ISSN 1022-7954, Russian Journal of Genetics, 2025, Vol. 61, No. 1, pp. 98–107. © Pleiades Publishing, Inc., 2025.

HUMAN GENETICS

Alu Polymorphisms of Autophagy and Apoptosis Regulatory Genes as Human Lifespan Factors

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Received June 7, 2024; revised July 11, 2024; accepted July 16, 2024

Abstract—To assess the contribution to survival of Alu insertions in the *ACE*, *PLAT*, *COL13A1*, *LAMA2*, *CDH4*, *SEMA6A*, *PKHD1L1*, *STK38L*, *HECW1*, and *TEAD1* genes, which are candidates of aging and longevity, amid the senile physiological and pathological phenotype, an analysis of association with life expectancy was carried out. Survival and mortality data were obtained for 1382 elderly people who were selected from the sample of Tatars residing in the Republic of Bashkortostan (total 1790 people from 18 to 109 years). Mortality risk was higher among carriers of the *STK38L* Alu-insertion genotype (Ya5ac2145**II*, $HR = 2.07$, $P = 0.022$). Alu insertion in the *HECW1* and *TEAD1* genes has demonstrated a survival protection effect (Ya5NBC182**II*, $HR = 0.71$, $P = 0.038$ and Ya5ac2013**II*, $HR = 0.74$, $P = 0.035$ respectively). The survival amid the persons with various clinical phenotypes was associated with the Alu polymorphism of the *SEMA6A* (Yb8NBC597**ID*, $HR = 0.54$, $P = 0.016$ for the cerebrovascular diseases), *TEAD1* (Ya5ac2013**II*, $HR = 0.57$, $P = 0.016$ for the cardiovascular pathologies), and *LAMA2* (Ya5-MLS19**ID*, $HR = 0.36$, $P = 0.03$ for multimorbidity status) genes. Thus, the genes involved in the regulation of autophagy and apoptosis were associated with survival and longevity.

Keywords: aging, longevity, Alu polymorphism, *TEAD1*, *HECW1*, *STK38L*, *LAMA2*, *SEMA6A* genes, survival analysis

DOI: 10.1134/S1022795424701448

INTRODUCTION

Human life expectancy is determined by a complex of environmental, behavioral, and hereditary factors. Moreover, a dynamic nature of endogenous mechanisms, which regulate the rate of body aging, determines specificity of the late stages of ontogenesis. The absolute and relative number of changes in the human body caused by impaired molecules, cells, organs, and their systems, in summary, results in a reduced functional activity and abnormal homeostasis of the whole organism and its parts, without the possibility of complete recovery. Accordingly, aging is characterized by an increased risk of developing a large number of diseases and an enhanced probability of death from all causes [1, 2]. It should be noted that the proportion of age-related pathologies, including circulatory and respiratory system and oncological diseases as the leading ones, varies in different age groups [3].

The study of the role of genomic polymorphism in the development of age-related diseases is one of the key areas of molecular genetic research aimed at determining life expectancy. In particular, a polymorphic state of DNA sites containing mobile genetic elements is associated with increased genome instability. Transposon insertions can cause various mutations and chromosomal rearrangements and affect the epigenetic landscape of the eukaryotic genome and processes regulating transcription and gene expression. These effects of insertion events to a major extent are observed at the later stages of ontogenesis [4]. The Alu repeats represent the most common family of human transposons. The Alu polymorphic variants located in the genes of key signaling pathways are involved in physiological and pathological intracellular processes [5, 6]. Previously, we established associations of Alu polymorphisms in the genes encoding protein kinase STK38L, protein ligase HECW1, calcium channel protein PKHD1L1, cellular receptor SEMA6A, transcription factor TEAD1, plasma enzymes ACE and PLAT, and CDH4 adhesion proteins and extracellular matrix COL13A1 and LAMA2 with longevity [7–9]. The involvement of these genes in the development of age-related diseases, including cardiovascular, neuro-

Table 1. The Alu polymorphisms included in the study, their location, PCR conditions, and size of amplified fragments

