Killifish project explores the genetic foundation of longevity

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Turquoise killifish. Credit: Wikipedia.

Researchers at the Stanford University School of Medicine have mapped the genome of an unusually short-lived fish, paving the way for scientists to use the organism to study how genes influence longevity.

The researchers will publish the genome map of the African turquoise killifish Dec. 3 in *Cell*, along with early insights into the genetic determinants of its life span. Using a statistical analysis that looks at mutation rates across different organisms, the scientists found evidence that some of the same rare genes that have persisted in the killifish gene pool over centuries have also persisted in the gene pools of some unusually long-lived animals. The researchers wonder if this means there are certain genes that evolution has "tuned" to create varying life spans.

"The range of life spans seen in nature is truly astonishing, and really we

have very little insight into how this has evolved or how this works," said Anne Brunet, PhD, professor of genetics at Stanford and senior author of the study. "By having the genome of this fish and comparing it to other species, we start seeing differences that could underlie life span differences both between species and also within a species."

The study's lead author is Dario Valenzano, PhD, a former postdoctoral scholar in Brunet's lab who now directs his own lab at the Max Planck Institute for Biology of Aging.

Brunet and members of her lab have worked for the past nine years to establish a colony of killifish at Stanford and to create online access to killifish gene maps for other researchers who want to study them. They hope that studying the killifish, some strains of which live only four to six months, will help them investigate why some species, like this fish, live less than a year, whereas others, like some whales, can live 200. They also hope the research will provide insights into longevity differences among humans.

Life in the fast lane

Evolved to both hatch and reproduce within the brief rainy seasons in Mozambique and Zimbabwe, the turquoise killifish has an extremely compressed life cycle. Brunet said she and her team believed that once the fish's genes were mapped out, they would provide an "exciting new opportunity to use an evolutionary lens to propose ideas about aging."

Using a range of genomic and genetic techniques, team members sequenced small segments of killifish DNA and then used specialized software to string these sequences together until they had assembled a full digital map of the turquoise killifish genome. They repeated this process in different strains of the fish to identify important genetic variations within the species.

"Once you have the genome, it really breaks open the possibility of using genetic manipulation experiments and more conceptual comparative genomics studies," Brunet said.

Brunet and her colleagues have already begun to examine genes that are unique to the short-lived killifish, as well as to cross-breed short-lived killifish with a longer-lived strain to look for genes tied to longevity.

When they mated long-lived fish with short-lived fish, they observed a cluster of genes shared between the long-lived grandparents and the long-lived grandchildren. They noted that several genes in this cluster are associated with longevity and aging in other species.

One of these genes is the killifish equivalent of a human gene whose mutation is associated with frontotemporal dementia, a disease that generally manifests in late adulthood. The researchers see this as another good sign that analyses of killifish genes can set the stage for important health discoveries about human biology.

"We don't know yet exactly how these findings are relevant to humans, but these are questions we are actively pursuing," Brunet said.

A community resource

Brunet said she and her colleagues were eager to establish the killifish as a model organism not only for their own future studies but for the research community. As they worked to assemble the killifish genome, they also built a user-friendly website—http://africanturquoisekillifishbrowser.org—that other researchers can access for free.

"They can go to our website, enter their favorite gene of interest, and then zoom in on the killifish equivalent," she said.

The paper will be published alongside another killifish genome paper by a German team in the same issue of *Cell*. Brunet said she is excited that other researchers have begun working with killifish and hopes the resources published by both teams will usher in a new level of emphasis on the animal as a model for longevity research.

"Having the genome transforms a nice, interesting organism into a model organism," she said.

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