

Drilling into the trends in genetics and epigenetics of aging and longevity

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An international group of scientists performed a comprehensive analysis of the genetic and epigenetic mechanisms and demonstrated that the majority of the genes, as well as genetic and epigenetic mechanisms that are involved in regulation of longevity, are highly interconnected and related to stress response. Also, for the first time, the group performed a comprehensive analysis of government research grants related to the genes involved in aging.

Since the dawn of civilization people were searching for clues to [longevity](#) and trying to extend human lifespan. But only in the past two decades with the advances in genetic sequencing, epigenetic analysis, and increased government investments the area experienced rapid expansion in the knowledge base, allowing scientists to develop comprehensive models and theories of aging. And while there is still much disagreement among scientists, the evolutionary theories are dominating the field. These theories predicted existence of certain [genes](#) that provide selective advantage early in life with adverse effects on lifespan later in life or longevity insurance genes. Indeed, the study of human and animal genetics is gradually identifying new genes that increase lifespan when overexpressed or mutated—gerontogenes. Furthermore, genetic and epigenetic mechanisms are being identified that have positive effects on longevity.

"The study of the effects of mutations and epimutations on life expectancy and the aging rate expands the range of potential pharmacological and genotherapeutic targets, as well as biomarkers of treatment of aging-dependent pathologies," said professor Alexey

Moskalev, PhD, DSc, head of the laboratories for aging research at the Institute of Biology of the Russian Academy of Sciences and at the Moscow Institute of Physics and Technology.

The international group of scientists performed a comprehensive analysis of the genetic and epigenetic mechanisms and demonstrated that the majority of the genes, as well as genetic and [epigenetic mechanisms](#) that are involved in regulation of longevity, are highly interconnected and related to [stress response](#). Also, for the first time, the group performed a comprehensive analysis of government research grants related to the genes involved in aging. One of the tools that may help understand the direction of scientific research that is still unpublished are research grant abstracts. To better understand the general trends in aging genetics, the funding and citation information for the longevity genes was collected using the International Aging Research Portfolio (IARP) system as well as the NCBI PubMed system.

Grants analysis led to interesting conclusions. The science of aging genetics is a comparatively new field. P53 was discovered in 1979 and implicated in aging in 1987. On average, genes in Table 2 were discovered 21 years ago and it took 9.7 years between the first citation and the first citation with "aging." The approximate amount of funding spent on genes related to aging is at over \$8.5 billion with over 195,000 citations with the most funding spent on genes involved in stress response. On average approximately 7.4% of the funding was spent on projects with "aging" in the grant application and this was consistent across all three categories. The average amount of funding per citation was over \$43,900. The largest amount of funding spent on a single gene with "aging" in the grant abstract was \$195 million, which represents fewer than 5% of the total funding spent on P53 research. SIRT1 and homologs is the only gene with over \$100 million spent on analyzing its role in aging with just under 14% of the funding spent on non-aging related projects. Most of the genes related to aging and longevity were associated with other biologic processes, and most of the funding and

publications citing these genes is related to areas other than aging.

"While most scientists rely on published research data and scientific conferences to follow the advances their areas of research, the vast amount of knowledge is codified in the published research grant abstracts and associated metadata. A comprehensive analysis of government grants and related publications shows that aging research is an emerging field and that only a minor fraction of the research dollars spent on genes implicated in aging and longevity was actually intended for aging research," said professor Alex Zhavoronkov, PhD, director of the Biogerontology Research Foundation, UK.

The team also performed the signaling pathway analysis of the genes implicated in aging and longevity and demonstrated that that most of the gerontogenes are members of the stress response pathways that confirm the existence of genetics "longevity program." As a rule, genes—regulators of longevity program—suppress mild stress response and mutations that make some of those pathways less efficient and provide life-extension benefits. Mild overexpression of effector longevity genes, involved with stress-response to DNA, protein, or other cellular damages, prolong lifespan. While moderate stress induces "longevity program" by stimulating expression of life assurance genes and promoting prevention or elimination of errors, including the novel and spontaneous ones, chronic or acute stress exposure exhausts the defense mechanisms and therefore accelerates aging. Pro-aging and anti-aging gene-determined processes exist on all levels of organismal system—from molecules to systems (metabolic, endocrine, immune, and inter-cellular communication). Their multi-level organization, the interpenetration of levels, a combination of regular and stochastic elements, is what makes the process of aging a fractal process.

More information: The results of the study will be published Open Access in the prestigious peer-reviewed journal *Cell Cycle*, available at <https://www.landesbioscience.com/journals/cc/article/28433/>.

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