Alu element	Gene, location*	Primer sequences	Annealing temperature, °C	Alleles (fragment size, bp)
Ya5ACE	*ACE* 17q23.3	F 5'-ctg gag acc act ccc atc ctt tct-3' R 5'-gat gtg gcc atc aca ttc gtc aga t-3'	68	*I* (490) *D* (190)
Ya5NBC182	*HECW1* 7p13	F 5'-gaa gga cta tgt agt tgc aga agc-3' R 5'-aac cca gtg gaa aca gaa gat g-3'	64	*I* (563) *D* (287)
Yb8NBC597	*SEMA6A* 5q23.1	F 5'-tga ggt gtt gca gac gat gt-3' R 5'-cgc atg ctt tag aga ata ccc-3'	63	*I* (429) *D* (108)
Yb8NBC516	*CDH4* 20q13.33	F 5'-ggg ctc agg gat act atg ctc-3' R 5'-gcc tag gcc tac cac tca ga-3'	60	*I* (445) *D* (124)
Ya5ac2145	*STK38L* 12p11.23	F 5'-tgt tct aat gac cat gcc tac tt-3' R 5'-tgc ctt tag gaa gct aca gat tta-3'	60	*I* (465) *D* (135)
Yb8AC702	*PKHD1L1* 8q23.2	F 5'-tgt ttg gaa ata agc caa aca at-3' R 5'-ggg tag caa cct ttt tca tct tt-3'	60	*I* (482) *D* (161)
Ya5ac2013	*TEAD1* 11p15.2	F 5'-tgg cag att ctg act ggc ta-3' R 5'-cac gta agg tga aaa ggg ga-3'	60	*I* (489) *D* (212)
TPA25	*PLAT* 8p11.21	F 5'-caa cca atg aaa acc act ga-3' R 5'-gtt ctc ctg aca tct tta ttg-3'	60	*I* (518) *D* (217)
Ya5ac1986	*COL13A1* 10q22.1	F 5'-tct agt ggg atg agg ata ac-3' R 5'-tgt gcc atg ggg taa gaa ac-3'	60	*I* (431) *D* (134)
Ya5-MLS19	*LAMA2* 6q22.33	F 5'-cta tga cgg agt aaa aag aag t-3' R 5'-gaa aga gtg cca acc ctg tcc-3'	63 (7 cycles) 60 (22 cycles)	*I* (401) *D* (106)

F—forward primer; R—reverse primer; bp—base pairs; * according to UCSC database.

degenerative, oncological, and metabolic diseases, has been established in several studies [10–20]. At the same time, their impact on survival, including on various clinical phenotypes and, moreover, at the age exceeding the average, has not been previously examined. The Alu transposons represent one of the key endogenous factors of evolutionary adaptation and development of humans as a species [21, 22]. In this regard, this type of genomic polymorphism can be considered as an important molecular genetic predictor of survival at a senile physiological background and, moreover, pathological comorbid condition.

In the present study, we have analyzed the effect of Alu polymorphic variants of the genes encoding structural cellular components, intercellular interactions, and those involved in key signaling pathways of cellular activity in the survival among older aged and long-lived individuals.

MATERIALS AND METHODS

The sample of residents of the Republic of Bashkortostan was formed during 2001–2015 and included 1790 individuals aged 18 to 109 years, Tatars by ethnicity. The criteria for inclusion of middle-aged individuals (aged 18–59 years) in the study included the absence of a medical history of diabetes mellitus, heart attack and/or stroke, and autoimmune and oncological diseases. For individuals of the older age cohort (60–89 years old), a history of atherosclerosis, cardiosclerosis, and cerebrosclerosis was allowed. The group of long-livers included all subjects who achieved the age of 90.

DNA samples were obtained via phenol-chloroform extraction from 8 mL of whole venous blood. The Alu polymorphisms in the *ACE*, *PLAT*, *COL13A1*, *LAMA2*, *CDH4*, *SEMA6A*, *PKHD1L1*, *STK38L*, *HECW1*, and *TEAD1* genes were selected as genetic predictors of survival based on evidence of their functional significance and previously linked with age-related disorders and longevity [7–20]. A genotyping was carried out via PCR followed by a separation of amplified fragments in 1% agarose gel. The identification conditions of Alu polymorphisms are shown in Table 1.

The data on survival and mortality of all individuals over 60 years and 115 individuals over 45 years, which were previously included in the research group (in total, 1382 individuals), was collected during 2022–2023 via interviewing their relatives. At the moment of finishing this stage of research (December 30, 2023), the data on the survival state of 1069 persons was obtained (response rate was 77.35%), while 944 individuals had died and 125 were alive. The examined

Table 2. Characteristics of the studied sample

Group	*n* (% from all cases)	Age range	$M \pm \sigma$
In total	1790 (100)	18–109*	67.85 ± 21.22
men	809 (45.2)		
women	981 (54.8)		
Age groups			
Middle age	631	18–65 (men)	43.93 ± 15.86
		18–74 (women)	
Older age	724	66–89 (men)	84.11 ± 10.45
		75–89 (women)	
Long-livers	435	90–114	94.5 ± 3.61
Survival state			
In total	1069	45–114	83.3 ± 10.8
alive	125 (11.7)	45–96	70.82 ± 11.8
died	944 (88.3)	45–114	85.59 ± 9.35
Mortality causes:			
senility	352 (37.29)	70–114	88.96 ± 6.21
CVD	241 (25.53)	46–104	84.67 ± 8.74
CBVD	166 (17.59)	53–105	87.09 ± 8.63
COPD	26 (2.75)	53–98	83.52 ± 8.19
T2DM in anamnesis	10 (1.06)	59–97	83.45 ± 8.19
cancer	41 (4.34)	45–99	78.82 ± 11.83
other reasons	42 (4.45)	49–97	78.98 ± 13.35
multimorbidity	66 (6.99)	59–100	84.22 ± 8.54

