federation. The data were gathered in three field studies during August/September of 1994 (555 individuals), May/June of 1999 (715 individuals), and September 2002 (240 individuals) by investigators from the Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University (Israel), and the Institute of Anthropology, Moscow University (Russia). The expeditions were part of a Chuvashia Skeletal Aging Study (ChuSAS) project whose main aim was to investigate the different aspects of skeletal aging within the Chuvashia population. All information collected and measurements taken during all expeditions were done by the same team of investigators. The investigated cohort comprised 359 families and included 787 men aged 18–89 years (mean 46.9) and 723 women aged 18–90 years (mean 48.5).

The Chuvashian population is characterized by a stable family structure with traditional relationships. For generations the Chuvashians have resided under the same environmental conditions and have not been exposed to an outside genetic flow (El'chinova et al. 2003). In the present study, we collected data from residents of a number of small villages (with a predominant Chuvashian population) located in the Volga region. A rural population is more homogeneous than urban in terms of ethnicity, occupation, and physical activity. The study participants shared similar living, economic, and professional conditions with most individuals employed in agriculture or in other occupations involving physical labor. Data from 80% to 90% of the families (including all family members who were living in the area at the time of the expedition) were obtained. Since almost every individual was related to one of the families, we were able to collect data on up to 90% of the population in each village. Data obtained from self-completed questionnaires and confirmed during the interview included sex, age, age at menarche, age at menopause and occupation. Menopause was defined as >12 months without menstruation. Age at last menstruation was considered as menopausal age. In order to minimize the possible recall bias, the investigators excluded from the analyses all women who had doubts about their age at menarche. The anthropometrical measurements (weight, stature, etc.) were also collected using standard methodology. In the studied sample, there were no individuals with

known rheumatoid or psoriatic arthritis or users of steroid medication. Subjects with post-traumatic hand osteoarthritis were excluded from the study. All procedures involved were consensual. The subjects signed an informed consent form, and the entire project was approved by the Helsinki Ethics Committee of Tel-Aviv University.

Additional information about the studied population can be found in our previous publications: sex- and age-related variations of the somatotype (Kalichman and Kobyliansky 2006), reproductive indices, such as age at menarche and at menopause (Kalichman et al. 2006 a, 2007a) and sex- and age-related variations of OSS (Kalichman et al. 2007b).

Hand radiographs

Single plain radiograms of both hands were taken from each study participant in the postero-anterior position with the X-ray source located 60 cm above, using a standard radiographic technique, as described in detail by Livshits et al. (1996). Hands were placed on the same film-containing plate to avoid any film or development variation. It was exposed for 5–10 s at 100–150 mA without intensifying screens at 50 kV.

OSS evaluation

An individual's OSS was determined by the occurrence of the following: (a) bone proliferations (spurs), including apiostoses (tufting of distal phalangeal tuberosity), osteophytes, enthesophytes of the juxta-articular area and at midshaft; (b) manifestations of bone porosity, such as resorption of trabeculae, development of lacuna (juxta-articular osteopenia) and erosion of cortex; (c) loci of osteosclerosis, defined as enostosis and sclerotic nuclei; and subchondral sclerosis; and (d) non-traumatic joint deformities, defined as narrowing of joint cavities and periarticular bone corrosion (Kobyliansky et al. 1995; Pavlovsky and Kobyliansky 1997; Karasik et al. 2005; Kalichman et al. 2007b). Phalanges of the 2nd to 5th fingers of the left hand were examined. The first finger (thumb) does not directly project in a standard X-ray and was therefore not utilized. The presence of a given feature, but not its level of development, was documented for each OSS estimate. The overall number of those skeletal aging features was used as an OSS.

