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# **Review Article**

# Mechanisms of Longevity Phenomenon in Azerbaijan

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#### **Abstract**

The goal of the study was to identify and explore the social-ethnic and medical-biological factors underlying the formation of the 'longevity phenomenon' in the Azerbaijan region. The study involved 260 long-lived (90-112 years of age) and 3,700 younger-aged subjects (45-89 years) from the Azerbaijan population. The discussed findings highlight the role and interaction of specific social-environmental factors (gerontocratic character of traditional ethnic culture, type of nutrition and psychological personality structure) and molecular-biological mechanisms (anthropometric constitutional types, peculiarities of the bioelectrical brain activity and chromosome polymorphism by heterochromatin) in the Azerbaijanian 'longevity phenomenon'.

**Keywords:** Anthropology; Azerbaijan; Brain bioelectrical activity; Cytogenetic; Longevity; Nutrition

# Introduction

Long-living people are the representatives of maximal species-specific lifespan. Search for the mechanisms and factors determining longevity has been carried out at the various levels from population to molecular-cellular [1]. The long-lived are registered in various regions of the globe. Still, the geography of longevity shows that these regions are distributed irregularly. High concentration of the long-lived is observed in the Caucasus [2]. Here there are national-ethnic groups with high longevity index. The highest longevity level is registered in Abkazia and Azerbaijan [3]. Among the aboriginal population of these regions there has naturally-historically emerged and been fixed the high concentration of the long-lived, called the phenomenon of group longevity [2].

#### Aim

Assessment of the effects of the social-ethnic and medical-biological factors on the formation of the 'longevity phenomenon' in Azerbaijan.

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# **Subjects and Methods**

As early as between 1987-1994 years, the Kiev Institute of Gerontology (Ukraine), the Academy of Sciences of Azerbaijan (A.I. Karaev Institute of Physiology) jointly with the Institute of Man (USA) and the Institute of Ethnography (Russia) carried out complex socio-ethnographic and medico-biological investigation of the aboriginal population of the Kazakh and Ismail areas of Azerbaijan, involving 3,700 persons in the age range 45-89 years and 260 long-lived of 90 years and over [3].

Since 2015 year the research on 'the longevity phenomenon' in Azerbaijan has been renewed by the investigators of Azerbaijan Medical Institute and A.I. Karaev Institute of Physiology who invited their colleagues from the Kiev Institute of Gerontology to join them [4]. The survey program includes study of ecology, national-ethnic characteristics of lifestyle [5], nutrition [6] and anthropology (race-morphologic signs) [7] etc., analyzed with the use of modern methods have been the nervous, cardiovascular, endocrine systems, the physical-chemical and biochemical composition of the blood [8,9]. A special interest has been paid to study the role of heredity in the "longevity phenomenon", family genealogy and polymorphism of separate genes [10].

#### **Examination program**

- Clinical (patient's complaints, neurologist's and physician's examination)
- Questionnaire to verify age, age-related subjective signs of aging
  [2]
- Biological age assessment [11,12]
- Anthropometric data [3,7]
- Brain bioelectrical activity based on electroencephalographic data [13,14]
- Duplex ultrasound examination of neck vessels and brain [4]
- Family history and tracing family longevity and family diseases such like cerebral-vascular pathology, age of the deceased and causes of their death [15]
- Cytogenetic investigations (variants of chromosome polymorphism as regards C-heterochromatin, absolute and relative sizes of C-band lengths on the chromosomes 1, 9, 16 and Y, heteromorphism of C-blocks on the homologues of the chromosomes 1, 9, 16 and Y [10,14,16,17]
- Factual nutrition using questionnaire weighing and questionnaire sheet methods [6].
- Ethnic-psychological testing (Eysenck test for extra and intraversion, Massachusetts personality questionnaire, Luscher test) [5,18].

#### **Results and Discussion**

Our earlier investigations established the role of the ethnic-psychological and genetic factors, type of nutrition and specifics of physical activity in the formation of the mechanism of group longevity phenomenon [3].