CVD—cardiovascular diseases; CBVD—cerebrovascular diseases; COPD—chronic obstructive pulmonary disease; T2DM—type 2 diabetes mellitus; *n*—sample (group) size; *M*—mean age; σ—standard deviation; * age at the moment of material collection.

sample was differentiated by age into control group, older aged individuals and long-livers. The upper limit for the control group corresponded to the parameter of average life span duration for the Republic of Bashkortostan, which was established on the basis of official data of the Federal State Statistics Service (https://rosstat.gov.ru/, application date January 25, 2024). The characteristics of formed groups are reported in Table 2.

The data were processed on the IBM SPSS V22.0 platform (Chicago, Illinois, USA) and using the Python software [23]. The frequencies of all Alu polymorphic genetic variants were checked for correspondence with the Hardy–Weinberg equilibrium in the control group. The age-related change in the distribution of genotype frequencies for each selected Alu polymorphism was assessed by pairwise comparison of age groups using the Pearson χ^2 test. A link between Alu polymorphisms and all-causes mortality was established using the Cox proportional hazard regression. Moreover, a stratified analysis of survival was carried out controlling for sex and mortality causes from various age-related diseases. Hazard ratio (*HR*) curves were constructed using the lifelines and matplotlib packages.

RESULTS

In the ethnic group of Tatars residing in the Republic of Bashkortostan, we characterized a distribution of allele and genotype frequencies of the Alu insertion polymorphic loci located in the introns of the *ACE*, *COL13A1*, *LAMA2*, *TEAD1*, *PLAT*, *PKHD1L1*, *STK38L*, *CDH4*, *HECW1*, and *SEMA6A* genes in the total sample also controlling for age. The observed distribution of genotype frequencies of all analyzed polymorphic markers corresponded to that theoretically expected from the Hardy–Weinberg equilibrium ($P_{HW} > 0.05$, Table 3). Changes in the spectrum of genotype frequencies with age were assessed via pairwise comparison of age groups for each selected Alu polymorphism using Pearson's χ^2 test (Table 3). More significant differences in genotype frequencies between age groups were reported for the *HECW1** Ya5NBC182 gene polymorphism ($P < 0.001$). Statistically significant changes in the distribution of geno-

Table 3. Distribution of genotype frequencies of the Alu polymorphisms in three age groups

Gene Alu polymorphism	Genotype	Middle age			Older age			Centenarians			
		n	*p*, %	P_{HW}	*n*	*p*, %	P_{χ^2}*	*n*	*p*, %	P_{χ^2}*	P_{χ^2}**
ACE Ya5ACE	*II*	104	23.53	0.85	176	25.43	0.361	94	23.50	0.072	0.296
	ID	200	45.25		318	45.95		198	49.50		
	DD	138	31.22		198	28.61		108	27.00		
HECW1 Ya5NBC182	*II*	189	42.19	0.47	250	45.29	0.041	125	45.29	<0.001	<0.001
	ID	203	45.31		219	39.67		128	46.38		
	DD	56	12.50		83	15.04		23	8.33		
SEMA6A Yb8NBC597	*II*	18	3.76	0.47	33	5.84	0.120	23	7.57	0.005	0.037
	ID	156	32.57		167	29.56		105	34.54		
	DD	305	63.67		365	64.60		176	57.89		
CDH4 Yb8NBC516	*II*	145	39.94	0.19	191	39.63	0.074	100	35.09	0.483	0.216
	ID	144	39.67		216	44.81		124	43.51		
	DD	74	20.39		75	15.56		61	21.40		
STK38L Ya5ac2145	*II*	10	2.06	0.06	12	2.11	0.004	4	1.28	0.008	0.522
	ID	78	16.05		102	17.96		63	20.19		
	DD	398	81.89		454	79.93		245	78.53		
PKHD1L1 Yb8AC702	*II*	119	23.20	0.54	133	20.75	0.421	72	20.06	0.025	0.160
	ID	284	55.36		346	53.98		186	51.81		
	DD	110	21.44		162	25.27		101	28.13		
TEAD1 Ya5ac2013	*II*	137	27.45	0.05	157	27.79	0.966	97	29.39	0.024	0.024
	ID	224	44.89		250	44.25		161	48.79		
	DD	138	27.66		158	27.96		72	21.82		
PLAT TPA25	*II*	134	23.76	0.57	157	24.30	0.591	87	23.71	0.561	0.126
	ID	253	44.86		296	45.82		158	43.05		
	DD	177	31.38		193	29.88		122	33.24		
COL13A1 Ya5ac1986	*II*	309	55.28	0.47	363	54.18	0.038	229	57.11	0.937	0.081
	ID	205	36.67		263	39.25		137	34.16		
	DD	45	8.05		44	6.57		35	8.73		
LAMA2 Ya5-MLS19	*II*	128	21.84	0.13	129	19.03	0.095	60	14.81	<0.001	<0.001
	ID	262	44.71		310	45.72		224	55.31		
	DD	196	33.45		239	35.25		121	29.88		

