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HUMAN GENETICS

The Study of Association of Polymorphic Markers of the *SOD1*, *SOD2*, and *SOD3* Genes with Longevity

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Abstract—For the first time, a study of genetic factors of longevity was conducted in the prevalent populations of 2511 residents of the Republic of Bashkortostan—Russians, Bashkirs, and Tatars. We investigated the polymorphic markers in the genes of the antioxidant defense enzymes—*SOD1* (rs2070424), *SOD2* (rs4880), and *SOD3* (rs1799895). We detected ethnicity-specific patterns of the distribution of genotype frequencies between Bashkir and Russian groups (rs2070424 of the *SOD1* gene, $P = 0.003$), as well as between Tatars and the groups of Russians and Bashkirs (rs4880 of the *SOD2* gene, $P < 0.001$ and 0.035, respectively). We found associations of the polymorphic markers in SOD family genes with age. Among Russians, the chances to attain longevity were higher in the *SOD1**A/A genotype carriers (OR = 1.025, $P = 0.001$) and lower in those with the *SOD1**A/G (OR = 0.975, $P = 0.001$) and *SOD2**A/A (OR = 0.985, $P = 0.002$) genotypes. Among Tatars, we observed a decrease in the *SOD2**A/A (OR = 0.989, $P = 0.029$) and *SOD2**V/V (OR = 0.985, $P < 0.001$) genotype frequencies and an increase in the *SOD2**A/V genotype frequency (OR = 1.023, $P < 0.001$). The analysis of genotype and/or allelic combinations of the studied polymorphic loci revealed 12 patterns associated with longevity among Tatars. The *SOD1**A and *SOD3**C alleles were present in most of the identified combinations. The *SOD2* rs4880 polymorphic marker was indicative of longevity: combinations including the *SOD2**V/V genotype were associated with lower chances of achieving longevity ($OR \le 0.45$, $P_{FDR} \le 0.0003$), and combinations including the *SOD2**A/V genotype were associated with higher chances of achieving longevity ($OR \ge 2.92$, $P_{FDR} \le 1.24 \times 10^{-6}$).

Keywords: human longevity, population, adaptation, superoxide dismutase genes, antioxidant defense, polymorphic marker, association analysis

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INTRODUCTION

Individual lifespan (LS) and the specificity of age-related changes in the human body have a multifactorial nature; i.e., they depend on environmental conditions, individual genetic predisposition, and their interaction. An existing concept of successful aging is characterized by the ability of an individual to maximally adapt to the functional age-related changes in his body [1]. Longevity, which is the individual's ability to achieve a life expectancy above the average in the population, represents a striking example of well-being in individual ontogenesis and successful adaptation.

Several endogenous processes, including the antioxidant defense system (ADS) as one of the most significant of them, are responsible for the body's adaptation to environmental factors and correspondingly changing internal environment. It is known that reactive oxygen species (ROS) play an important role in the complex system of regulation of multiple cell functions, which are observed under physiological conditions and the impact of pathogenic factors on the cell. Oxidative stress is considered to be one of the pathophysiological mechanisms involved in the development of many age-related diseases, such as atherosclerosis, cerebral circulation insufficiency, coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), and oncological and neurodegenerative pathologies [2]. On the other hand, owing to ROS reactivity, they stimulate the immune system, activate ion transport, and trigger apoptosis, therefore regulating the main functions of the cell. Accordingly, ROS can be considered as adaptation inducers [3]. The rate and efficiency of the ADS may represent one of the factors that determine the lifespan and longevity.

The most significant components of the ADS are superoxide dismutases (SOD)—the enzymes belong-

† Deceased.

ing to the class of oxidoreductases, which catalyze the redox reaction, characterized by disproportion transformation of superoxide anions into molecular oxygen and hydrogen peroxide. The experiments with model objects demonstrated that an increased expression level of genes encoding ADS enzymes, including SOD, is correlated with prolonged lifespan [4, 5]. A search for polymorphic markers in the *SOD* genes has been conducted in age-related pathologies, which detected the associations with diseases affecting immune, inflammatory, and apoptotic processes [6]. Therefore, polymorphisms in the *SOD* genes may represent both the molecular-genetic predictors of age-dependent pathologies that limit the lifespan and hereditary factors of longevity.