#### The socio-psychological factors of 'longevity "phenomenon'

The pattern of traditional ethnic culture is ascribed to the so-cio-psychological factors of 'longevity "phenomenon'. The Caucasian elders are the guardians of etiquette rules who act as religious leaders. Owing to preservation of their psychic/cognitive functions they actively participate in family and village life. This creates psychological comfort for the centenarians, gives them real power and intensive communication that in turn supports and trains their psychic. High age deserves respect and admiration in the Caucasus that sometimes determines their age overstatement.

#### Age verification

In this connection the age of long-lived was verified in Azerbaijan. Age assessment was based on self-reporting of the dates/years of marriage, birth of children, participation in civil war etc., which were related with historic events, natural calamities, their relatives' and children's age. The results of verification allowed assess the number of true long-living persons and confirmed the presence of 'longevity phenomenon' in the territory of Azerbaijan, as the index of centenarians in the Caucasus is 3-4 fold higher than in other regions of the globe [2].

#### Psychological personality structure

Thus, the socio-psychological status of long-lived is high in Azerbaijan. There arises a question "What is the psychological personality structure like in the long-lived?" As is known, person's character undergoes changes from birth to old age. However the main features of the character and its psychological profile are preserved. The character pivot is one's attitude to the environment, to the people and to one's own personality. The majority elders are very excitable like children. These virtues form sensitivity to various irritants though such reactions are short-term and do not penetrate into personality depth. They are not fixed on emotions/feelings and situations [5].

For the assessment of the type of personality, emotionality and will power, various psycho-diagnostic techniques were used, such as locus control scales, lusher test and MMSE [5]. According to the authors' findings, the long-lived are characterized by internality, i.e., presence of internal control, as they feel themselves the masters of their life/fate. They predominately consider: "while fulfilling the will of the God, I should act in this way, meaning that the outcome of the event depends on me". The Azerbaijani oldest people have highly preserved intellect and feeling of humor [19].

In Azerbaijan, the long-lived have an ambivalent attitude to old age. That is, ritual parallels emotional. They shade the fact of aging and oust worry caused by aging. They exhibit very low level of anxiety, high social adaptability and wide emotional associations [20]. In 80% of the interviewed cases the long-lived did not consider their age very high. They possess psychological protection against recognition of the fact of aging and inevitable death which is determined by the peculiarities of their character such as low anxiety level, communicativeness and pliability of psychic reactions [21,22]. It is worth to recall the utterance of Gufeland in 1853: "among the influences shortening lifespan predominant are the fear, sadness, depression, envy and hatred". The known proverb says: 'good will is the reward and evil is the punishment' for oneself. It is known that time perception changes with aging: in as much as man is getting older his subjective perception of the quickened time passage increases [23]. The long-living Azerbaijani, compared even with the long-living Ukrainians and Byelorussians,

have less marked feeling of 'quickened time passage' and they stand nearer to the age group of 40-50 year old [24].

The centenarians are good-wishers and never refer to long-passed events as most aging people do. Among severely ill there are no hypochondriacs even among the sick persons [18]. The majority long-lived are extraverts and communicative, sanguine in temperament, disposed to pleasure and easily adaptive to their social environment [5]. Speaking about their volitional sphere, the long-lived have modest pretensions. Through their whole life course practically all of them give preferences to calmness and peaceful solution of conflicts. The volitional process has no high tension and is aimed mainly at the preservation of their personal and social status-quo [5].

#### Behavioral stereotypes

The problem of stress and aging has its own peculiarities in Azerbaijan. Here prevail specific forms of behavior and stereotypes that have been worked out through ages to overcome impacts of stress factors. A large role in these behavioral stereotypes must be ascribed to the participation and compassion of the considerable number of people (relatives, neighbors and acquaintances) during extreme events such as the death or illness of close relatives and friends. The pattern of such moral and material support and cooperation is large-scope. Person in grief does not bear it solely but rather feels support and assistance of his relatives, neighbors and friends [5,18].