n—group size; *p*—genotype frequency; P_{HW}—*P*-value for the Hardy–Weinberg criterion; P_{χ^2}—*P*-value for Pearsons's χ^2 test; * results relative to the group of middle-aged individuals; ** results relative to the group of older aged individuals.

type frequencies in the *LAMA2**Ya5-MLS19, *TEAD1** Ya5ac2013, and *SEMA6A**Yb8NBC597 gene polymorphisms were detected in centenarians ($P < 0.05$). In older aged individuals and long-livers, we observed a deviation in the distribution of genotype frequencies in the genetic marker *STK38L**Ya5ac2145 ($P < 0.01$). Moreover, the distribution of genotype frequencies of the *COL13A1**Ya5ac1986 gene polymorphism among older aged individuals and of the *PKHD1L1** Yb8AC702 gene polymorphism among long-livers differed from that observed in the control group of middle-aged participants ($P < 0.05$).

To evaluate the role of established Alu polymorphic markers of aging and longevity in determining life expectancy and achievement of centenarian age, we carried out a survival analysis. According to the results obtained, the relative risk of all-causes mortality was statistically significantly higher in carriers of the Alu insertions in the *STK38L* gene, while carriers of insertions in the *TEAD1* and *HECW1* genes showed a decrease in relative risk (Table 4).

A detailed analysis of revealed findings demonstrated that the presence of insertion genotype of the *STK38L* gene in homozygote enhanced twofold the all-causes mortality risk in the total group of examined

Table 4. Association of Alu polymorphism of candidate genes of aging and longevity with all-causes mortality

Gene Alu polymorphisms	Genotype	Total sample		Men		Women	
		HR (95% CI_{HR})	*P*	*HR* (95% CI_{HR})	*P*	*HR* (95% CI_{HR})	*P*
ACE Ya5ACE	*ID*	1.11 (0.88–1.4)	0.396	1.08 (0.72–1.63)	0.701	1.09 (0.8–1.48)	0.577
	II	0.98 (0.74–1.3)	0.911	0.99 (0.59–1.66)	0.974	0.88 (0.61–1.26)	0.475
HECW1 Ya5NBC182	*ID*	0.67 (0.49–0.93)	0.015	0.61 (0.33–1.1)	0.102	0.65 (0.44–0.98)	0.037
	II	0.71 (0.52–0.98)	0.038	0.63 (0.35–1.14)	0.126	0.7 (0.47–1.04)	0.076
SEMA6A Yb8NBC597	*ID*	0.98 (0.79–1.22)	0.854	1.06 (0.72–1.56)	0.784	0.97 (0.73–1.28)	0.825
	II	0.63 (0.39–1.02)	0.058	0.62 (0.18–2.13)	0.447	0.7 (0.41–1.19)	0.184
CDH4 Yb8NBC516	*ID*	1.11 (0.88–1.59)	0.276	0.78 (0.44–1.37)	0.380	1.28 (0.88–1.85)	0.198
	II	1.16 (0.86–1.57)	0.327	0.95 (0.54–1.66)	0.857	1.16 (0.8–1.69)	0.438
STK38L Ya5ac2145	*ID*	0.98 (0.76–1.28)	0.907	0.88 (0.57–1.36)	0.559	0.97 (0.68–1.39)	0.879
	II	2.07 (1.11–3.86)	0.022	2.38 (1.04–5.46)	0.041	1.55 (0.54–4.46)	0.415
PKHD1L1 Yb8AC702	*ID*	1.07 (0.82–1.4)	0.632	1.46 (0.89–2.41)	0.138	1.02 (0.72–1.44)	0.919
	II	1.11 (0.82–1.51)	0.501	1.55 (0.88–2.73)	0.132	0.91 (0.62–1.35)	0.651
TEAD1 Ya5ac2013	*ID*	0.91 (0.71–1.16)	0.443	0.95 (0.61–1.49)	0.835	0.83 (0.6–1.15)	0.261
	II	0.74 (0.57–0.98)	0.035	0.79 (0.47–1.31)	0.353	0.72 (0.51–1.02)	0.066
PLAT TPA25	*ID*	1.12 (0.89–1.42)	0.323	0.76 (0.5–1.15)	0.199	1.36 (0.99–1.85)	0.056
	II	1.16 (0.89–1.51)	0.283	0.93 (0.59–1.46)	0.764	1.29 (0.91–1.83)	0.151
COL13A1 Ya5ac1986	*ID*	1.17 (0.72–1.92)	0.53	1.55 (0.59–4.09)	0.379	1.01 (0.56–1.85)	0.962
	II	0.99 (0.61–1.62)	0.989	1.31 (0.49–3.52)	0.586	0.81 (0.45–1.44)	0.472
LAMA2 Ya5-MLS19	*ID*	0.92 (0.73–1.15)	0.473	1.25 (0.84–1.86)	0.261	0.84 (0.62–1.13)	0.243
	II	1.08 (0.81–1.44)	0.609	1.41 (0.8–2.49)	0.238	0.92 (0.63–1.35)	0.672

