Fish-eye view. Hidden genetic variation in typical *Astyanax mexicanus* (*top*) may quickly lead to eye loss in cavefish populations (*bottom*).

EVOLUTION

Cavefish Study Supports Controversial Evolutionary Mechanism

To the classic case studies of evolution, such as Darwin's finches and the peppered moth, a small group of researchers would now add the Mexican tetra. This small, freshwater fish is mostly found as a drably colored inhabitant of creeks and rivers. But at least a half dozen times, populations have taken up residence in caves, where they have been transformed. They remain the same species, but are now eyeless and nearly albino.

On page 1372, a research team presents evidence that a controversial evolutionary mechanism was at work in the adaptation of the blind cavefish to their lightless environment. Nicolas Rohner, an evolutionary geneticist at Harvard Medical School in Boston, and his colleagues found that in the sighted tetras, a molecule called heat shock protein 90 (HSP90) masks variation in genes, such as those governing the size of the fish's eye. The team proposes that the stresses of cave life disturbed the function of HSP90 and unmasked the genetic variation, providing a rich template upon which natural selection acted. The study bolsters those who have long believed HSP90 is an evolutionary force, says Kazuo Takahashi, a quantitative geneticist at Okayama University in Japan. "Its impact is huge."

In 1998, biologist Susan Lindquist, now at the Massachusetts Institute of Technology in Cambridge, and her colleagues were the first to propose that HSP90 acts as an evolutionary "capacitor," by analogy to the electrical storage device. They showed that some fruit flies making less HSP90 than normal developed bizarre-looking eyes, legs, and other traits. Lindquist suggested that HSP90 normally masks underlying mutations, which are revealed in its absence.

HSP90 is a so-called molecular chaperone, which ensures proteins take on and maintain their correct shape, even if their amino acid sequence varies slightly because of mutations. By doing this for proteins important for development, the researchers proposed, HSP90 could theoretically hide the existence of accumulated mutations. Reduce its presence in an embryo, and the effects of those mutations would appear—providing grist for natural selection. Skeptics criticized the fruit fly studies as too artificial, however, and similar findings in a plant by Lindquist's team won few converts.

Then Lindquist heard about the unusual Mexican blind cavefish and wondered if their eyes, like fruit fly eyes, were under HSP90's influence. She approached Rohner and his Harvard boss, developmental biologist Cliff Tabin, who had long studied these fish, and convinced them to investigate.

When Rohner treated fish embryos with an inhibitor of HSP90, some fish developed larger or smaller eyes and eye sockets than untreated fish, consistent with the idea that the chaperone masked phenotypic variation. Breeding the small-eye fish resulted in young that had small eyes as well, indicating that the size was genetically based.

Rohner then looked for an environmental stressor that might naturally release such variation and found that the underground water was much less salty than the surface water. When he placed surface fish embryos in water of such low salinity, the adults developed eyes and eye sockets that varied in size. In caves, smaller eyes should require less energy to grow and use, and thus would likely be favored by natural selection, Rohner suggests. "What is beautiful about this paper is that the HSP90-dependent change resembles a natural adaptation," says Christine Queitsch, a geneticist at the University of Washington, Seattle.

To some biologists, the cavefish study is persuasive that HSP90 acts as an evolutionary capacitor in a natural setting. "This is a superb example of a full circle, starting from lab results, making a controversial hypothesis, and testing it in the wild," says Ritwick Sawarkar, a molecular biologist at the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, Germany. This "will pave a way for further research in many other species in [the] wild." Lindquist is pleased as well. "It's a capstone, establishing that [HSP90] can explain a lot of complex evolution in higher organisms," she says.

Others are cautious. "The story of HSP90 and its relations with evolution is more complex," suggests Maria Pia Bozzetti, a geneticist at the University of Salento in Lecce, Italy. She suspects that the loss of HSP90 promotes new genetic variation by releasing mobile DNA elements called transposons.

Although the study showed that HSP90 is important to development, "its contribution to the evolution of eye loss is still unclear," says Takahashi, who thinks that many evolutionary capacitors may exist. Other distinctive aspects of the blind cavefish, such as their color, weren't under the chaperone's control. "HSP90 is by far the strongest candidate, but by no means the only candidate, to buffer variation," Sawarkar agrees. **–ELIZABETH PENNISI**

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