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HUMAN GENETICS

Analysis of *FOXO1A* and *FOXO3A* Gene Allele Association with Human Longevity

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Abstract—Seeking human longevity association with gene polymorphisms in transcription factors in the Tatar ethnic group, we conducted an analysis for age-related genotype frequencies in polymorphic sites of *FOXO1A* (rs4943794, 72327C>G) and *FOXO3A* (rs3800231, 35-2764A>G) genes. Genotyping was conducted using the PCR-RFLP approach. According to the results of logistic regression analysis, during maturity and old age periods, a decrease in the number of *FOXO1A*G/*G* (OR = 0.984, $P = 0.004$) genotype carriers occurs and an increase in the number of *FOXO1A*C/*G* (OR = 1.035, $P = 0.014$) and *FOXO1A*C/*C* (OR = 1.024, $P = 0.033$) genotype carriers occurs in the sample of subjects before gender adjustments. In the sample of long-livers, the number of *FOXO1A*C/*C* (OR = 0.772, $P = 0.028$) genotype carriers decreased among women, while the number of *FOXO3A*G/*G* (OR = 1.008, $P = 0.0001$) genotype carriers increased among both men and women. Therefore, the *FOXO1A* gene polymorphic site rs4943794 is associated with an acquisition of old and senescent age in a sample before gender adjustments and with women's longevity. *FOXO3A* gene polymorphic site rs3800231 is associated with longevity in both women and men.

Keywords: lifespan, human longevity, transcription factor genes, genetic polymorphism, association analysis
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INTRODUCTION

Human longevity is a complex phenomenon, which involves interaction between heredity, way of life, and environmental factors. About 25% of all the composing conditions for acquisition of 90 years of age and older depend on genetics [1]. At the same time, the importance of heredity in development of the long-liver status increased in old and senescent ages [2, 3]. One of the approaches to searching for longevity genes is association studies using allele variants of candidate genes for old age and senescence. During the association studies, the samples of individuals of different age are compared. It was suggested that allele and genotype frequencies which affect the individual survival could change in the genotype pool with increasing age, while among long-livers (old and senescent subjects) allelic variant incidence frequency of the genes which promote long lifespan (LS) should be increased.

For the studies on molecular and genetic mechanisms of longevity, the genes characterized by a wide spectrum of pleiotropic effects are of special interest. In particular, such a capacity is possessed by genes encoding transcription factors (TFs) FOXO (forkhead family of transcription factors). They represent homologs of the daf-16 gene, a key regulator of the INS/IGF1 (insulin/insulin-like growth factor) signaling pathway and a lifespan modulator in nematode (*Caenohabditis elegans*) [4, 5]. FOXO TFs play an important role in regulation of the cell cycle, proliferation, differentiation, cell apoptosis, and DNA reparation, as well as in antioxidant defense and resistance to stress. It is suggested that in humans the contribution of these proteins to longevity could result from a balance of insulin sensitivity and insulin resistance, which is mediated by the INS/IGF1 signaling pathway [6].

The results of several studies, including genome wide association studies, confirmed the association of some polymorphic sites in *FOXO1A* and *FOXO3A* genes with longevity, death, and lifespan limiting diseases [1, 7–14]. For the rs3800231 polymorphic locus of the *FOXO3A* gene, the highest significance level of association with longevity was observed [9]. The rs4943794 polymorphic locus of the *FOXO1A* gene was associated with type 2 diabetes mellitus [7] and with the age of death [13].

The aim of our study was to investigate age-dependent changes in allele and genotype frequencies at polymorphic sites for the *FOXO1A* (rs4943794, 72327C>G) and *FOXO3A* (rs3800231, 35-2764A>G) genes and assess their importance in acquisition of human longevity.

MATERIALS AND METHODS

The examined sample included 1508 unrelated subjects (654 men and 854 women) from 21 to 109 years of age of Tatar ethnicity residing in Bashkortostan. The informed consent of each subject was obtained prior to questioning and taking biological material (8 mL of blood from elbow vein).