HR—hazard rate; CI—confidence interval; *P*-value—significance level.

individuals (Ya5ac2145**II*, $HR = 2.07$, $P = 0.02$; Fig. 1a). The Alu insertions in the *TEAD1* and *HECW1* genes are associated with a diminished mortality risk ($HR = 0.74$, $P = 0.035$ for the *TEAD1* Ya5ac2013**II* genotype; $HR = 0.71$, $P = 0.038$ and $HR = 0.67$, $P = 0.015$ for the *HECW1* Ya5NBC182**II* and *ID* genotypes, respectively; Figs. 1b–1d).

A survival analysis controlling for sex demonstrated a similar trend in the parameters of relative mortality rate separately for men and women (Table 4). In addition, more pronounced association with all-causes mortality risk was revealed for homozygous Alu-insertion genotype of the *STK38L* gene in men (Ya5ac2145**II*, $HR = 2.38$, $P = 0.041$; Fig. 2). Although the presence of Alu insertions in the *TEAD1* and *HECW1* genes reduces mortality risk, it, however, remains under the level of significance (CI 0.47–1.31 and CI 0.61–1.49 for the *TEAD1* Ya5ac2013**II* and *ID* genotypes, respectively; CI 0.35–1.14 and CI 0.33–1.11 for the *HECW1* Ya5NBC182**II* and *ID* genotypes, respectively; Table 4). The presence of heterozygous genotype in the *HECW1* gene was linked to a reduced all-causes mortality risk in women (Ya5NBC182**ID*, $HR = 0.65$, $P = 0.037$; Fig. 3).

A survival analysis in the groups of individuals differentiated by mortality causes demonstrated the association of Alu insertions in the *SEMA6A*, *TEAD1*, and *LAMA2* genes with diminished mortality risk under various pathological phenotypes. The presence of Alu insertion in the heterozygous variant in the *SEMA6A* gene was associated with a decreased mortality risk from cerebrovascular diseases (Yb8NBC597**ID*, $HR = 0.54$, $P = 0.016$; Fig. 4a). The mortality risk from cardiovascular diseases was reduced in carriers of homozygous Alu insertion genotypes in the *TEAD1* gene (Ya5ac2013**II*, $HR = 0.57$, $P = 0.016$; Fig. 4b). Moreover, the reduced mortality risk was associated with the Alu insertion in the *LAMA2* gene among individuals with multimorbidity (Ya5-MLS19**ID*, $HR = 0.36$, $P = 0.03$; Fig. 4c).

