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Polymorphic variants of autophagy regulated genes: survival rates for the aged-related pathologies and longevity

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Motivation and Aim: Longevity is exceptional highly adaptive phenotype characterized by the reaching the long life expectancy while maintaining physical and cognitive abilities. Current research on longevity focuses on elucidating the endogenous and exogenous stresses manage the aging process [1]. Gradual and irreversible decline in cellular and tissue functions is observed in physiological and to a greater extent in pathological senility [2]. The achievement of longevity at the background of the age-associated diseases and the ability of long-lived individuals to adapt to a chronic pathological age background suggests the existence of adaptive endogenous mechanisms. With the better understanding of the detailed molecular mechanisms, the role of mitochondrial biogenesis and molecules that provide redox homeostasis in autophagy, which is one of the key programs for self-renewal of intracellular structures, is being strengthened [3]. The functional connection of mitochondria with cellular components involved in the process of autophagy is provided by the dynamic system of mitochondria and endoplasmic reticulum membranes [4]. The aim of our study is to search for combined polymorphic profile of genes involved in redox regulation of autophagy process, in physiological aging and age-related pathology.

Methods and Algorithms: Total sample was formed of 2806 unrelated individuals in age from 18 to 114 years and inhabiting the Republic of Bashkortostan of Russia. The mortality and survival data for the persons over 45, collected since 2001 to 2015 were built. It has allowed forming the comparison groups for assessing survival to the age of longevity and differentiating the general sample to the main clinical phenotypes based on the verified cause of death of the individual. In the groups differentiated by age and clinical status, we studied the functional polymorphic loci of genes involved in signaling pathways of enzymatic antioxidant defense, redox homeostasis, autophagy, and membrane contact components of mitochondria and endoplasmic reticulum. SNPs were genotyped by a TaqMan real-time PCR assay. Statistical analysis was carried out using the IBM SPSS Statistics (V22.0, Chicago, IL, USA), APSampler software (V.3.6.0, [5]), and R package "SNPassoc". The associations of the studied SNPs and their combinations with the age-related diseases and longevity were analyzed by the logistic regression with the different genetic models and with the Markov chain Monte Carlo method. Survival analysis was performed using the Cox proportional hazards regression.

Results: The genotype frequencies in selected SNPs of the antioxidant genes – *NFE2L2, MSRA, SOD1, SOD2, NQO1, CAT, GSR, GSTP1, GPX1,* autophagy regulated genes –

AKT1, MTOR, SIRT1, HIF1A, TP53, TOMM40, that are involved in the connection between the mitochondria and endoplasmic reticulum membrane, were established in the group of middle-aged individuals (control group, n = 1120), as well as in the groups of ageing (n = 1085) and long-lived (n = 601) persons. The obtained genotype frequencies of all studied SNPs among the control subjects were in compliance with the Hardy–Weinberg equilibrium ($p_{HWE} > 0.05$).

The old age (66–89 for men and 75–89 for women) was associated with *CAT* rs1001179*T allele (OR = 1.29 in the dominant model, p = 0.013) and *SIRT1* rs3758391*T allele (OR = 0.67 in the log-additive model, p < 0.001). Longevity (over 90) was associated with *SOD1* rs2070424*C minor allele (OR = 0.12 in the recessive model, p = 0.01). The analysis of gene-gene combinations has identified the age-related SNP's clusters. Totally, we have identified 169 multilocus patterns associated with longevity. The most significant combinations were the CAT*T+MSRA*TT+GPXI*T (OR = 5.64, $p_{FDR} = 0.002$), HIF1A*C+MSRA*T+SOD1*AA (OR = 5.2, $p_{FDR} = 0.006$), MSRA*T+SOD1*AA (OR = 4.86, $p_{FDR} = 0.012$), NQO1*C+GSR*T+SOD2*T (OR = 0.09, $p_{FDR} = 0.01$), GSTP1*A+SOD1*A+SOD2*CT (OR=3.5, $p_{FDR} = 2.93\times10^{-9}$), GSTP1*A+GSR*G (OR = 4.84, $p_{FDR} = 4.04\times10^{-9}$), and AKT1*G+HIF1A*C+GSTP1*GG (OR = 0.14, $p_{FDR} = 4.02\times10^{-9}$).

The follow-up study with the added survival analysis has revealed the elements that are core meaningful for longevity status. So, the combination of the MSRA*C and SOD1*G alleles, with the NQO1*TC genotype is rarer among long-lived women in compare with those individuals who died from all causes before reaching the longevity (OR = 0.1, $p_{FDR} = 0.035$). The cancer mortality was associated with the *CAT* rs1001179*TT (HR = 2.83, p = 0.031) and SOD1 rs2070424*AG (HR = 1.58, p = 0.018) genotype. The *PONI**G+*MSRA**C+*NQO1**T+*SOD1**G allele combination was associated with the highest risk of all-causes mortality among men (HR = 29.56, $p = 9.47\times10^{-4}$). The AKT1*GG+HIF1A*T+SIRT1*T genetic pattern had a protective effect on survival status in all studied individuals (HR = 0.71, p = 0.014).

Conclusion: We have identified the single and multilocus predictors of survival and mortality under the certain clinical phenotypes in the advanced age, as well as longevity genetic markers. We assume that these genes and their networks are involved in a stable, highly adaptive phenotype that allows to minimize the negative effects of the age-related pathologies and to reach the longevity.

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