Genomic DNA specimens were isolated from lymphocytes from the peripheral venous blood by phenol-chloroform extraction [15]. Genotyping of the *FOXO1A* (rs4943794, 72327C>G) and *FOXO3A* (rs3800231, 35-2764A>G) gene polymorphic sites was conducted using polymerase chain reaction (PCR) followed by restriction analysis. Oligonucleotide primers (F 5'-caa ctg aac aaa aca tgg caa taa-3', R 5'-caa tcg tgt aag gct gtg gtg ag-3' for the polymorphic site rs4943794 of the *FOXO1A* gene and F 5'-caa tct gtt ttc ctt ctg tca c-3', R 5'-aat cac cac ttt ccc ttt ctg c-3' for the polymorphic site rs3800231 of the *FOXO3A* gene), as well as restriction endonucleases (*Apo*I for the polymorphic site rs4943794 of the *FOXO1A* gene and *Rsa*I for the polymorphic site rs3800231 of the *FOXO3A* gene), were selected using the www.ncbi.nlm.nih.gov/snp/ database and DNAStar software.

The test for electrophoretic mobility of DNA fragments was carried out in 7% polyacrylamide gel. The gel was stained with 1% ethidium bromide solution and visualised in UV light using the GE documenting system (Vilber-Lourmat, France).

Statistical analysis was conducted with SPSS V.21.0 software. The equivalence of the empirically obtained genotype frequency distribution to that theoretically expected was assessed according to the Hardy–Weinberg equation using Arlequn 3.0 software. All the samples contained subjects of the age groups identified according to the common classification recommended by World Health Organization [16]: adults (22–60 years old for men, $n = 282$, and 21–55 years old for women, $n = 77$; $N = 359$), elderly subjects (61–74 years old for men, $n = 98$, and 56–74 years old for women, $n = 236$; $N = 334$), senescent subjects (75–89 years old for men and women, $n = 241$ and 370, respectively; $N = 611$, and long-livers (90–109 years old for men and women, $n = 33$ and 171, respectively; $N = 204$). Allele and genotype frequencies in various age groups were pairwise compared using the exact double-sided Fisher test. The differences in allele and genotype frequencies were considered significant at $P < 0.05$; the FDR coefficient was used for correction for multiple comparisons (WinPepi V.11.39).

As we suggested that genotype frequency affecting individual survival could change in a genotype pool with increasing age, we studied age-related genotype frequency alterations, which were assessed as an ODD ratio (OR, SPSS V.21.0) using logistic regression analysis. At the same time, the probability of genotype incidence was assumed to be a function of the binary logistic regression equation, while the age was an independent variable. Age intervals were determined by ROC analysis.

RESULTS

Here, we characterized a distribution of allele and genotype frequencies in the polymorphic locus 72327C>G of the *FOXO1A* gene in the Tatar population (Table 1). The observed genotype frequency distribution corresponded to Hardy–Weinberg equilibrium ($P = 0.617$). No difference in the genotype and allele frequencies was noted between samples of men and women ($\chi^2 = 2.758$, $P = 0.252$).

An examination of the age dependence of the allele and genotype frequency distribution in the 72327C>G polymorphism of the *FOXO1A* gene revealed that, in the total sample of senescent subjects, the *FOXO1A*C/*C* genotype frequency was higher than that in a subset of adults (7.05% versus 3.51%, $P = 0.022$, $P_{FDR} = 0.083$). The *FOXO1A*C* and *FOXO1A*G* alleles were represented with frequencies of 25.37 and 74.63% among elderly subjects and 25.08 and 74.92% in senescent subjects. In the adult subgroup, the frequencies of *FOXO1A*C* and *FOXO1A*G* alleles were 20.54 and 79.46%. The differences between groups of adults and subsets of subjects of old and senescent age achieved statistical significance ($P = 0.036$ and $P = 0.012$, respectively) in comparative analysis without correction for multiple comparisons. At the same time, the P index appeared higher than 0.05 using the FDR coefficient ($P_{FDR} = 0.108$ and 0.072, respectively).

The *FOXO1A*C* and *FOXO1A*G* alleles were observed with frequencies of 25.65 and 74.35% among senescent men and 14.06 and 85.94% ($P = 0.044$, $P_{FDR} = 0.120$) in the group of long-livers, respectively. In women, no differences in allele and genotype frequencies among the groups of different ages were observed.

Presumably, upon correction for multiple comparisons, the differences in allele and genotype frequencies between various age groups cannot reach the significance level of $P = 0.05$, but they are close to the significance level of $P = 0.1$.

Data analysis with binary logistic regression (Table 2) in the gender undifferentiated sample showed that the chances of *FOXO1A*C/*G* genotype detection increased (OR = 1.035, $P = 0.014$) in the age group between 35 and 64 years old. The chances of *FOXO1A*C/*C* genotype detection also increased in the age group between 26 and 78 years old (OR = 1.024, $P = 0.033$), while the chances of *FOXO1A*G/*G* genotype detection in the age group between 28 and 75 years old decreased (OR = 0.984, $P = 0.004$).