Each radiograph was read by an experienced skeletal researcher according to the accepted protocol of OSS evaluation. Ten X-rays were read and then re-read by the investigator to estimate the intra-observer reliability of the readings. All discrepancies were reviewed for systematic errors. This exercise continued until the reliability was high ($k > 0.8$). Afterwards, the investigator read the remaining X-rays, still blinded to patient identifiers. Before reading each batch of X-rays one re-read 5 X-rays, which had been previously read, to "calibrate" one's readings to a standard. The intra-observer reliability (kappa statistics) was 0.82 ($P < 0.01$). The intraclass correlation for the OSS was 0.92 ($P < 0.01$).

OSS reflects amount of skeletal changes occurring stochastically during the life-span, and therefore it is characterized by strong increase of trait variance with age (Kalichman et al. 2007b and Fig. 1). It is reasonable to assume that not the deviation of OSS from the age-group mean, but only relative rate of OSS accumulation with age can be inherited. Consequently we constructed a trait using the standardization in age-sex groups to equalize the means and variances in the whole age range for both sexes. The resulting trait, TOSS (transformed OSS) was further analyzed. The biological meaning of this trait is the relative position of individual (higher or lower than average values of OSS) in his/her age-sex group expressed in the units of SD specific for each group. This accurately fit the definition of BA as the functional status of an individual in reference to his or her chronological peers (Borkan and Norris 1986).

Statistical and genetic analysis

Prior to any other evaluations, the descriptive statistics reflecting the basic characteristics of the studied sample were computed in the whole sample and within age groups of 5 years.

At the first stage we computed familial (spouses, parent-offspring and sib-sib) correlations between the corresponding TOSS levels to examine the potential genetic effect on the skeletal biomarker of BA.

The segregation analysis, as implemented in the statistical package MAN (Malkin and Ginsburg 2003), was utilized in this study to test a mode of inheritance of the skeletal biomarker of BA—TOSS. Only individuals older than 29 were included in the analysis, since the high prevalence of zero OSS

Fig. 1 Mean OSS values and standard deviations (SD) in age groups of 5 years for men and women
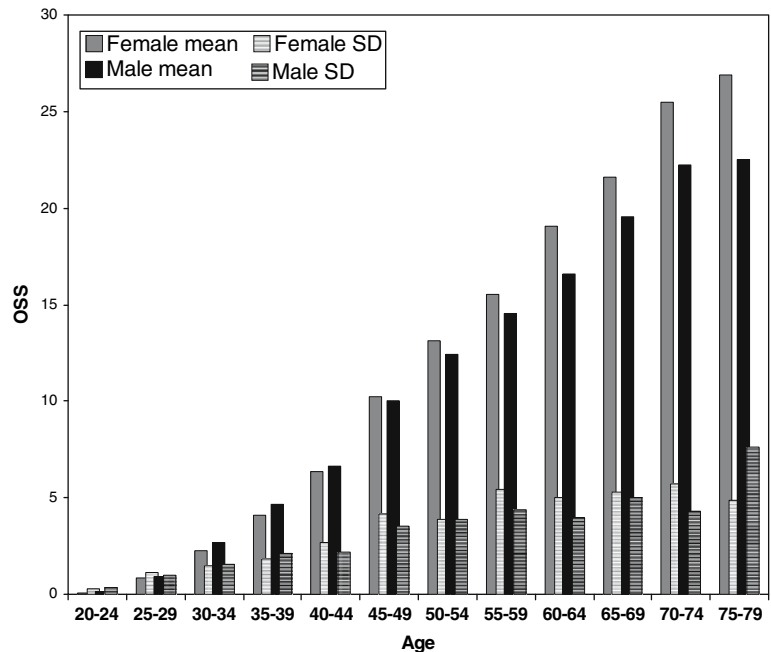
values in younger individuals make the standardization approach unacceptable. More precisely, in two 5-year age groups younger than 30 years the distribution of TOSS significantly deviated from normal (Chi-square χ^2-test for frequencies gave $P < 10^{-6}$), whereas in all older age groups did not ($P > 0.01$). Only pedigrees having at least one measured pair of relatives were included in the analysis. The mixed model of inheritance (Morton and MacLean 1974; Elston 1981; Lalouel 1983; Beaty 1997; Ginsburg and Livshits 1999) estimates the effects of a potential major gene and possible multifactorial effects, and is described in detail in numerous publications, including the aforementioned. The parameters that had been estimated in the general model are defined as follows: p—the population frequency of allele A_1 (assuming diallelic gene locus); μ_{gs}—the average genotypic value of individuals having genotype g and sex s ($g = 1$, 2, and 3 corresponds to genotypes A_1A_1, A_1A_2, and A_2A_2, respectively); σ^2_g—the trait variance in individuals having the same major gene genotype g, it estimates the trait variation resulting from the effect of all possible environmental factors and potential minor genes; τ_g—the transmission probability parameter, which estimates the probability that a parent of genotype g transmits allele A_1 to the next generation; ρ, β, and ε are partial correlations

