SCIENCE

The Surprise Hiding in the DNA of Pet Fish

Domesticated betta fish have evolved a sex gene not found in wild fish of their species.

By Sarah Zhang

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In 1975, scientists tried spaying a few hundred female betta fish. We all know what happens to spayed cats and dogs: They become sterile. Betta fish are different. A third of the surviving bettas regenerated an ovary—which, okay, interesting enough. But the remaining two-thirds did something much, much stranger: They grew testes. They turned brighter and darker in color too—like male bettas. They grew elongated fins—like males. They even started making sperm—like males, obviously. When mated with other female betta fish, these females-turned-males produced offspring that looked

From this, the scientists essentially concluded that we understand nothing about fish sex.

How fish become male or female is far weirder and more varied than the XX-female, XY-male chromosome system of humans. (Though even the human story can get complicated.) Clownfish, for example, are all born male, but one male in a group will irreversibly turn into a dominant female. In Atlantic silversides, sex is influenced by water temperature: Warm means male, cold means female. In a family of fish called cichlids, some species have a sex-chromosome system similar to that of humans, while closely related species have a system similar to that of birds. To spice things up, some species have both humanlike XY and birdlike ZW chromosomes. At least 20 sex-determination strategies have been found in the family alone, says Thomas Kocher, a biologist at the University of Maryland at College Park, and he expects that many more are still undiscovered. No one really knows why fish have such a diversity of strategies for sex determination—it's "one of the biggest questions in evolutionary biology at the moment," says Manfred Schartl, a developmental biologist at the University of Würzburg, in Germany.

Betta fish, it turns out, might be a case study in how a novel sex strategy emerges. Two new studies suggest that pet betta fish evolved a sex-determination gene that does not work the same way in wild bettas of the same or closely related species. "The way that sex is determined changes very, very quickly across the evolutionary tree," says Hannes Svardal, now a biologist at the University of Antwerp who co-authored one of the new studies. And betta fish, he adds, seem like an "extreme case" of sex determination changing within a species. In our bid to breed more beautiful and fiercer fish, we might have given them a sex gene too.

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dizzying array of colors and shapes, but Svardal liked the less ostentatious wild ones, and he traveled to their native Southeast Asia to collect them with his father in his youth. A few years ago, his teenage hobby ended up inspiring a new line of research: Bettas were originally bred as fighting fish in Thailand, and Svardal thought they might be an easy-to-keep model organism for studying aggression. (Consider other species bred for aggression: chicken, bulls. Not so easy to keep in a lab.) He got connected with Andrés Bendesky, an evolutionary geneticist now at Columbia University's Zuckerman Institute, who had the same idea. This, not sex, was their original interest. Together, they sequenced nearly 100 domesticated and wild betta fish. Independently, a second group led by scientists at Nanchang University, in China, and UC Berkeley began its own years-long betta-fish project, sequencing nearly 800 betta fish. Both studies were recently posted as preprints online and are under review at a scientific journal.

The two teams independently combed through their fish genomes, looking for any and every mutation that might correlate with a difference in looks or behavior. Both quickly homed in on a gene called *dmrt1* whose sequence differed between domesticated male and female betta fish. *dmrt1* is linked to sex determination in birds, reptiles, and other species of fish too. In domesticated betta fish, the male version of *dmrt1* essentially acts like a Y chromosome; just one copy of the male version is enough to make a fish male. The teams did not see the same close correlation between *dmrt1* and sex in wild bettas of the same or related species.

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But—and this is a big *but*—even in domesticated bettas, *dmrt1* was not 100 percent determinative of sex. Both teams noticed that a small proportion, up to 10 percent or so, of fish with the male version of *dmrt1* were actually female, and vice versa. In other words, some female fish were XY and some male fish were XX. Clearly, genetics alone does not determine sex in betta fish.

This finding actually helps make sense of the offspring from the surgically sex-reversed bettas from 1975. Most of the females whose ovaries were removed must have started as XX females. The surgery, for some reason, triggered a switch to male, but a fish that was still genetically XX mating with another XX female could produce only XX babies

with one parent, which would have produced a mix of baby male and female bettas.

What, if not genetics, influences sex in betta fish then? Betta-fish breeders—who enter competitions akin to the Westminster Dog Show—have swapped many theories: temperature, pH level, even the age of the mother or father fish. Many have also noticed that when females are kept together, one will turn into a male—without any surgical or hormonal intervention from humans. When Bendesky has polled the audience at betta-fish shows, asking if they have personally seen adult females turn into males, he says, "they all raise their hand."

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Betta fish aren't the first fish for which domestication has scrambled sex determination. The zebrafish, an extremely common lab animal, actually lost its sex chromosome through domestication. Without a sex chromosome, sex can become unpredictable, which turns into a problem if scientists want to perpetuate a particular line of zebrafish for experiments. "I know of colleagues who have lost mutant lines because suddenly there was no male or female," Schartl told me. Betta-fish breeders long ago might have ended up selecting for *dmrt1* precisely because they wanted more predictable ratios of male to female bettas. Males tend to fetch higher prices in pet stores because of their more ostentatious color and fins, and they are the ones used in fights in Thailand. For breeding, you need both sexes, though. One breeder told me that he actually prefers more females because he can cross one good male with multiple females.

Wild and domesticated betta fish have also regularly exchanged genes over the years: Breeders cross their domesticated lines with wild fish to introduce new traits, and domesticated bettas can escape or be let go into the wild. You can even see it in their DNA. "There is this gene flow [in] both directions," Svardal says. In particular, the genetic spillover from domesticated to wild suggests that humans can end up changing wild fish without meaning to. In aquaculture where fish are bred for food, tipping the sex ratio has long been an industry obsession in order to increase the number of males or females, whichever are bigger depending on the species. But these domesticated fish can escape and breed with wild populations, thereby changing those fish too. "You're not really returning to the wild the same genetic structure," says David Conover, a fish biologist at Stony Brook University. What happens in fish tanks

In recent years, the rise of DNA sequencing has ignited new interest in and methods for studying sex determination. The early days were much lonelier. When Gene Lucas, the founder of the International Betta Congress, was trying to study sex determination in betta fish in the 1960s, the big genetics departments were interested in breeding better chickens or cows for agriculture, he told me. Nobody was interested in a hobbyist animal. How the times have changed: In addition to the two groups who published recent preprints on the betta-fish genome, a third group in Singapore also published a similar paper in April (though that group did not investigate sex determination specifically). "We thought, *Ah, now we finally found a niche without anyone else working. We can take our time*," says Rasmus Nielsen, a geneticist at UC Berkeley who co-authored one of the preprints. Instead, he and his co-authors found themselves racing to get their preprint up after the other preprint posted two weeks ago. Genetics has exploded into such a big field that even a relatively obscure animal has multiple groups competing to sequence its DNA.

Still, when it comes to the mystery of sex, these betta-fish-genome studies can give only a partial explanation. We know every letter of the betta-fish genome now. We can pinpoint the genes that make the fish royal blue versus steel blue. But we still cannot explain exactly why some fish end up being the opposite sex than their genes would suggest. To get there, we need to look beyond DNA. Fifty years later, those female-turned-male betta fish still remain a scientific mystery.

Sarah Zhang is a staff writer at *The Atlantic*.

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