The present study aimed to perform an analysis of associations of polymorphic markers in the *SOD1*, *SOD2*, and *SOD3* genes encoding enzymes of the antioxidant defense system with longevity in different populations from the Republic of Bashkortostan.

MATERIALS AND METHODS

The sample consisted of 2511 individuals aged 16 to 109 years, residents of the Republic of Bashkortostan (RB), belonging to the Russian (n = 490), Bashkir (n = 492), and Tatar (n = 1529) populations. The study participants were assigned to a certain ethnic group according to the self-reporting data on the ethnicity of their ancestors in three generations. A selection criterion for the inclusion was the absence of individual history of cardiovascular, neurodegenerative, and oncological diseases. The survey and collection of biological material (8 mL of blood from the cubital vein) were conducted on the basis of the written informed consent of the subjects to participate in the study.

Genomic DNA was isolated from peripheral blood lymphocytes via phenol-chloroform extraction [7]. The allelic variants of the examined polymorphisms in the *SOD1* (rs2070424) and *SOD2* (rs4880) genes were determined by polymerase chain reaction (PCR) using allele-specific primers. Experimental conditions and oligonucleotide sequences for identification of polymorphic markers were selected using the PrimerSelect 5.05 application from the DNAStar Inc software package and the NCBI database (https://www.ncbi.nlm.nih.gov/). DNA fragments were electrophoretically separated in 7% polyacrylamide gel, stained in 1% ethidium bromide, and visualized in ultraviolet light on the Mega-Bioprint 1100 gel-documenting system (Vilber Lourmat, France). Identification of the *SOD3* gene (rs1799895) alleles was carried out via real-time PCR using commercial reagent kits (Eurogen, http://evrogen.ru) and fluorescent TaqMan probes complementary to the examined DNA polymorphic region in accordance with the manufacturer's protocol (DNA-Synthesis, http://www.oligos.ru/).

The correspondence of the distribution of observed genotype frequencies to the theoretically expected Hardy–Weinberg equilibrium and the analysis of population heterogeneity were performed in the Arlequin software program (V.3.0). The total sample was stratified into age groups in accordance with anthropometric, physiological, and biochemical specificity of ontogenesis [8]. The age dynamics of genotype frequencies was studied using logistic regression analysis (SPSS V.21.0). In this case, the probability of observing the genotype was the function of the binary logistic regression, while age served as the independent variable. Age intervals were determined using ROC analysis. The search for combinations of the examined polymorphic markers associated with longevity was performed under the APSampler software program (V.3.6.1) [9]. The FDR coefficient (WinPepi V.11.39) was used as a correction for multiple comparisons; the differences were considered significant at $P_{FDR} < 0.05$.

RESULTS

As a result of the study, we characterized the distribution of allele and genotype frequencies of rs2070424 in the *SOD1* gene in populations from the Republic of Bashkortostan (Table 1). The empirically observed distribution of genotype frequencies in all ethnic groups corresponded to the theoretically expected Hardy–Weinberg equilibrium distribution ($P > 0.05$). In addition, the genotype and allele frequencies in groups of men and women did not significantly differ from each other.

Differences in the distribution of allele and genotype frequencies were observed between the examined populations (Table 2). According to the results of the study, the Bashkir ethnic group differed from the Russian ethnic group ($P = 0.003$) and from the Tatar ethnic group at a trend level ($P = 0.061$). In addition, this group demonstrated an increase in the frequency of the *SOD1**G/G genotype compared to Russians (at a significance level of 0.006) and to Tatars (at a significance level of 0.044).

As a result of logistic regression analysis, we revealed that, in Russians aged from 36 to 98 years, there were higher chances of detecting the *SOD1**A/A genotype (OR = 1.025, $P = 0.001$) and lower chances of detecting the *SOD1**A/G genotype (OR = 0.975, $P = 0.001$) (Table 3).