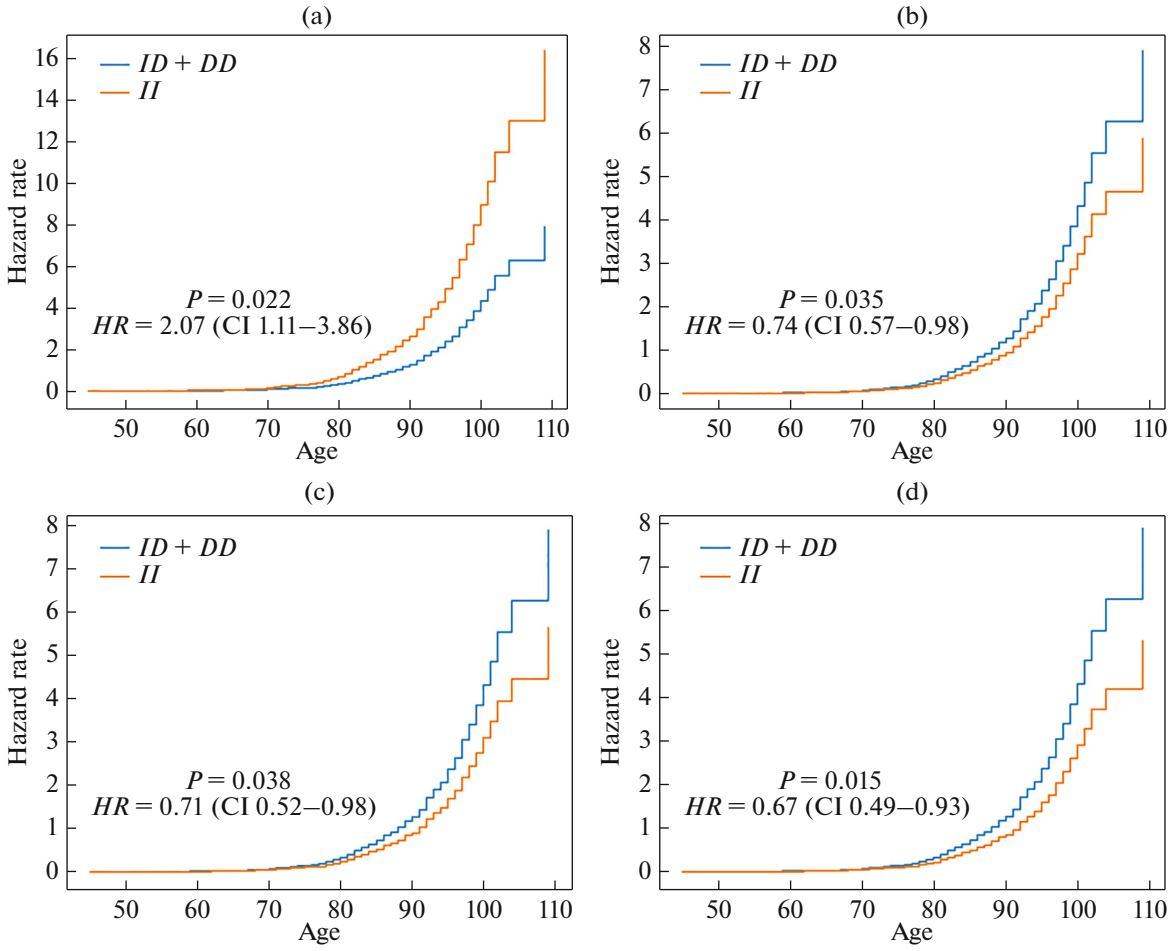

Fig. 1. Accumulated risk of all-causes mortality in the general group associated with the Alu insertion in the *STK38L* (a), *TEAD1* (b), and *HECW1* (c, d) genes.

DISCUSSION

Within the framework of the study of human aging and longevity, the survival analysis was carried out among individuals who have achieved the age exceeding the population average on the basis of Alu polymorphic variants in the genes encoding key structural and functional proteins as predictors. According to the results obtained, the *STK38L* Ya5ac2145 Alu-insertion genotype is associated with mortality risk, while a survival-protective effect was demonstrated for the genotypes of the Alu insertions in the *HECW1* Ya5NBC182 and *TEAD1* Ya5ac2013 gene loci. Moreover, the Alu insertion loci of the *SEMA6A* Yb8NBC597 and *LAMA2* Ya5-MLS19 were associated with survival in various clinical phenotypes. The genes associated with survival under the conditions of senile phenotype are involved in the regulatory pathways controlling apoptosis and autophagy.

HECW1 is C2 and WW domain-containing protein from ubiquitin ligase E3 family and belongs to the NEDD4 family of transcription factors (TF), which regulate cytoplasmic translation, ribonucleoprotein complex and ribosomal biogenesis, and KEGG pathways including Akt, p53, autophagy, and apoptosis [24]. Together with other members of the NEDD4 family, HECW1 binds to LC3, being a key protein of the autophagy system, thereby regulating this cellular process. The autophagy-inhibiting knockdown effect of the NEDD4 has been demonstrated in cancer cells [25]. Moreover, HECW1 exaggerates proapoptotic activity of p53 regardless of its catalytic activity [26]. In general, protein degradation controlled by ubiquitin ligase E3 plays a fundamental role in self-renewal, maintenance, and differentiation of cancer stem cells [27]. Accordingly, HECW1 activity is essential for the development of age-dependent pathological phenotype. The HECW1 protein is abundant in neuronal tissues and, owing to its involvement in protein homeostasis, is a key element in the normal and pathological development of the nervous system [28]. Interestingly, an inverse correlation exists between oncological and neurodegenerative diseases, which can be mainly attributed to p53 protein cellular location, thus affecting the processes of apoptosis and autophagy [29]. In