#### Physical activity

Life mode of the centenarians is characterized by high motor activity that to certain extent influences on the mechanisms of longevity. It is known that motion regime leads to many positive effects. Motion and physical loading produce anti-stress action owing to activation of the nervous and hormonal mechanisms, improvement of tissue blood supply and cardiac heart activity [25]. Mental working ability increases and the mood improves; several kinds of metabolism, lipid in particular, are normalized: cholesterol level in the blood decreases and high-density lipoproteins level increases. It has been proved that the level of risk factors of cardio-vascular and nervous diseases correlate inversely with the level of physical activity [26,27].

#### **Family**

Family organization in Azerbaijan is linked with the specifics of marriage. Long-living men enter into marriage rather late at the age of 30-40 years and women at 14-15 years. In long-living women menstruation is late, starting at the age of 14-15 years and menopause at 50-55 years. Love in the sense of sexual relations has very great significance. The significance of love is more highly valued by the elders than by the young [28,29].

#### Anthropology

Analysis of the anthropologic indicators in the Azerbaijani long-lived has shown greater skeletal mass. By this index they differ from other ethnic groups (Imerites, Turkmenians and Russians). A distinguishing characteristic of the Azerbaijani long-lived is the well-developed musculature with sufficiently preserved vitality. In long-living men there prevails muscle (40%) and muscle-thoracic (18.2%) body type while obese (31%) and stenoplastic (23%) body type prevail in long-living women [7]. The Azerbaijani long-living are not high rather medium-sized, according to the intergroup population scale, rural inhabitants. The male and female height is respectively 166.7 and 154.5 cm. Body weight is  $65.5\pm14.6$  kg for males and  $62.3\pm16.1$  kg for females [3,7].

# Brain functional state

Examination of the blood lipid contents of the Azerbaijani long-lived has revealed the low absolute content of total cholesterol and low-density lipoprotein cholesterol against relatively elevated content of high-density lipoprotein cholesterol. Maximal total cholesterol concentration makes 175±21.4 (mg/100 ml), LDL-1006.3 and HDL-55.5±2.5 [3,30]. Analysis of age-related changes of the brain functional state, according to the data of brain bioelectrical activity, has showed decrease of the alpha-rhythm frequency parameters and an insignificant increase of the latent reaction to the light. In other national- ethnic groups (Ukrainians and Russians) age-related bioelectrical activity changes occur 10-15 years earlier than in the Azerbaijani [13,15]. Thus the alpha-rhythm frequency (main rhythm of the brain bioelectrical activity) corresponds to that characteristic of the 60-70 year old individuals [14] (Figure 1).

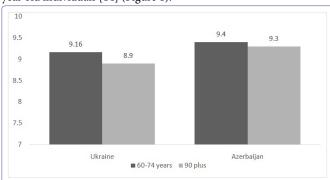
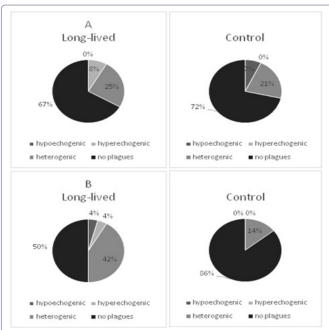


Figure 1: Frequency of the alpha rhythm in the long-lived and 60-74 year subjects in Azerbaijan and Ukraine, Hz.



**Figure 2**: The frequency of various types of atherosclerotic plaques in the right (A) and left (B) internal carotid arteries in the long-lived and control subjects.

The tempo of age-related cerebral circulation changes and myocardial contractile capacity in the long-living Azerbaijani is also slowed compared to other national-regional groups [9,31]. The results of complex clinical-instrumental investigation of individuals over 90 years residing in the Kazakh and Islamabad areas of Azerbaijan show that within morbidity structure of hypertensive disease makes 12%, IHD 35%, residual stroke phenomena 2% and extra pyramidal deficiency 9%. Health level of the long-lived of Ukraine is significantly lower and complex pathology is more pronounced. 65% of the examined Ukrainian long-lived had hypertensive disease, 80% IHD and 12% Parkinson's disease [24].