The analysis of the distribution of allele and genotype frequencies of rs4880 in the *SOD2* gene was performed in three populations from the Republic of Bashkortostan (Table 1). The empirically observed distribution of genotype frequencies corresponded to the theoretically expected equilibrium distribution ($P > 0.05$). The distribution of genotype frequencies in Tatars significantly differed from Russians ($P < 0.001$) and Bashkirs ($P = 0.035$) (Table 2). In general, the genotype frequencies of rs4880 in the *SOD2* gene in

Russians, Tatars, and Bashkirs did not significantly differ from European populations (http://grch37.ensembl.org/).

According to the data analysis performed using binary logistic regression (Table 3), in the total sample (without stratification by sex) of Russians the chances of detecting the *SOD2**A/A genotype decreased with age (from 16 to 98 years) (OR = 0.985, $P = 0.002$). We detected that changes in the frequencies occurred at 60 years: the frequency of the *SOD2**A allele and *SOD2**A/A genotype changed between the groups of 16–60 years and 61–98 years (for allele, 49.59 and 40.41%, respectively, $P = 0.005$, $P_{FDR} = 0.012$; for genotype, 22.73 and 11.02%, respectively, $P = 0.0007$, $P_{FDR} = 0.008$).

The differences in the distribution of genotype frequencies ($P = 0.001$) between men and women were observed in Tatars, which were due to a significant decrease in the frequency of the heterozygous genotype in men—42.45% vs. 51.91% in women ($P = 0.00015$). Subsequent analysis of age-dependent changes in the genotype and allele frequencies in this locus in the groups stratified by sex demonstrated a decrease in the frequency of homozygous *SOD2**A/A (OR = 0.989, $P = 0.029$) and *SOD2**V/V genotypes (OR = 0.985, $P < 0.001$), while the frequency of *SOD2**A/V genotype (OR = 1.023, $P < 0.001$) increased within 22–89 years in men of Tatar ethnicity. No statistically significant age-dependent differences in allele and genotype frequencies were detected in women.

According to the results of analysis of rs1799895 in the *SOD3* gene, the distribution of allele and genotype frequencies in all three ethnic groups did not differ from the normal distribution corresponding to the Hardy–Weinberg equilibrium (Table 1). Different populations from the Republic of Bashkortostan did not differ between each other (Table 2) and other European populations (http://grch37.ensembl.org/).

No statistically significant age-dependent changes in the allele and genotype frequencies were observed in any of the analyzed ethnic groups.

Using the APSampler algorithm, we revealed 12 combinations of genotypes and alleles associated with longevity in the Tatar population (Table 4). The *SOD1**A and *SOD3**C alleles represent the elements included in detected combinations. The *SOD1**A/A genotype is included in the combination associated with an enhanced probability of achieving longevity (OR = 1.91, $P = 0.0026$, $P_{FDR} = 0.009$), while *SOD3**C/C genotype is included in the combination associated with a reduced probability of achieving longevity (OR = 0.4, $P = 2.05 \times 10^{-5}$, $P_{FDR} = 0.0002$). The rs4880**SOD2* has a predominant impact in various combinations, while its allelic state seems to be crucial for achieving longevity. Therefore, all four combinations associated with a decreased chance of achieving longevity include the *SOD2**V allele in a homozygous state. The highest OR values with the lowest probability of type I error were demonstrated for the combinations including the *SOD2**A/V genotype (OR ≥ 2.92, $P \le 5.65 \times 10^{-8}$, $P_{FDR} \le 1.24 \times 10^{-6}$).

Table 1. Distribution of allele and genotype frequencies (%) over gene polymorphisms of superoxide dismutases in three ethnic groups

Allele/genotype	Ethnic group		
	Russians	Tatars	Bashkirs
rs2070424**SOD1*			
*A	92.35	91.27	88.82
*G	7.65	8.73	11.18
*A/A	84.9	83.33	79.88
*A/G	14.9	15.87	17.89
*G/G	0.2	0.8	2.24
rs4880**SOD2*			
*A	44.97	43.23	44.79
*V	55.03	56.77	55.21
*A/A	16.84	19.56	18.20
*A/V	56.26	47.35	53.17
*V/V	26.90	33.09	28.63
rs1799895**SOD3*			
*C	98.46	98.51	98.25
*G	1.54	1.49	1.75
*C/C	96.93	97.02	96.51
*C/G	3.07	2.98	3.49
*G/G	0.00	0.00	0.00