between the trait's residuals adjusted for a major gene effect, in spouses, parents/offspring, and the siblings, respectively. A transmission probability test, described by Ginsburg and Livshits (1999), was used to estimate the significance of the major gene (MG) effect. A best-fitting and most parsimonious Mendelian model was established after dropping all non-significant parameters.

Using the procedure implemented in the package MAN (Malkin and Ginsburg 2003) and parameters estimated for the most parsimonious model, we determined the most likely MG genotype combination for each pedigree. We divided our sample into groups according to sex and the determined individual genotype of putative BA-related MG for genotypes having distinguishable genotypic values.

To analyze the age dependence of OSS, as a primary (directly measured) BA-related index, in groups of potentially different inherited BA, we used the stochastic model, described in detail by Kobyliansky et al. (1995). We estimated for each group the following aging population parameters: t_0—the earliest age at which the first signs of OSS can be found, q—the individual probability of revealing the first signs of OSS changes per chronological time unit, assuming an individual's age $\geq t_0$, and B—the coefficient characterizing the rate of OSS changes

per time unit (per year) after the process of aging has started. Next, we built the age-dependent expectation of the mean OSS level for each group according to sex and predicted MG genotype. Using the likelihood ratio test, we compared the extent of stochastic model approximation, both accounting for the MG genotype group and without it. Eventually we used ANOVA as implemented in STATISTICA 6.0 (StatSoft 2000) to test the differences between parameters of female organism development such as age at menarche and age at menopause in MG genotype groups.

Results

Figure 1 shows the OSS mean values and SD in age groups of 5 years. Up to age 45, men have higher OSS scores than women. After age 45 OSS in women was higher, compared with men and the sex difference in the OSS scores increases up to the end of the age range. The OSS variance in age groups increases rapidly up to age 50.

Familial correlations of TOSS (Table 1) showed no significant correlation for spouses, but parent-offspring and sibling correlations were significant. This indicates the existence of a clear familial aggregation of TOSS variation in the Chuvashian pedigrees, which cannot be explained by pure common environmental effects. We investigated the nature of TOSS inheritance later using segregation analysis. Because of the method by which TOSS was constructed (standardization within each sex-age group), in the segregation model the sex effects were not significant. The other results are presented in Table 2 and support the MG hypothesis regarding trait inheritance. The most parsimonious Mendelian model was dominant. The recessive allele with a population frequency of 0.6 corresponded to relatively slow aging. For the most parsimonious Mendelian model, $H^2 = 0.315$; total proportion of TOSS variance explained by the model was 0.349. Using