According to the results of clinical-instrumental examination of the long-lived, carried out in 2015 year in the Lenkaran district of Azerbaijan, the arterial hypertension was diagnosed in 20% and Ischemic Heart Disease (IHD) in 40%. Thus there are no differences as to hypertension and IHD prevalence in the long-lived in various regions of Azerbaijan [4].

Noteworthy is the high maintenance of cerebral circulation in the long-living of Azerbaijan. Thus, according to the data of doppler ultrasound examination of the head and neck vessels of the long-lived, carried out in the 2015 year, we registered initial signs of cerebral atherosclerosis proved by normal sizes of the Intima-Media Complex (IMC) of common carotid artery (0.8-1.0 mm) in 50% and only slightly increased IMC in 50% (1.1-1.2 mm) in the examined long-lived residing in the Lenkaran district. The frequency of ICA stenosis was more than 50-75% being diagnosed in 14% of the examined long-lived and in 21.4% among populational elderly subjects (control).

Noteworthy is the high maintenance of cerebral blood circulation in the long-living of Azerbaijan. Thus, according to above-mentioned doppler ultrasound examination of head and neck vessels of in the long-lived, we registered only initial signs of cerebral atherosclerosis. We performed analysis of the incidence and structure of atherosclerotic plaques in the Internal Carotid Artery (ICA) in the long-living individuals and control subjects. The absence of atherosclerotic plaques in the right ICA was observed in 66% of the long-lived and in 50% in the left ICA. Their absence in the control subjects was respectively 71.4% and 85.7% (Figure 2).

The most 'aggressive' hypoechogenic atherosclerotic plagues were registered in the left Internal Carotid Artery (ICA) in 4.2% of long-lived and in the right ICA in 7.1% of control subjects. The frequency of hypoechogenic (stable) atherosclerotic plagues was registered in the right ICA in 8.3% and in the left ICA in 4.2% of long-lived. This type of plagues was not found in the control subjects. It is noteworthy that both long-lived and control individuals showed predominant occurrence of the heterogenic (mixed) atherosclerotic plagues: in 25% in the right ICA and in 41.7% in the left ICA; and respectively in 21.4% and in 14.3% in the control (Figure 2).

The indices of common carotid intima media and the frequency and structure of the atherosclerotic plaques suggest that structural changes of extra cranial vessels in the carotid basin of the long-lived correspond to these indices in the elderly subjects (control).

In the long-lived the Linear Systolic Blood Flow Velocity (LSBFV) is somewhat decreased compared with elderly subjects (control). In the former the blood flow velocity in the right ICA makes  $66.6\pm7.1$  cm/s (p< 0.05) and in the left  $69.9\pm3.7$  cm/s (p<0.05), whereas in the control group these indices are respectively  $84.1\pm3.2$  and  $81.8\pm2.5$  cm/s; in the medialmedullary artery  $67.9\pm7.9$  from the right and  $76.7\pm4.2$  cm/s (p<0.05) from the left and in the control subjects respectively  $74.2\pm4.8$  and  $87.6\pm33$  cm/s.

On evidence derived from the peripheral Resistance Indicators (RI), no angiospasm was detectable in the vessels of the carotid and vertebra-basilar basins in the long-lived. In the long-lived, Ri in the

right Internal Carotid Artery (ICA) is  $0.71\pm0.01$ , in the left ICA -  $0.66\pm0.02$ , and in the elderly subjects respectively  $0.65\pm.07$  and  $0.64\pm0.08$ ; in the from the right  $0.6\pm0.02$  and from the left  $0.61\pm0.01$  and in the medial medullary artery  $0.58\pm0.09$  and  $0.57\pm0.07$  in the control, respectively.