DISCUSSION

In the present study, for the first time, an analysis of genetic factors predisposing to longevity was conducted in common populations from the Republic of Bashkortostan. We suggest that the achievement of an age exceeding that observed for the average population represents an example of successful adaptation of the body. The activation of oxidative processes is considered to be one of the manifestations of the adaptation of the body to harmful environmental factors. A group of SOD enzymes is the first element in the chain of reactions of ROS conversion.

The studies on the role of SOD enzymes in the pathogenesis of various diseases and aging are being conducted. The majority of studies indicate a decrease in superoxidase activity in pathologies accompanied by oxidative stress [2, 6]. The involvement of SOD in lifespan and longevity was studied, in particular, on model objects, which makes it possible to expand our concept on the effect of this enzyme on the cell structures in different tissues. The overexpression of the

Table 2. Analysis of heterogeneity of ethnic groups with respect to distribution of allele and genotype frequencies of gene polymorphisms of superoxide dismutases

Ethnic group	Russians	Bashkirs	Tatars
rs2070424**SOD1*			
Russians	–	0.009	0.349
Bashkirs	0.003	–	0.042
Tatars	0.226	0.061	–
rs4880**SOD2*			
Russians	–	0.963	0.354
Bashkirs	0.388	–	0.395
Tatars	<0.001	0.035	–
rs1799895**SOD3*			
Russians	–	0.726	1.000
Bashkirs	0.578	–	0.629
Tatars	1.000	0.545	–

The level of heterogeneity is presented as the *P*-value of the exact Fisher's criterion: *P*-values below the diagonal were obtained as a result of comparison of genotype frequencies; *P*-values above the diagonal were obtained upon comparison of allele frequencies.

SOD2 and SOD1 enzymes was shown to increase the survival of yeast cells by 30% [10]. An enhanced expression of the *SOD2* gene caused a diminished ROS content in the mitochondria of hippocampal neurons and increased lifespan in mice [11]. The association between changes in SOD2 activity, diet, risk of developing type 2 diabetes mellitus, and lifespan was shown in rats [12]. In turn, an increased lifespan and improved vital signs in *C. elegans* were associated with an increased expression of the *SOD3* gene [13].

More than three thousand polymorphisms were identified in the *SOD1* gene (21q22.1). Some of them demonstrated associations with multifactorial diseases including cardiovascular, neurodegenerative, oncological, and metabolic ones [14–18].

The rs2070424 representing the adenine to guanine substitution (251A>G) is located in the third intron of the *SOD1* gene. Although the functional role of the 251A>G polymorphic variant of the *SOD1* gene remains incompletely defined, the association of the rare *SOD1**G allele with an increased level of gene expression was detected [19]. Variability in allele and genotype frequencies of this polymorphism was observed between populations with a significant gradient of increasing frequency of the rare *SOD1**G allele from the north to the south and especially from the west to the east (http://grch37.ensembl.org/). The genotype frequencies of rs2070424 in the *SOD1* gene vary within the range observed in European residents. At the same time, the probability of the presence of the *SOD1**G allele and the *SOD1**G/G genotype rose in the order "Russians–Tatars–Bashkir." The detected differences in allele and genotype frequencies between the ethnic groups can be explained by a higher Asian component in the Bashkir population. High frequency of the rare *SOD1**G allele in the residents from the southern and Asian regions of the planet is congruent with the results of the previous study on the enzyme activity, since an increased activity of ADS enzymes is adaptationally beneficial under the conditions of high insolation and a background risk of viral and parasitic infections [19].