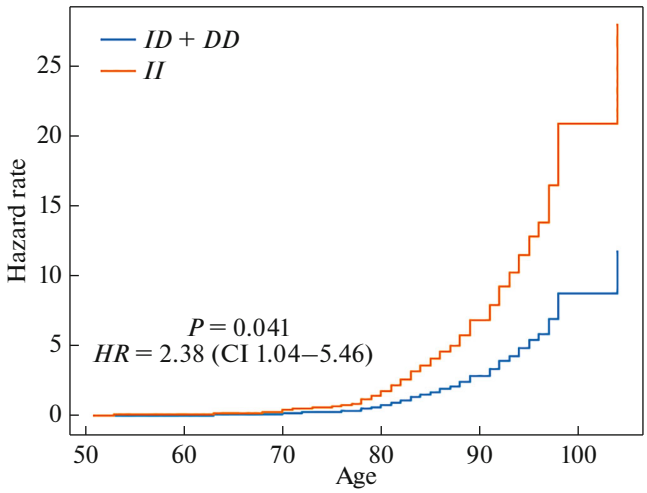

Fig. 2. Accumulated risk of all-causes mortality among men associated with Alu insertion in the *STK38L* gene.

the present study the association of survival and longevity with the *HECW1* Ya5NBC182 Alu insertion was established. It can be assumed that Alu transposons, which affect gene activity, represent the molecular basis for adaptive plasticity of nervous system tissues. However, a tissue-specific nature of the involvement of HECW1 in the complex regulation network of apoptosis and autophagy, especially at the later stages of human life, requires further comprehensive analysis.

The TEAD1 transcription factor and STK38L protein kinase are the members of the conservative Hippo pathway regulating organ size and tissue homeostasis [30]. Recent studies demonstrated the role of the Hippo signaling cascade in stimulating apoptosis and autophagy [10]. A deletion of genes, which is related to autophagy and interacts with Hippo kinase cascades, is associated with an increasing trend to spontaneous development of different diseases [31]. The TEAD1 protein (TF of TEA domain) is one of the main downstream nuclear effectors of Hippo signaling. It is able to bind to the consensus DNA sequence 5'-CATTCC-3', called the MCAT element [32]. As a result of interaction with various cofactors such as YAP (yes-associated protein) and TAZ (transcription coactivator with PDZ binding motif), TEAD binds to MCAT-containing genes that regulate cell growth. It was reported that the expression of TEAD proteins was enhanced in various types of cancer and correlated with poor survival in patients with cancer [11]. In addition, TEAD regulates the expression of multiple genes involved in the development of the cardiovascular system and is involved in pathophysiological processes, which promote a development of cardiovascular diseases, as the main molecular component of the YAP/TAZ signaling pathway [33]. It can be suggested that a reduced activity of the *TEAD1* gene, which is involved in the control of proliferation and apoptosis, caused by the Alu insertion Ya5ac2013 contributes to survival and protects from cardiac and vascular pathologies in senile phenotype.

Additional enzymes of the Hippo pathway include the NDR family of protein kinases, in particular, NDR1/STK38 and NDR2/STK38L [34, 35]. These kinases regulate a wide range of age-sensitive cellular processes such as cell cycle control, intercellular communication, apoptosis, autophagy, and nutrient homeostasis [36]. Empirically, the involvement of STK38 kinase in systemic metabolism has been experimentally demonstrated: a high-fat diet significantly resulted in its increase, which, in turn, caused the development of inflammation and insulin resistance

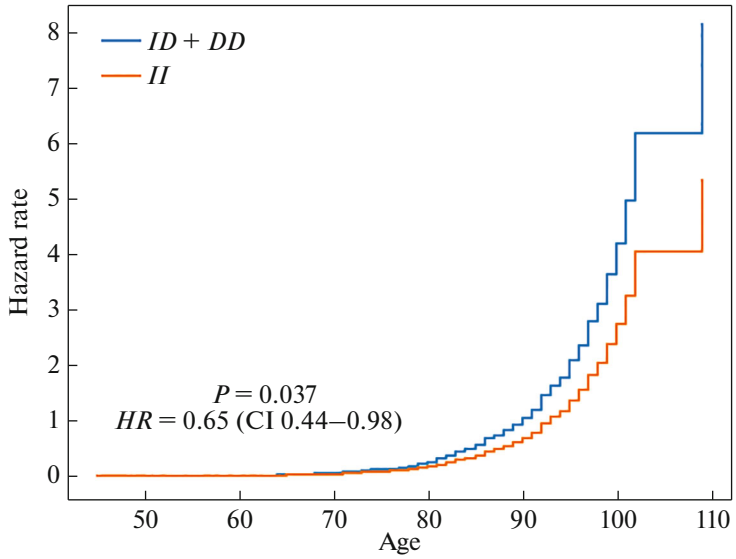

Fig. 3. Accumulated risk of all-causes mortality among women associated with Alu insertion in the *HECW1* gene.

