Researchers uncover genetic basis of natural variation in aging rate

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Aging is characterized by a progressive decline in physiological functions and is a major risk factor for neurodegenerative disorders, cancer and diabetes. Previous studies on aging mainly focused on the regulation of longevity, and more than 100 genes and numerous small compounds have been identified that regulate lifespan in organisms from yeast to mammals.

Lifespan extension induced by genetic mutations has been shown in recent studies not to delay age-related behavioral decline, suggesting that longevity and behavioral aging may be two dissociable processes. With the increase of life expectancy, prevention of age-related functional impairment has emerged as a major challenge. Despite the great advances in genetic control of animal lifespan, little was known about the regulatory mechanisms of healthy aging, i.e., aging with limited loss of physiological function.

Now, a new study carried out by researchers from Dr. CAI Shiqing's lab at the Institute of Neuroscience, CAS Center for Excellence in Brain Science and Intelligence Technology of the Chinese Academy of Sciences has uncovered a genetic basis for natural variation in aging rates. The study was published in *Nature*.

The rate of aging is highly variable among individuals. It is believed that this variation is governed by environmental and genetic factors. Despite great interest in studying natural variation in aging rates to identify factors that control healthy aging, no such factor had been found. In order to explore this question, researchers from Dr. CAI Shiqing's lab studied the genetic origin of variability in the rate of aging using Caenorhabditis elegans as an animal model.

C. elegans is a tiny, free-living nematode, about 1 mm in length. Due to its short lifespan and clear genetic background, C. elegans has been widely used in aging research. Many conserved longevity pathways were first identified in C. elegans.

Natural isolates of C. elegans from different parts of the world were shown in this research to have distinct rates of decline in virility, feeding behavior and locomotion during aging. The researchers found that genetic variations in a novel neuropeptide coding gene (rgba-1) and its receptor gene npr-28 regulate the aging rate of worm behavior among wild isolates.

RGBA-1 from glial cells activates NPR-28 signaling in serotonergic and dopaminergic neurons to regulate behavioral decline in aging animals. The function of RGBA-1/NPR-28 signaling on behavioral aging depends on SIR-2.1-mediated activation of the mitochondrial unfolded protein response, a pathway known to modulate aging.

The researchers also performed population genetic analysis of rgba-1 and npr-28 and found that the two genes might have been subjected to a recent selective sweep, a natural selection process that leads to the reduction or elimination of genetic variations among individuals.

This study reveals the first genetic pathway underlying natural variation in the rate of aging, and uncovers the important role of neuropeptide-mediated glia-neuron signaling in controlling the aging rate. Further studies on natural variation in the rate of aging will pave the way for a comprehensive understanding of the biological regulation of healthy aging.

The antagonistic pleiotropy theory of the evolution of aging, proposed by George Williams in 1957, suggested that naturally selected genes promote survival and reproductive success in early life, but accelerate aging in later life. In contrast, this study suggests that the evolutionary selection of genes that offer benefits in early life could also result in a concomitant extension of lifespan or extension of health span, or both.

This research indicates that aging rates may have been affected by the emergence of new genes, natural selection, and interaction between different genetic loci, thus providing new insights into the evolutionary theory of aging.

More information: Jiang-An Yin et al, Genetic variation in glia–neuron signalling modulates ageing rate, *Nature* (2017). DOI: 10.1038/nature24463

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