No statistical significance in achieving longevity was observed for rs2070424 of the *SOD1* gene in Europeans, including individuals from Denmark [20] and Germany [21]. At the same time, associations of the *SOD1**A and *SOD1**G alleles were reported with several diseases, including oncological and metabolic ones [16–18, 22]. In three examined ethnic groups from the Republic of Bashkortostan, we detected an increase in the frequency of the *SOD1**A/A genotype, which is protective for a development of several age-dependent diseases. According to the results of analysis of allele and/or genotype combinations using the APSampler algorithm, the *SOD1**A allele was more frequent in patterns associated with an increased

Table 3. Association of gene polymorphisms of superoxide dismutases with age using logistic regression

Genotype	Ethnic group	Age range	AUC	*P*	OR	CI_{OR}
Total sample without differentiation by sex						
*SOD1**A/A	Russians	36–98	0.371	0.001	1.025	1.010–1.041
*SOD1**A/G			0.631	0.001	0.975	0.960–0.990
*SOD2**A/A		16–98	0.406	0.002	0.985	0.976–0.995
Men						
*SOD2**A/A	Tatars	22–89	0.428	0.029	0.989	0.980–0.999
*SOD2**V/V			0.414	<0.001	0.985	0.977–0.993
*SOD2**A/V			0.631	<0.001	1.023	1.015–1.032

AUC—area under ROC curve, *P*—level of significance, OR—odds ratio of observed event, CI_{OR}—95% confidence interval for OR.

Table 4. Combinations of alleles/genotypes associated with longevity in Tatars obtained using the APSampler algorithm

Combinations			*p*, %					
rs2070424**SOD1*	rs4880**SOD2*	rs1799895**SOD3*	centenarians (90–109 years)	juvenile and middle-aged (16–60 years)	*P*	P_{FDR}	OR	CI_{OR}
A	A/V	C	55.73	23.71	2.23×10^{-10}	1.47×10^{-8}	4.05	2.59–6.33
	A/V	C	54.44	23.62	5.11×10^{-10}	1.69×10^{-8}	3.87	2.49–5.99
A	A/V		54.01	28.68	5.65×10^{-8}	1.24×10^{-6}	2.92	1.97–4.33
A	A	C	71.84	50.52	2.09×10^{-5}	0.0002	2.50	1.62–3.86
	A	C	70.95	50.25	4.03×10^{-5}	0.0003	2.37	1.62–3.86
A	A		71.12	52.36	4.24×10^{-5}	0.0003	2.24	1.51–3.35
A	V	C	83.33	72.17	0.007	0.023	1.93	1.16–3.20
A/A	V	C	73.56	52.28	0.0026	0.009	1.91	1.23–2.97
	V/V	C/C	27.78	48.74	2.05×10^{-5}	0.0002	0.40	0.26–0.62
A	V/V	C	27.59	48.45	2.88×10^{-5}	0.0002	0.41	0.26–0.63
	V/V	C	29.61	49.75	4.03×10^{-5}	0.0003	0.42	0.28–0.64
A	V/V		28.34	46.90	4.94×10^{-5}	0.0003	0.45	0.30–0.67

p—frequency of observed combinations in age groups, *P*—level of significance, P_{FDR}—level of significance after correction for multiple testing, OR—odds ratio for observed event, CI_{OR}—95% confidence interval for OR.

chance of achieving longevity, and it was in a homozygous state in one of them.

According to the https://www.genecards.org/ database, the *SOD2* gene (6q25.3) includes more than 24000 polymorphisms. One of the missense mutations in the gene represents valine to alanine substitution in the 16th unit of the SOD2 protein chain (16V>A, rs4880). A change in the secondary structure of the signal peptide and, hence, destabilization of its alpha-helical region caused by this polymorphism affect the rate of enzyme transfer from the cytoplasm to the mitochondria, which may cause an absolute or relative local enzymatic deficit [23]. It was shown that the SOD2 activity was 40% higher in carriers of the *SOD2**A allele [24].

Various genotypes of rs4880 in the *SOD2* gene can be associated with cancer; however, according to various studies, they depended on certain environmental factors [25]. The *SOD2**V/V genotype was associated with acute coronary disease in women [26], while the *SOD2**V allele was associated with Parkinson's disease [27]. A protective effect of the *SOD2**A allele on the risk of developing type 2 diabetes mellitus and its complications was demonstrated [28]. On the other hand, earlier studies reported that the *SOD2**A allele was associated with some neurodegenerative diseases [29, 30]. Also, the *SOD2**A/A genotype was identified as a genetic marker of premature brain aging in healthy individuals [31].