In the sample of men, the *FOXO1A*C/*G* (OR = 1.052, $P = 0.008$) genotype was associated with age in subjects from 35 to 64 years old and the *FOXO1A*G/*G* (OR = 0.990, $P = 0.036$) genotype was associated with

Table 1. Age-related allele and genotype frequency distribution for 72327C>G polymorphic site of the *FOXO1A* gene

Age period		Genotype frequency ($p \pm s_p$, %)			Allele frequency ($p \pm s_p$, %)	
		*C/*C	*C/*G	*G/*G	*C	*G
Gender undifferentiated sample						
1	Mature	3.51 ± 0.96[3]	34.05 ± 2.46	62.43 ± 2.52	20.54 ± 1.49[2, 3]	79.46 ± 1.49[2, 3]
2	Elderly	6.57 ± 1.35	37.61 ± 2.65	55.82 ± 2.71	25.37 ± 1.68[1]	74.63 ± 1.68[1]
3	Senescent	7.05 ± 1.05[1]	36.07 ± 1.97	56.88 ± 2.03	25.08 ± 1.26[1]	74.92 ± 1.26[1]
4	Long-livers	5.85 ± 1.71	35.11 ± 3.48	59.04 ± 3.59	23.4 ± 2.18	76.6 ± 2.18
Total sample		5.91 ± 0.61	35.8 ± 1.24	58.29 ± 1.28	23.81 ± 0.78	76.19 ± 0.78
Men						
1	Mature	3.71 ± 1.1	33.90 ± 2.76	62.37 ± 2.82	20.68 ± 1.67	79.32 ± 1.67
2	Elderly	5.05 ± 2.2	36.36 ± 4.83	58.59 ± 4.95	23.23 ± 3	76.77 ± 3
3	Senescent	6.47 ± 1.62	38.36 ± 3.19	55.17 ± 3.27	25.65 ± 2.03[4]	74.35 ± 2.03[4]
4	Long-livers	–	28.12 ± 7.95	71.88 ± 7.95	14.06 ± 4.35[3]	85.94 ± 4.35[3]
Total sample		4.71 ± 0.83	35.56 ± 1.87	59.73 ± 1.91	22.49 ± 1.15	77.51 ± 1.15
Women						
1	Mature	2.67 ± 1.86	34.67 ± 5.5	62.67 ± 5.59	20.00 ± 3.27	80.00 ± 3.27
2	Elderly	7.2 ± 1.68	38.14 ± 3.16	54.66 ± 3.24	26.27 ± 2.03	73.73 ± 2.03
3	Senescent	7.42 ± 1.37	34.62 ± 2.49	57.97 ± 2.59	24.73 ± 1.6	75.27 ± 1.6
4	Long-livers	7.05 ± 2.05	36.54 ± 3.86	56.41 ± 3.97	25.32 ± 2.46	74.68 ± 2.46
Total sample		6.86 ± 0.88	35.98 ± 1.66	57.16 ± 1.72	24.85 ± 1.06	75.15 ± 1.06

Here and in Table 3, the index sign indicates the numbers of age groups the differences between which are significant (without correction for multiple comparisons); p is the frequency; s_p is the frequency error.

Table 2. Analysis of associations of the *FOXO1A* gene 72327C>G polymorphic site with age by binary logistic regression

Genotype	Age period	P	OR	CI_{OR}
Gender undifferentiated sample				
*C/*C	26–78	0.033	1.024	1.002–1.046
*C/*G	35–64	0.014	1.035	1.007–1.063
*G/*G	28–75	0.004	0.984	0.973–0.995
Men				
*C/*G	35–64	0.008	1.052	1.013–1.093
*G/*G	25–80	0.036	0.990	0.980–0.999
Women				
*C/*C	88–109	0.028	0.772	0.612–0.973
*G/*G	21–70	0.039	0.976	0.954–0.999

Here and in Table 4, P is the significance level, OR is the odd ratio, and CI_{OR} is the OR confidential interval.

