Genetic origins of hybrid dysfunction

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Three hybrid swordtail males displaying varying degrees of melanin invasion, from a small spot -- like spots typically found in sheepshead swordtails (middle) -- to very advanced melanoma (back). Credit: Daniel Powell

In a small pool nestled between two waterfalls in Hidalgo, Mexico, lives

a population of hybrid fish—the result of many generations of interbreeding between highland and sheepshead swordtails. The lab of Molly Schumer, assistant professor of biology at Stanford University, has been collecting these fish for years to study the evolution of hybrids.

"We're just realizing that hybridization affects species all across the tree of life, including our own species—many of us carry genes from Neanderthals and Denisovans," said Schumer, referring to two ancient human species that interbred with our ancestors. "Understanding hybridization and the negative and positive effects that can come from genes that have moved between species is important in understanding our own genomes and those of other species with which we interact."

In a new paper, published May 14 in *Science*, the researchers pinpoint two genes responsible for a melanoma that often develops near the tails of male highland-sheepshead hybrids. The finding marks only the second time that a hybrid dysfunction has been traced to specific genes in vertebrates. (The only other case where scientists have narrowed hybrid dysfunction in vertebrates down to the single-gene level is in a longstanding hybrid population of mice in Europe and their relatives.)

A special population

People have long known that the offspring of two different species tend to have genetic flaws. For example, mules—which are donkeys-horse hybrids—are infertile. Ironically, in order to find the genes responsible for such dysfunctions, researchers need hybrids that are fit enough to breed for several generations after the initial hybridization. Otherwise, the pieces of their genomes that come from the parental species are so large that it is nearly impossible to trace the influence of any one gene.

This is what makes the highland-sheepshead hybrids an exceptional case study. They have been interbreeding for about 45 generations, resulting

in genomes that contain smaller chunks of parental DNA, which are easier to inspect at a single-gene level.

"We've known about genetic incompatibility between the genes of two species since the 1940s. Despite that, we don't know many of the genes that cause these negative interactions," said Daniel Powell, a postdoctoral fellow in the Schumer lab and lead author of the paper. "Our lab has clearly defined natural hybrids and we've developed the genomic resources for both parental species. These fish represent a unique system for addressing this question."

Two hybrid male swordtail fish representing the extreme versions of the trait these researchers studied. The male on the left has melanoma and the male on the right has only a small spot. Credit: Daniel Powell

In order to home in on the genes responsible for melanoma in hybrids, the researchers first turned their attention to the pure sheepshead swordtails and the genetic origin of a black spot some of these fish develop—which is non-cancerous but found in the same location as the hybrids' melanoma. Analyzing the genomes of nearly 400 individual fish, they linked the black spot with the presence of a gene called xmrk. Following that lead, the researchers concluded that xmrk was also more highly expressed in hybrids with melanoma compared to those without it—altogether, it could explain 75 percent of all variation in the spotting they studied in both the pure sheepshead and hybrid fishes.

The researchers also found that another gene called cd97—which some hybrids inherit from their highland swordtail ancestors—was more highly expressed in the highland swordtails and in hybrids than in sheepshead swordtails. Further genetic evidence suggests that cd97 and xmrk interact in some way to produce melanoma in the hybrids.

Interestingly, even though neither gene is associated with melanoma in the parental swordtails species, they're both linked to cancer in other animals. In a distantly related swordtail hybrid, for example, xmrk interacts with another gene—not cd97—to cause melanoma, and a gene related to cd97 has been associated with cancer in humans.

Taken together, these findings yield a puzzling picture. "We've ended up with competing but not mutually exclusive ideas about hybrid incompatibility and disease," said Powell. "We've lent credibility to the idea that some genes might be vulnerable to breaking down in different species—which is surprising, given the randomness of evolution. But we also have evidence for the idea that there is a diversity of genetic causes for similar dysfunctions."

The best kind of project

Schumer says she took a bit of a gamble when she focused her studies on hybridization, but her bet is paying off.

"When I started my Ph.D. in 2011, it was really not accepted that hybridization was common in animals. The best-known examples were mules and fruit flies. It's been such a massive shift and a fun time to be working on this question," said Schumer, who is senior author of the paper and a member of Stanford Bio-X. "What we've arrived at now is the best kind of project in science: one that raises way more questions than answers and spins you off in a bunch of different directions."

Through future work, the researchers want to figure out why hybrid swordtails with melanoma are less likely to survive in the wild and in captivity. They are also curious to know why so many of these fish have the melanoma—it's possible that, when it comes to mate selection, females prefer males with the large black spots generated by melanoma. Already, they have lined up several ideas to further understand whether genes go wrong in a repeatable way in hybrids, or if what they've found in xmrk and cd97 is closer to coincidence.

More information: D.L. Powell el al., "Natural hybridization reveals incompatible alleles that cause melanoma in swordtail fish," *Science* (2020). science.sciencemag.org/cgi/doi … 1126/science.aba5216

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