this model, we predicted the most likely MG genotype combination for each pedigree included in the analysis. Because of the dominant nature of the most parsimonious model, we divided all individuals into two groups with potentially different genotypic values: (1) homozygous on allele A_1 and (2) all the rest. Using a stochastic model of aging (Kobyliansky et al. 1995), we constructed the model of age dependence of directly measured OSS for a whole sample and for each predicted genotype group separately with and without considering the effects of sex. Table 3 presents the parameters of four resulting models and a comparison between them. According to the likelihood ratio test (LRT), Model 1, which included only the effect of age, has a significantly worse extent of approximation than both Model 2, which included the effect of genotype-age, and Model 3, which included the effect of sex-age. The extent of approximation was significantly higher for the effect of genotype-age, which explained 47% of the residual OSS variance after only adjustment for age, and lower for the effect of sex-age (5%). Model 4, which includes all age-sex-genotype effects, showed a significantly higher extent of approximation in comparison with other models and explained 52% of the residual OSS variance after adjustment for age. After adjustment for age and sex, the residual parent-offspring correlation of OSS was significant, but became non-significant after adjustment for the sex-age-genotype.

Figure 2 shows a scatterplot of OSS-age for the predicted genotypes in both sexes and the corresponding curves of age-dependent OSS expectation given by the stochastic model. For women in the group of genotype A_1A_1 (with slow skeletal aging), the age at menarche was significantly higher ($P = 0.012$) than in the group of genotypes A_1A_2 or A_2A_2; the group mean difference was 0.45 year. The difference in the age at menopause was in the same direction, but not significant for the whole sample. Note that our sample includes women strongly influenced by difficult life conditions during World War II. In these women the variance in the age at menopause is increased in comparison with the normal population. For women whose year of birth ≥ 1937 (the normal part of the population), the age at menopause was higher in group A_1A_1 than in other group ($P = 0.054$); the group mean difference was 1.6 year.

Table 1 Familial correlations of TOSS

Relatives	R	N of pairs	P
Spouses	0.08	333	0.15
Parent-offspring	0.12	755	0.002
Sib pairs	0.31	189	0.0008

Table 2 Segregation analysis for TOSS (OSS standardized in age groups of 5 years for each sex)

Parameter	Main models			Restricted models		
	General 1	Mendelian 2	Equal τ-s 3	Arbitrary τ-s 4	Mendelian most parsimonious 5	Equal τ-s 6
P	0.600	0.628	0.252	0.558	0.598 ± 0.033	0.563
μ_1	−0.727	−0.724	−1.080	−0.758	−0.729 ± 0.057	−0.702
μ_2	0.481	0.525	−0.329	0.380	0.429 ± 0.061	0.362
μ_3	0.362	0.385	0.383	0.380!	0.429!	0.362!
σ_1^2	0.299	0.325	0.074	0.255	0.303 ± 0.045	0.289
σ_2^2	1.074	0.988	0.504	1.165	1.067 ± 0.103	1.181
σ_3^2	0.205	0.232	1.049	0.255!	0.303!	0.289!
ρ	0.085	0.104	0.099	[0.000]	[0.000]	[0.000]
β	0.006	−0.029	0.033	[0.000]	[0.000]	[0.000]
ε	0.325	0.228	0.311	0.327	0.249 ± 0.067	0.327
τ_1	0.910	[1.000]	0.272	0.916	[1.000]	0.614
τ_2	0.632	[0.500]	0.272!	0.618	[0.500]	0.614!
τ_3	0.001	[0.000]	0.272!	0.020	[0.000]	0.614!
Log LH	−1425.66	−1428.27	−1435.91	−1427.29	−1429.61	−1440.51
χ^2	–	5.22 [NS] (1)	20.5** (1)	1.63 [NS] (1)	4.64 [NS] (4)	26.44** (4)

NS—$P > 0.05$; ** $P < 0.01$

Number in parentheses in the χ^2—row specifies a comparative column

Constraints denotation: [ ]— parameter is fixed to shown value; !— parameter is constrained to be equal to the parameter above in the table

To compare our findings with results of other authors, we quantitatively analyzed the similarity of differently constructed BA indices. The correlation between the BA index proposed by Karasik et al. (2004) and TOSS was 0.82 in the Chuvashian population. The correlations between the BA index, used by Livshits et al. (1996), versus the BA of Karasik et al. (2004) and TOSS were estimated as 0.80 and 0.89, correspondingly. Though the resemblance of the indices may be influenced by population type, the aforementioned BA indices are sufficiently similar.