Table 3. Age-related allele and genotype frequency distribution of 35-2764A>G polymorphic site of the *FOXO3A* gene

Age period		Genotype frequency ($p \pm s_p$, %)			Allele frequency ($p \pm s_p$, %)	
		*A/*A	*A/*G	*G/*G	*A	*G
Gender undifferentiated sample						
1	Mature	11.42 ± 1.68	54.60 ± 2.63[2*]	33.98 ± 2.5[2*, 3]	38.72 ± 1.82	61.28 ± 1.82[2]
2	Elderly	13.17 ± 1.85	39.82 ± 2.68[1*]	47.01 ± 2.73[1*]	33.08 ± 1.82	66.92 ± 1.82[1]
3	Senescent	15.06 ± 1.45	42.72 ± 2	42.23 ± 2[1]	36.42 ± 1.38	63.58 ± 1.38
4	Long-livers	13.73 ± 2.41	46.08 ± 3.49	40.2 ± 3.43	36.76 ± 2.39	63.24 ± 2.39
Total sample		13.59 ± 0.88	45.36 ± 1.28	41.05 ± 1.27	36.27 ± 0.88	63.73 ± 0.88
Men						
1	Mature	10.99 ± 1.86	54.61 ± 2.96[2]	34.40 ± 2.83[2]	38.30 ± 2.05[2]	61.70 ± 2.05[2]
2	Elderly	8.16 ± 2.77	40.82 ± 4.96[1]	51.02 ± 5.05[1]	28.57 ± 3.23[1]	71.43 ± 3.23[1]
3	Senescent	13.69 ± 2.21	46.06 ± 3.21	40.25 ± 3.16	36.72 ± 2.2	63.28 ± 2.2
4	Long-livers	15.15 ± 6.24	36.36 ± 8.37	48.48 ± 8.7	33.33 ± 5.8	66.67 ± 5.8
Total sample		11.77 ± 1.26	48.47 ± 1.95	39.76 ± 1.91	36.01 ± 1.33	63.99 ± 1.33
Women						
1	Mature	12.99 ± 3.83	54.55 ± 5.67[2, 3]	32.47 ± 5.34	40.26 ± 3.95	59.74 ± 3.95
2	Elderly	15.25 ± 2.34	39.41 ± 3.18[1]	45.34 ± 3.24	34.96 ± 2.19	65.04 ± 2.19
3	Senescent	15.95 ± 1.9	40.54 ± 2.55[1]	43.51 ± 2.58	36.22 ± 1.77	63.78 ± 1.77
4	Long-livers	13.45 ± 2.61	47.95 ± 3.82	38.6 ± 3.72	37.43 ± 2.62	62.57 ± 2.62
Total sample		14.99 ± 1.22	42.97 ± 1.69	42.04 ± 1.69	36.48 ± 1.16	63.52 ± 1.16

Asterisk after the index indicates the numbers of age groups between which the differences are significant after introduction of correction for multiple comparisons.

age in the range from 25 to 80 years old. In the sample of women at the age from 21 to 70 years old, the probability of detection of the *FOXO1A**G/*G* (OR = 0.976, $P = 0.039$) genotype with increase in age decreased, while at the age from 88 to 109 years old the chances of *FOXO1A**C/*C* (OR = 0.772, $P = 0.028$) genotype detection also decreased.

It is likely that a decrease in *FOXO1A**G/*G* genotype carriers and an increase in *FOXO1A**C/*G* genotype carriers occurs among both men and women during the mature and elderly periods. In addition, comparing the obtained data related to the changes in *FOXO1A**C/*C* genotype frequency in the total sample and among women suggests that these genotype carriers could have different chances of survival during different age periods.

The distribution of allele and genotype frequencies in the FOXO3A polymorphic locus of the *FOXO3A* gene in the Tatar population is presented in Table 3. The observed genotype frequency distribution corresponds to the theoretically expected Hardy–Weinberg equilibrium ($P = 0.469$). At the same time, samples of men and women differ $\chi^2 = 6.660$, $P = 0.036$) according to the distribution of genotype frequencies. Considering age periodization, the distribution of genotype frequencies in the sample of senescent women deviated from the Hardy–Weinberg equilibrium ($P = 0.020$). This suggests that a selection for this polymorphism occurs during aging.