Published data reported findings on the decrease in the activity of the SOD2 enzyme in centenarians (100–105 years) compared to individuals aged 60 to 79 years [32]. No associations of rs4880 in the *SOD2* gene were observed with longevity in individuals from Italy [33] and Germany [21]. However, a recent study [34] demonstrated an enhanced expression of the *SOD2* gene in natural killer cells (NK cells) in individuals older than 80 years. This observation made it possible to conclude the role of this enzyme in the homeostasis of NK cells, which is necessary for healthy aging. The mortality was lower in carriers of the *SOD2**A allele over the age of 90 years [35]. In addition, the association of rs4880 in the *SOD2* gene with survival was established in Danish women [20].

The inconsistency of the published studies on the relations between the structural and functional specificity of the SOD2 and the encoding gene with age-related diseases, lifespan, and longevity was also reported in this study. The rs4880 in the *SOD2* gene was associated with lifespan in Russians and Tatars, and a decrease in the frequency of homozygous genotypes with age was characteristic of both ethnic groups. At the same time, the analysis of allele and genotype combinations demonstrated that the *SOD2**V/V genotype was associated with a low chance of achieving longevity among Tatars. The protein encoded by this allelic variant of the gene is assumed to possess slower transport to mitochondria and, hence, higher proba-

bility of proteasome cleavage in the cell. Moreover, it may be associated with a reduced mRNA stability [24]. The inclusion of the heterozygous *SOD2**A/V genotype in the patterns associated with the highest odds ratio of achieving longevity is probably due to the presence of the *SOD2**A allele, which also becomes a component of the combinations that positively correlate with longevity (Table 4). Accordingly, the *SOD2**A allele, which encodes the enzyme with higher efficiency of cell defense from ROS, is associated with longevity in Tatars in the present study.

The *SOD3* gene (4p15.3-p15.1) encodes the extracellular form of SOD, which is rarely detected in the majority of tissues. However, the tissues directly contacting atmospheric oxygen dissolved in the blood (lungs, blood vessels, and heart) are characterized by an increased concentration of this enzyme. In the vascular system, SOD3 is assigned to heparan sulfate-epithelial proteoglycans. The rs1799895 represents a transversion at the position 691 (C>G) in exon 3. It results in changes in the structure of the heparin-binding domain of the protein (231R>G), which disrupts the ability of the enzyme to bind to the external surface of endothelial cells. Therefore, the mutation in this polymorphic locus causes multiple (~10-fold) increase in plasma SOD3 without changes in the transcriptional activity of the gene and, hence, a decreased enzymatic activity in tissues [36].

The frequency of the mutant *SOD3**G allele is low in populations worldwide (MAF (minor allele frequency) is 0.02) (http://grch37.ensembl.org/). The distribution of genotype frequencies of this polymorphic variant in the examined ethnic groups was similar to that in Europeans.

In the available publications, we were unable to find any studies on the associations of the rs1799895 in the *SOD3* gene with longevity. However, the results of association studies of age-dependent diseases indicate the role of the mutant allele of the rs1799895 in the development of several age-related pathologies. A risk of cardiovascular insufficiency was reported to be increased in diabetic subjects bearing the heterozygous genotype [37]. The presence of the *SOD3**G allele in the homozygous state was associated with an increased risk of coronary artery disease and ischemic stroke, with certain forms of cancer, and, overall, with mortality [38]. According to our data, the *SOD3**C/C genotype in combination with the SOD2*V/V genotype was associated with reduced chances of achieving longevity among Tatars.

Therefore, in this study based on the analysis of three ethnic groups from the Republic of Bashkortostan, we revealed the ethnicity-specific pattern of allele and genotype frequencies of the genes encoding the ADS enzymes, which are related to the adaptive possibilities of an individual. The association of rs2070424**SOD1* and rs4880**SOD2* with longevity was established. This observation may indicate the involvement of genes encoding enzymes involved in ROS metabolism in aging, the development of age-related diseases, and the development of the longevity phenotype.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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