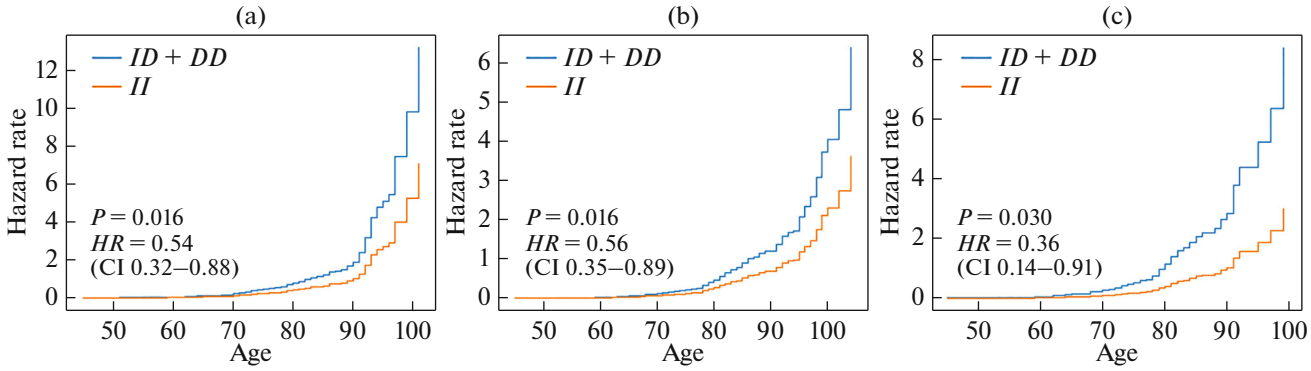

Fig. 4. Accumulated risk of mortality in the groups differentiated by mortality causes: from cerebrovascular diseases associated with the Alu insertion in the *SEMA6A* gene (a); from cardiovascular diseases associated with the Alu insertion in the *TEAD1* gene (b); in the case of multimorbidity associated with the Alu insertion in the *LAMA2* gene (c).

[37]. It has been established that *STK38/STK38L* acts as the main factor of stress response and plays an important role in autophagy [10]. The expression of the *STK38L* gene is reduced under the stress factors, while a decreased rate correlates with chronological age [36]. The revealed association of the *STK38L* Ya5ac2145 Alu insertion, which is linked to diminished gene activity, with all-causes mortality risk in the studied group is consistent with presented published findings.

In the present study, the association with survival was established against a background of the multimorbid state of the genotype heterozygous for the Alu insertion in the *LAMA2* gene, which encodes laminin as a main component of a basal membrane. As a result of the study of the role of laminin gene expression in the development of various senile processes, contradictory findings were revealed, which can be explained by tissue specificity of this protein [12]. Interestingly, the expression of autophagy genes is increased in muscles with a deficiency of the α2-chain of laminin [13]. From the point of view of adaptation and survival in old age, the results of the present study can be considered as the interaction of various compensatory mechanisms.

The involvement of Alu insertion polymorphism of the *SEMA6A* gene in survival under cerebrovascular events directly confirms the role of semaphorin-6 in the structural and functional organization of the nervous system [14]. In addition, multiple studies demonstrated that semaphorins affected cell proliferation, migration, and apoptosis by affecting vascular wall components and thereby participating in various pathological processes of the circulatory system [15].

Therefore, Alu polymorphic variants, which were associated with survival and mortality, are located in the genes involved in apoptosis and autophagy. Recent advances in understanding the temporal and spatial consequences of impaired regulation of autophagy for tissue homeostasis have revealed a complex and multifactorial relationship between autophagy and aging. Autophagy as a highly conservative way of destroying defective cellular components represents an important endogenous mechanism, which provides withdrawal of cellular stress conditions, while chronic activation of autophagy may cause cell death [38]. In general, the data obtained are consistent with the concept of an age-dependent decrease in the number of autophagy-related proteins, which provide transport to lysosomes, which indicate that impaired autophagy is one of the important factors of aging [34]. The Alu retrotransposons can affect genes functioning via multiple pathways, mainly resulting in a reduced level of gene expression. This suggests that this type of genetic polymorphism may be associated with a number of pathological age-dependent phenotypes and, accordingly, with human life expectancy and quality of life.

FUNDING

The present study was supported by the Russian Science Foundation (no. 24-25-00179, https://rscf.ru/project/24-25-00179/).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee at the Institute of Biochemistry and Genetics—Subdivision of the Ufa Federal Research Centre of the Russian Academy of Sciences (Protocol of Approval no. 8, June 6, 2024).

All procedures performed in the study 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 each participant enrolled in the study. All participants were adults.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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Translated by A. Kazantseva