How Genes Modulate Patterns of Aging-Related Changes on the Way to 100: Lessons from Biodemographic Analyses of Longitudinal Data

Anatoliy I. Yashin*, Konstantin G. Arbeev*, Deqing Wu*, Alexander Kulminski*, Liubov Arbeeva*, Irina Kulminskaya*, Igor Akushevich* and Svetlana V. Ukraintseva*

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* Social Science Research Institute's Center for Population Health and Aging and Duke Population Research Institute, Duke University, Durham, N.C.

ABSTRACT

Background and Objective. To clarify mechanisms of genetic regulation of human aging and longevity traits a number of genome wide association studies (GWAS) of these traits have been performed. However, the results of these analyses were controversial and had limited success. Most genetic associations detected in GWAS of these traits have not reached a genome-wide level of statistical significance. The results were also not replicated in the studies of independent populations. Among many possible reasons this situation might be caused by the lack of attention to the possibility of pleiotropic effects of genetic variants on aging and longevity traits. One more reason deals with mortality selection process in genetically heterogeneous populations. This process is responsible for the difference in genetic structure between groups of adult and the old individuals which influence results of genetic analyses. Neither of these two reasons was taken into account in genetic association analyses. An important limitation of conducted studies is that dealing with longitudinal data they were not able to address the problem of how genetic influences on life span are mediated by physiological variables and other biomarkers during the life course. The objective of this paper is to address these issues.

Data and Methods. We used genetic data on the apolipoprotein E (APOE) common polymorphisms (e2, e3, and e4), as well as genetic single nucleotide polymorphisms (SNP) data, together with phenotypic longitudinal data on life span and physiological variables collected in the Framingham Heart Study (FHS to investigate problems described above. We evaluated the roles of the APOE alleles in risks of major human diseases including cardiovascular disease, cancer, and neurodegenerative diseases. We used simulation study to show that approach to combining data improves the quality of GWAS. We used longitudinal data to compare average age trajectories of physiological indices between carriers and non-carriers of selected genetic variants. We used stochastic process model of human mortality and aging to investigate genetic influence on hidden biomarkers of aging and on dynamic interaction between aging and longevity.

Results. Our results show a complex role of the APOE gene in risks of the selected diseases which are age-, generation-, and gender-specific. The results highlight antagonistic pleiotropic effects at different ages, across generations, and across diseases. We showed that the use of different quality control (QC) procedures results in different sets of genetic variants associated with life span. The use of mixed model in GWAS of human lifespan resulted in detection of 24 genetic variants negatively associated with life span. We showed that the joint analyses of genetic data at the time of bio-specimen collection and follow up data substantially improved significance of associations of selected 24 SNPs with life span. We also showed that aging related changes in physiological variables and in hidden biomarkers of aging differ for the groups of carriers and non-carriers of selected variants.

Conclusions. The results of these analyses showed that genetic variants may have pleiotropic associations with aging and longevity related traits. These results demonstrated benefits of using biodemographic concepts and models in genetic association studies of these traits. Our findings showed that the absence of large number of genetic variants with deleterious effects may make substantial contribution to exceptional longevity. These effects are dynamically mediated by a number of physiological variables and hidden biomarkers of aging. The results of these research demonstrated benefits of using biodemographic principles and integrative statistical models of mortality risks in genetic studies of human aging and longevity.