Noteworthy is the functional maintenance of cerebral hemodynamic in the vertebra-basilar basin. Thus in the long-lived the LSBFV in the occipital artery makes  $63.79\pm6.1$  cm/s (p<0.05) compared to  $50.5\pm5.8$  cm/s in the control. In the long-lived the size of the vertebral artery is larger (right 2.95 mm and left 2.88 mm) compared to the elderly subjects (right 2.68 mm and left 2.84 mm) that corresponds to active blood flow in the vertebral-basilar system [4].

Thus, the long-lived have an insignificant decrease of cerebral hemodynamic in the carotid basin vessels against the background of activated hemodynamic in the Vertebra-Basilar Basin (VBB) vessels. The VBB basin supplies blood to the stem reticular-diencephalon structures of the brain that, probably, determines the wide range of central regulation of the cardio-vascular system in the long-lived.

The pattern of age changes in the cardiovascular and nervous systems and morbidity structure in various national-ethnic groups of (Abkhazians, Azerbaijani, Georgians and Ukrainians) gave grounds not only to make an assumption about slowed mode of aging in the regions with high longevity level but also to formulate a hypothesis about the syndromes of aging [14,21]. These syndromes or portraits of aging are also characteristic of the long-lived. Thus a relatively high functional level of the cardiovascular system and a low prevalence of this system pathology (IHD and arterial hypertension) are maintained

	Content	Recommended values by Yu. Grigorov [6]
Vitamins		
Alpha-tocopherol	17.3±1.1	13.5
Ascorbic acid	125.1±3.0	80
Carotin	1.58±0.14	2.0
Nicotinic acid	20.8±1.8	12
Thiamine	1.54±0.09	1,1
Riboflavin	1.46±0.08	1,3
Pyridoxine	2.36±0.11	2
Amino acids		
Methionine	1253±126	2000
Cystine	1281±92	2000
Glutamic acid	16377±917	16000
Minerals		
Magnesium	562±42	400
Copper	3000±200	2000
Zink	12.3±0.9	15
Selen	190±16	50-200

**Table 1:** Chemical composition of nutrition ration in the Azerbaijani long-lived, mg/day.

# Nutrition

Traditional stereotype of nutrition of the long-lived contributes significantly to the mechanism of formation of the regional longevity and to the structure of the cardiovascular and nervous system pathology. Food of the Azerbaijani is low-caloric that includes milk

products, vegetables and fruits. High contents of sour milk and milk products in their diet make it similar to intestinal microflora of healthy children. Special mentioning should be made about high content of vegetable products and consequently, ballast substances. High consumption of bitter red pepper sauces containing capsaicin normalizes lipid metabolism, decreases AP, regulates blood coagulation processes and thermoregulation. Special note should be made about the amino acids content of food taken by the elders. Among amino acids the role of which in 'longevity phenomenon' has been proved experimentally we distinguish the tryptophan (its deficit). Along with its reduced intake with food, the content of tyrosine is increased. As is known an increased content of tyrosine in the food increased lifespan of experimental animals. Food content of methionine, Cysteine and glutamic acid meets recommended norms. Food of the long-lived has high contents of polyunsaturated fatty acids and biologically most valuable linoleic acid taken with maize/corn and sunflower oil. However cholesterol is lacking in their food [6] (Table 1).

One of the popular theories of aging is the free-radical theory linking aging process with gradual accumulation of free radicals and with reduced antioxidant defense power [32,33]. The free radicals posses high destructive power and destroy molecules in the DNA nucleus. The organism receives elements-constituents of the antioxidant system from food. They are called the antioxidants. The followings possess an antioxidant effect: group B and P vitamins, carotene, A and E vitamins, amino acids (methionine, glutamic acid), mineral components (magnesium, zinc, selen), many substances of the vegetable origin (flavonoids and polyphenols, which are found in the apples, grapes, red wines; beetroot dye-stuffs (Betaine) and others. The food of the long-lived is enriched with natural antioxidants. High antioxidant protection of food is formed owing to the following peculiarities of nutrition: comparatively low intake of fats, optimal ratio of the polyunsaturated and saturated fats, high intake of vitamin E and antioxidants in the food products [32,33].