Discussion

In the present study, we evaluated the extent and mode of inheritance of a skeletal biomarker of BA. We constructed this biomarker (TOSS) to be maximally fitted according to the BA definition; it reflects the intensity of an individual's skeletal changes in relation to its coevals of the same sex, and the range of the index does not depend on the age cohort.

We previously evaluated the association between OSS, as an index of BA, with morbidity in a general Chuvasha population (Kalichman et al. 2006b). Statistically significant association was found in the present study between age-adjusted OSS and rheumatic morbidity. Morbidities such as ischemic heart disease, pulmonary diseases, traumatic brain injuries and gynecological diseases also showed differences between mean values of OSS in affected vs. non-affected individuals. However, after correction for multiple testing, the statistical significance was insufficient. The association between OSS and diabetes mellitus was close to significant ($P = 0.07$) and we surmise that with a larger sample of diabetic individuals, a clear-cut association will be confirmed.

It is well-established that genetic factors play an important role in an individual's BA (Karasik et al. 2005). Our finding suggests the familial aggregations of TOSS variation within the Chuvashian pedigrees. The evaluation of heritability of the skeletal biomarker of BA in segregation analysis suggested the existence of a MG effect with a most parsimonious

Table 3 Parameters of stochastic aging models estimated for OSS data without grouping (1) and grouped according to predicted genotype (2), sex (3), or both sex and predicted genotype (4)

	Parameter	All	A_1A_1	A_1A_2 or A_2A_2
All	t_0	21.223 ± 0.933	21.705 ± 0.884	22.225 ± 1.179
	q	0.118 ± 0.015	0.077 ± 0.010	0.217 ± 0.044
	B	0.552 ± 0.004	0.518 ± 0.004	0.600 ± 0.004
	TM	29.689	34.619	26.838
		Model 1 (3 d.f.)	Model 2 (6 d.f.)	
		R^2=0.838	R^2=0.915	
		Log LH=−3476.8	Log LH=−3065.5	
		–	χ^2= 822.6 (1)	
Men	t_0	20.524 ± 1.231	21.573 ± 1.142	21.886 ± 1.683
	q	0.127 ± 0.024	0.098 ± 0.014	0.233 ± 0.071
	B	0.501 ± 0.005	0.449 ± 0.005	0.556 ± 0.005
	TM	28.400	31.740	26.182
Women	t_0	22.078 ± 1.342	21.840 ± 1.169	22.623 ± 1.601
	q	0.107 ± 0.019	0.057 ± 0.000	0.187 ± 0.046
	B	0.617 ± 0.007	0.629 ± 0.008	0.657 ± 0.007
	TM	31.400	39.373	27.979
		Model 3 (6 d.f.)	Model 4 (12 d.f.)	
		R^2=0.846	R^2=0.923	
		Log LH=−3443.3	Log LH=−3000.7	
		χ^2= 67.0 (1)	χ^2= 952.2 (1); 129.6 (2); 885.2(3);	

A_1A_1— genotype corresponding to lower values of TOSS in segregation analysis; t_0— the minimal age at which initial bone changes occurred in a group; q—the group probability that an individual will first develop involutive bone change after age t_0; B—the group rate of aging (bone change) per time unit; TM—the expected mean age in a group in which the first bone change occurred; number in parentheses indicates the comparative model for LRT; all LRT values are significant with $P < 10^{-6}$