In the elderly subjects, the *FOXO3A**G* allele and *FOXO3A**G/*G* genotype are represented with frequencies of 66.92 and 47.01%, respectively, while in mature subjects, they are represented with frequencies of 61.28 and 33.98%. The observed differences of genotype frequency were statistically significant ($P = 0.0006$, $P_{FDR} = 0.009$). Likewise, the *FOXO3A**G/*G* genotype frequency among senescent subjects was higher compared with that in mature subjects (42.23% versus 33.98%, $P = 0.012$, $P_{FDR} = 0.072$), but these differences did not reach statistical significance after correction for multiple comparisons. The *FOXO3A**A/*G* genotype was revealed with lower frequency in the elderly subjects compared with the mature subjects (39.82% versus 54.60%, $P = 0.0001$, $P_{FDR} = 0.003$).

Among elderly men, the frequencies of *FOXO3A**A* and *FOXO3A**G* alleles (28.57 and 71.43%) differed from those in the group of mature subjects (38.30 and 61.70%, $P = 0.015$, $P_{FDR} = 0.075$). In addition, the group

Table 4. Analysis of associations of the *FOXO3A* gene 35-2764A>G polymorphic site with age by binary logistic regression

Genotype	Age period	*P*	OR	CI_{OR}
Gender undifferentiated sample				
**A*/*G*	21–109	0.0001	0.992	0.988–0.996
**G*/*G*	21–109	0.0001	1.008	1.003–1.012
Men				
**A*/*G*	22–100	0.002	0.991	0.986–0.997
**G*/*G*	22–100	0.001	1.010	1.004–1.016
Women				
**A*/*G*	22–78	0.023	0.986	0.973–0.998
	78–109	0.046	1.031	1.001–1.063
**G*/*G*	21–70	0.027	1.027	1.003–1.052

of elderly subjects differed from the group of mature subjects in genotype frequencies: *FOXO3A*G/*G* (51.02 and 34.40%, respectively, $P = 0.005$, $P_{FDR} = 0.050$) and *FOXO3A*A/*G* (40.82 and 54.61%, respectively, $P = 0.019$, $P_{FDR} = 0.081$).

According to the binary logistic regression analysis (Table 4), the chances of *FOXO3A*A/*G* genotype detection (OR = 0.991, $P = 0.002$) are decreased, while the chances of *FOXO3A*G/*G* genotype detection are increased (OR = 1.010, $P = 0.001$) in men 22–100 years old. Among women, the chances of *FOXO3A*A/*G* genotype detection within the range from 22 to 78 years old are decreased (OR = 0.986, $P = 0.023$), and within the range from 78 to 109 years old, they are increased (OR = 1.031, $P = 0.046$). The chances for detection of the *FOXO3A*G/*G* genotype with increasing age are higher within the range from 21 to 70 years old (OR = 1.027, $P = 0.027$).

Therefore, to achieve longevity, it is important to carry the *FOXO3A*G/*G* genotype.

DISCUSSION

Our results suggest that the polymorphic region rs4943794 of the *FOXO1A* (72327C>G gene could be important for living to an old and senescent age, as well as for longevity in women. Polymorphic locus rs3800231 of the *FOXO3A* (35-2764A>G gene was associated with longevity in both men and women.

The revealed age-dependent associations of the polymorphic sites of the *FOXO1A* and *FOXO3A* genes could be associated with the functions which FOXO TFs play in many cellular regulatory processes and with allelic status-dependent gene expression of these genes. The results of other studies make it possible to reveal an association between variability in the primary structure of genes encoding FOXO TFs, the level of these gene expressions, and some pathological conditions characterized by relatively late disease manifestation. For example, the importance of the *FOXO1A* and *FOXO3A* genes was demonstrated for initiation of several pathological states of the cardiovascular system, such as diabetic cardiomyopathy, heart hypertrophy, ischemic heart disease, and stroke [17–22]. The mechanisms involved in *FOXO3A* gene contribution to stroke development are unknown. It is likely that FOXO3A TFs serve as triggers of signaling pathways regulating expression of "oxidant defense" genes [23] as formation of oxidative reactions in response to stress is one of the important conditions of stroke pathogenesis [22, 24].

In the study conducted on a sample of long-livers from the Netherlands (The Leiden 85-plus Study), a haplotype of four SNP markers (rs2802288, rs2883881, rs12200646, and rs13220810) in the *FOXO3A* gene was associated with a high risk of stroke development and increased mortality [25]. In several research laboratories, a number of studies on association of *FOXO1A* gene polymorphic variants with type 2 diabetes mellitus (D2M) development were conducted [7, 26]. An increase in *FOXO1A* gene expression induces a decrease in the level of the pancreatic regulatory factor (PDX1, pancreatic and duodenal homeobox1), which is capable of augmenting the activity of insulin signaling. This facilitates increased gluconeogenesis and glucose exit from liver [27]. Disturbance of the insulin metabolism stimulates D2M development [28]. A haplotype which includes six SNP markers of the *FOXO1A* gene (rs7337995, rs9532580, rs7981045, rs4943794, rs2721069, and rs2701891) and which has protective action with respect to D2M development has been isolated in Germans [7].