A wide prevalence of cardiovascular diseases is nowadays ascribed to the deficit of the polyunsaturated acids and excessive intake of cholesterol in the food [30]. In addition, the observable vitamin E deficit and its ratio with food content of polyunsaturated fatty acids also play role: the greater its ratio, the higher so called antioxidant protection of the food.

Noteworthy is the high intake of the garlic and onions by the long-lived. In the Egyptian papyrus of 1550 year devoted to medicine there are 22 recipes mentioning garlic. The garlic reduces the level of cholesterol and total lipids in the blood. It contains components with distinctly expressed antitumor activities, which are as active as aspirin [23]. Tea is part of the traditional nutrition of the long-lived. Regular use of freshly-brewed tea promotes vitamin C accumulation. Tea causes expansion of skin pores and enhances sweating that reduces skin temperature. It is clear that tea in hot climate helps organism's adaptation.

#### Chromosomes

To elucidate impacts of the genetic factors on 'longevity phenomenon' formation, the genealogical and cytogenetic investigations were carried out. According to the genealogical analysis, the frequency of family longevity was revealed in 81% in Azerbaijan and in 42% in Ukraine [4]. Studies on the material substrate of heredity, chromosomal apparatus, showed that in the long-living males the large blocks of C-heterochromatin are on the Y-chromosome (1.51±0.06 мкм сотратеd to 1.29±0.09 мкм) in the control and long Y-chromosome

(index Y/F in the long-lived (1.05 $\pm$ 0.05 compared to 0.85 $\pm$ 0.07 in the control). In the long-living females the large block of C-heterochromatin are on the chromosome 9 (1.31 $\pm$ 0.14  $\mu$ M compared to 0.86 $\pm$ 0.06  $\mu$ M in the control) evidencing for the high activity of ribosomal RNA synthesis [14,17,34].

Studies carried out in the long-lived of the three regions (Azerbaijan, Abkhasia and Ukraine) allowed identify both, general and ethnic variants of chromosomal polymorphism by the heterochromatin. The general variant of chromosomal polymorphism is characterized by the presence in the long-living males of three regions of the long Y-chromosome and a large block of C-heterochromatin on the Y-chromosome and chromosome 1. The long Y-chromosome was also found in the relatives of the long-lived. In the long-living females of Azerbaijan, Abkhasia and Ukraine the variants of chromosomal polymorphism are characterized by the presence of the large block of C-heterochromatin on the chromosome 9 and a high frequency of the associations of the acrocentric chromosomes evidencing for the high activity of ribosomal RNA synthesis [16,17,35].

Thus certain cytogenetic markers by heterochromatin are characteristic for the long-lived. Data about the role of heterochromatin in the evolution, association of chromosomal polymorphism variants with essential phenotypic characteristics (reproduction, viability) and pathological processes (malignancies), regulating the impact of heterochromatin sizes on the gene recombination and, lastly, the difference of eco-resistance of the homo- and heterozygote's by C-chromatin allow us believe that variants of chromosomal polymorphism in the long-lived are the manifestation of certain molecular-genetic mechanisms determining longevity [16,23,35].

### Conclusion

Complex analysis of the role of social-environmental and genetic processes in the formation of the longevity phenomenon in Azerbaijan has allowed us formulate the proposition that this phenomenon is the result of complex harmonic interaction of the environmental, national-ethnic-psychological factors and the peculiarities of genetic organization. We believe that further investigation of the 'longevity phenomenon' in Azerbaijan with the use of modern informative clinical-instrumental, molecular-genetic and biochemical methods will allow decode complex mechanisms of longevity formation and maybe these data will be used successfully for increasing of the populational and human individual lifespan.

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