Fig. 2 OSS values for predicted genotype groups: black—A_1A_1, gray—A_1A_2 or A_2A_2
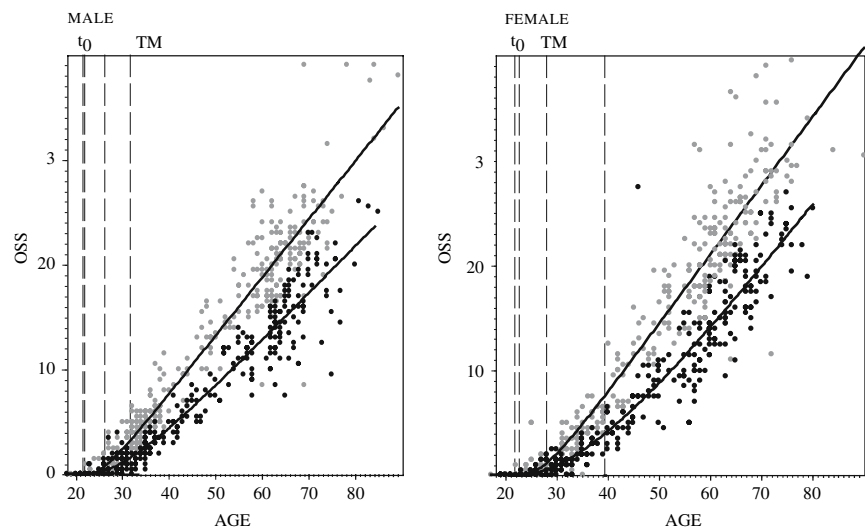
dominant model. A number of BA indices, based on age-related skeletal changes, were previously proposed and analyzed in different populations. Livshits et al. (1996) analyzed the OSS measurement in the Turkmenian population. They used the age-adjusted OSS values as a BA index. This index showed a

significant familial parent-offspring correlation of 0.1 ± 0.09, which is approximately the same as for TOSS in our study (0.12). Nevertheless, in their segregation analysis of the age-adjusted OSS, the Mendelian model was rejected. A possible reason is that a simple age adjustment does not equalize the residual variance of OSS, which significantly increases with age. As a result, parents and offspring received a BA index with different amplitude and this difference probably prevented establishing MG inheritance in segregation analysis. Other phenotypes of BA, as well, are characterized by substantial heritability. Thus, functional age (other term for BA) has been assessed by a general linear regression model of many biomarkers in Minnesota twins (27–88 years old). A subset of these biomarkers (mostly physiological variables) identified by a factor analysis had heritability of ~59% (Finkel et al. 1995). Duggirala et al. (2002) have reported that BA, measured according to Uttley and Crawford (1994), had a substantial genetic component (heritability ranging from 0.27 ± 0.11 in one Mennonite geographical subsample to 0.47 ± 0.18 in the other).

Karasik et al. (2004) studied a sample that included 1,402 members of 288 pedigrees from the Framingham Heart Study; the log-transformation was used to reduce the growth of OSS variance with age. A special BA index was constructed by adjusting the individual's age for log-transformed OSS with cubic polynomial. The log-transformation automatically excludes from the analysis all individuals with zero OSS (note that for ages >30, the zero OSS value is meaningful and denotes a low BA). For the resulting trait, the genetic variance component analysis showed that sex, height, the body mass index, and, in women, menopausal status and estrogen use, jointly explained approximately 6% of the total variance of BA index. Genetic factors explained an additional 57%. The genome search for this BA index revealed a number of potential chromosomal regions in the two-point analysis, but for multipoint, only the region on chromosome 21 remained significant.

The variance component analysis, used by Karasik et al. (2004), a priori assumes a polygene mode of inheritance. Our segregation analysis results confirm the findings about a significant genetic effect and furthermore suggest the existence of a MG effect in an individual's TOSS with a dominant most parsimonious model. The MG hypotheses may be, to some

extent, supported by the fact that in the multipoint variance component linkage analysis by Karasik et al. (2004) only one chromosomal region showed a significant LOD score >3 (likelihood ratio greater than 10^3). We found that genetic factors (MG genotypes) explained 47% of the residual OSS variance after adjustment for age, and after including the sex-genotype interaction, they explained 52% of the residual variance. For TOSS the MG effect was 32%.

