

NEWS RELEASE

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Gene Critical for Neurotransmitter Synthesis Also Affects Longevity

FOR IMMEDIATE RELEASE

Dopamine and serotonin, two neurotransmitters in the central nervous system, are intimately involved in muscle control, memory, sleep, and emotional behavior. They are also linked to illnesses such as Parkinson's disease and mood disorders. Now, regulation of longevity may be added to this list.

Three natural variants in the gene for DOPA decarboxylase (DDC), an enzyme required for the production of dopamine and serotonin, together accounted for 15 percent of the genetic contribution to variation in life span among strains of the fruit fly *Drosophila melanogaster*, according to recent research by geneticists at North Carolina State University.

"This is a surprisingly large effect for a gene affecting a complex trait, such as longevity or body size, which is typically controlled by many genes with relatively small effects," said Dr. Trudy Mackay, William Neal Reynolds Professor of genetics at NC State and director of the study.

Results of the study appear in the paper "Dopa decarboxylase affects variation in *Drosophila* longevity," published in the July 27 online edition of *Nature Genetics*.

The fruit fly is a handy model organism for studying the genetics of longevity and other complex traits in animals. "We can make designer genotypes in fruit flies and test the effects of mutations," said Mackay.

The three variants interacted in a complex way to affect variation in longevity. Some variants in the DDC gene increased life span of the fruit flies and others decreased it. Interestingly, some variants that were associated with increased life span were not present in the population as frequently as expected, while others associated with decreased life span were more

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common than expected. Natural selection processes do not simply favor longevity; instead, they promote variability in life span.

The research was a collaboration among scientists at NC State University and the Institute of Molecular Genetics of the Russian Academy of Sciences in Moscow. It was funded in part by grants from the National Institutes of Health, the Russian Fund of Basic Research, and the Russian Academy of Science.

“Our results have real implications for humans,” said Mackay. “The DDC gene is a strong candidate for regulation of longevity in humans. The various genome projects active today have revealed an astounding similarity in the genetic makeup of organisms as disparate as yeast, *Drosophila*, and humans. For instance, over two-thirds of the known human disease genes have corresponding genes in *Drosophila*, and genes affecting key biological processes seem to be conserved across all animals.”

Mackay and her team of geneticists have been working to identify genes affecting life span in *Drosophila* in order to discover the genetic basis of complex traits: what genes and mutations affect the trait, how genes interact with other genes and with the environment, and the molecular basis of the interactions.

“If everything is interactive, the effect of a single gene on a complex trait may be marginal,” said Mackay. “But it’s not impossible to foresee future pharmacological interventions that could improve the quality of life of the aging population.”

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Note to editors: The abstract of the paper follows.

“Dopa decarboxylase affects variation in *Drosophila* longevity”

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Abstract: Mutational analyses in model organisms have shown that genes affecting metabolism and stress resistance regulate life span¹, but the genes responsible for variation in longevity in natural populations are largely unidentified. Previously, we mapped quantitative trait loci (QTL) affecting variation in longevity between two *Drosophila melanogaster* strains². Here, we show that the longevity QTL in the 36E; 38B cytogenetic interval on chromosome 2 contains multiple closely linked QTL, including the Dopa decarboxylase (*Ddc*) locus. Complementation tests to mutations show that *Ddc* is a positional candidate gene for life span in these strains. Linkage disequilibrium (LD) mapping in a sample of 173 alleles from a single population shows that three common molecular polymorphisms in *Ddc* account for 15.5% of the genetic contribution to variance in life span from chromosome 2. The polymorphisms are in strong LD, and the effects of the haplotypes on longevity suggest maintenance of the polymorphisms by

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Dopamine 3

balancing selection. DDC catalyzes the final step in the synthesis of the neurotransmitters, dopamine and serotonin³. Thus, these data implicate variation in the synthesis of bioamines as a major factor contributing to natural variation in individual life span.