In the framework of the discussed issue, it is worth noting that alteration of the transcriptional activity of the *FOXO1A* and *FOXO3A* genes can induce malignant tumors in many tissues and organs [29–31]. Therefore, it is possible to conclude the involvement of the *FOXO1A* and *FOXO3A* genes in formation of predisposition for the development of diseases which limit life span.

It is also worth noting that the studies on associations with life span and longevity for *FOXO3A* gene allelic variants are characterized by a strong reproducibility of the results in different world populations [1, 8–12, 23]. Therefore, this gene, together with the *APOE* gene, has a special importance among candidate genes for aging and longevity studies. A total of 1383 polymorphic SNP loci were identified in the *FOXO3A* gene (6q21, 4 exons, 124952 bp) [http://www.genecards.org/]. In Japanese residing in the United States, an association with longevity of polymorphic marker rs2802292 of the *FOXO3A* gene was revealed [8]. In Germans, an association of polymorphic markers rs6911407, rs9400239, rs3800231, and rs479744 with longevity and also an association of polymorphic markers rs6911407, rs768023, rs2802288, rs2802290, rs13220810, rs7762395, rs9400239, rs3800231, rs1268170, rs473268, and rs479744 of the *FOXO3A* gene with lifespan over 100 years old were discovered. The highest level of significance of these associations was shown for the rs3800231 polymorphic marker ($P < 0.00005$). However, in the study of a French sample, significant associations of three polymorphic markers rs3800231, rs7762395, and rs768023, which were observed in Germans, were not confirmed [9]. In Italians, the rs2802292 polymorphic marker was associated with lifespan, while another polymorphic site rs2802288, which is in linkage disequilibrium with rs2802292, appeared to be associated with lifespan in men but not in women [10]. At the same time, two polymorphic sites rs1935949 and rs4946935 were associated with longevity in Ashkenazy Jewish women [11]. In a Danish population, the associations of polymorphic sites rs13217795, rs2764264, rs479744, and rs9400239 with longevity observed previously in other studies were reproduced, while associations of rs12206094, rs13220810, rs7762395, and rs9486902 polymorphic markers with longevity were also revealed [12].

In various world populations, 1396 SNP-polymorphic variants in the *FOXO1A* gene (13q14.1, 3 exons, 110934 bp) were identified [http://www.genecards.org/]. For some of them, an association with longevity was shown. For example, genome-wide association analysis (GWAS) data collected during the Framingham heart study made it possible to reveal an association of polymorphic markers rs10507486 and rs4943794 with the age of death [13]. In a population of Chinese residents, an association of polymorphic markers rs2755209 and rs2755213 with longevity of women was found. It was also shown that, in a group of one-hundred-year-old women, the frequency of minor alleles decreased [23]. At the same time, in a German population, an association of polymorphic markers of the *FOXO1A* gene with longevity was not confirmed [14].

In the present study, genotyping was conducted using 19 polymorphic markers, including rs4943794. According to our results, polymorphic marker rs4943794 of the *FOXO1A* gene is also associated with reaching old and senescent ages in ethnic Tatars. Association of this polymorphic marker of the *FOXO1A* gene with longevity was revealed among women. This supports the results of the previous study [23], which partially explains the results obtained by a small group size of male long-livers. At the same time, it is worth noting that the sensitivity to insulin is gender-specific in various periods of ontogenesis and is also affected by many types of stress observed both in humans and in animal model systems [32, 33]. For example, in female rats, a high-fat and carbohydrate diet does not induce insulin resistance to the same extent as in males [34, 35]. At the same time, in aging women with D2M, the level of insulin resistance and susceptibility of the heart to ischemic disturbances appeared to be significantly higher than in men [36]. Presumably, gender specific traits of human longevity are associated with sex dimorphism with respect to the insulin resistance.

Therefore, the results of our study indicate the association of polymorphic marker rs3800231 of the *FOXO3A* gene with longevity in ethnic Tatars, while polymorphic marker rs4943794 of the *FOXO1A* gene is associated with longevity in women.

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