Additionally, we compared the age dependence of OSS by directly measuring the individual's skeletal health index in predicted MG genotype groups. Kobyliansky et al. (1995) proposed a two-stage stochastic statistical model of the population aging pattern for OSS. The implied stages are as follows: (1) the period of life between birth and the apparent onset of skeletal changes ($t < t_i$), defined as the latent period, and (2) the period of visible changes beginning after t_i (which is not the same in different individuals), when involutive changes occur continuously throughout the remaining life. Applying this model separately in predicted genotype groups, we compared their aging features by means of model parameters (t_0, q, B). The earliest age of the first visible changes, t_0, was almost the same in all sex-genotype groups, about 22 years. The probability per year of transition from the latent to the visible changes period, q, was for genotype A_1A_1 about 1/3 of probability for other individuals. This was especially expressed for women and it results in greater values of the average transition age TM (39.3 years in A_1A_1-group and 31.7 for the others). The rate of aging, B, was also significantly different in the predicted genotype groups, but this difference was expressed more for men. Thus, we can conclude that the inherited difference in the aging pattern lies in men, mostly in the rate of aging, but in women, it is in the age of onset of the period of visible changes.

An additional finding was that in the group A_1A_1 (slow aging), for women, the age at menarche was significantly greater ($P = 0.012$) than in the group {A_1A_2 OR A_2A_2}. For women born after 1937 (those whose maturation period was not influenced by WW II or the subsequent rehabilitation period), the age at menopause was also greater in the group A_1A_1 ($P = 0.054$). Thus, there is a positive relation between the rate of sexual development and the rate of aging, characterized by degenerative skeletal changes. The

rate of sexual development is positively associated with intensity of normal metabolism, which also may lead to accelerated aging. Early onset of menarche is also known to be linked to other aging conditions such as elevated blood pressure and glucose intolerance, compared with later maturing girls, independent of body composition (Remsberg et al. 2005).

The main molecular characteristic of aging is the progressive accumulation of damages in macromolecules that result on macro level in heterogeneity of tissues and degenerative changes. Rattan (2006) pointed out three major sources of this damage: (1) reactive oxygen species (ROS) and free radicals formed due to external inducers of damage (for example ultra-violet rays), and as a consequence of cellular metabolism; (2) nutritional glucose and its metabolites, and their biochemical interactions with ROS; and (3) spontaneous errors in biochemical processes, such as DNA duplication, transcription, post-transcriptional processing, translation, and post-translational. Bessenyei et al. (2004) reviewed data concerning SNPs associated with life span positioned in a variety of genes regulating metabolic processes, apoptosis, stress response (see also Singh et al. 2006) and immune response. Several polymorphisms in ER-alpha (estrogen receptor that are known to play significant role in skeletal development) were reported to be associated with life span (Bessenyei et al. 2004) and with both osteoarthritis (Jin et al. 2004) and osteoporosis (Albagha et al. 2005) related phenotypes. The VDR (vitamin D receptor) gene is also known to be associated with both types of degenerative changes in certain skeletal sites (Uitterlinden et al. 1997; Yue et al. 2005). A great number of genes with significant association signals were cited in recent reviews of Loughlin (2005) (osteoarthritis) and Liu et al. (2006) (osteoporosis). de Boer et al. (2002) described studies of mice with a mutation in XPD, a gene encoding a DNA helicase that functions in both repair and transcription. Mice with mutation were found to exhibit many symptoms of premature aging, including osteoporosis and kyphosis, osteosclerosis, early greying, cachexia, infertility, and reduced life-span. So OSS, the index comprising various accumulated degenerative skeletal changes, despite to different molecular mechanisms, which are involved in bone loss, cartilage loss and other OSS components, may be under genetic control of some polymorphic genes taking part in

DNA repair pathways, transcription and translation control and/or some polymorphic genes controlling intensity of normal metabolism, that influence the rate of molecular damage (Kirkwood and Austad 2000). This supports the assumption that OSS as a skeletal biomarker of BA can be used to evaluate the organism's general aging status.

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