Sex and the single gene: New research shows a genetic 'master switch' determines sex in most animals

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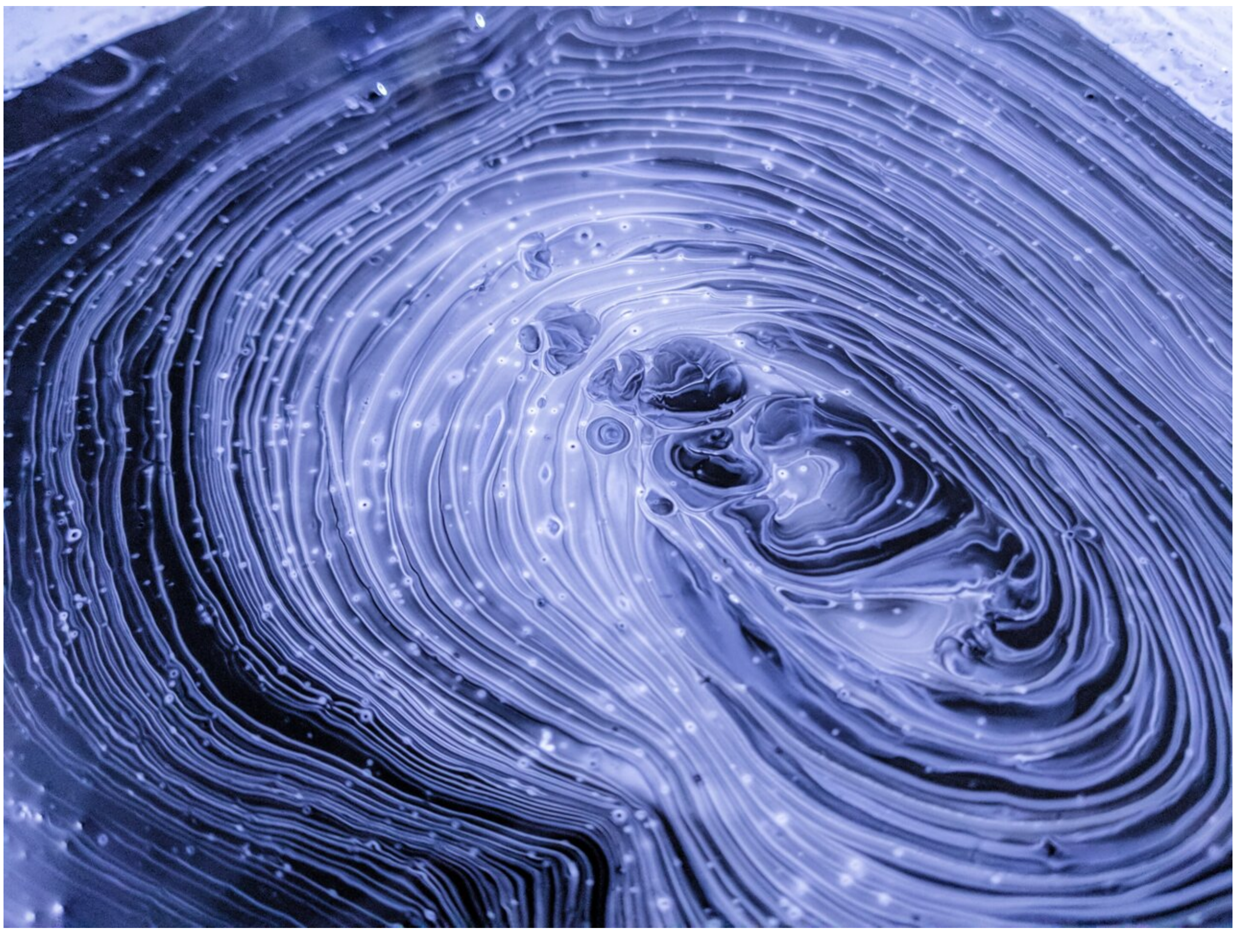

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In humans and other animals, sex is usually determined by a single gene. However, there are claims that in some species, such as platyfish, it takes a whole "parliament" of genes acting together to determine whether offspring develop as a male or female.

In a new analysis published in *Trends in Genetics*, we took a close look at these claims. We found they describe abnormal situations, such as hybrids between two species with different sex-determining systems, or when one sex system is in the process of replacing another.

We conclude that sex is normally determined by a single gene. Evolutionary theory suggests this is the most stable state of affairs, as it ensures a 1:1 ratio of male and female animals.

The human 'master switch' for sex

In mammals, females have two X chromosomes, whereas males have an X and a Y. The Y chromosome bears a gene called SRY, which acts as a "master switch": an XY embryo, carrying SRY, develops into a biological male, and an XX embryo, lacking SRY, develops into a biological female.

This makes the inheritance of sex simple. Females make eggs, which carry a single X chromosome, while males make sperm, half carrying an X and half carrying a Y.

Random fusion of eggs and sperm delivers half XX females and half XY males, for a 1:1 sex ratio.

Sex in other vertebrates

Among animals with backbones (vertebrates), there is a huge variety of systems that determine sex. However, they usually come down to the action of a single gene.

Many fish, frogs and some turtles have systems like ours, in which a male-dominant gene on the Y chromosome directs testis development. Some vertebrates have the opposite—a female-dominant gene on the X chromosome.

Other vertebrates use a dosage difference of a single gene. In birds, males have two copies of a Z chromosome with the sex-determining gene DMRT1. Females have a single Z and a W chromosome that lacks DMRT1. Sex depends on DMRT1 dosage: two copies in ZZ males, versus one in ZW females.

Surprisingly, many different genes act as the master switch in different species. But they all act by triggering the same male or female differentiation pathway.

These single-gene systems deliver equal numbers of males and females, which theory says is the optimal balance for a stable system. If the ratio favors one sex, individuals that produce more of the other sex will leave more descendants and their genes will spread until a 1:1 ratio is achieved.

Some exceptional species

Some aquarium fish have more complex systems. Genetic crosses in platyfish appear to show two or more genes that determine male or female development; the sea bass seems to have at least three sex genes.

Some frogs and lizards seem to determine sex using two or more sex genes.

Then there are species with two or more pairs of sex chromosomes. The platypus has five X and five Y chromosomes. Is there a sex gene on each Y? How will a poor baby platypus know how to develop if it gets three Ys and two Xs from its dad?

And what about species, like the African clawed toad, which have two copies of their whole genome, so should have two pairs of sex chromosomes and sex genes?

So there are lots of exceptional species that seem to have multiple sex chromosomes and sex genes in defiance of the expectation that only a single sex gene can produce a stable system.

Polygenic sex—is there any such thing?

In species where we cannot find a single master switch gene, it is common to talk about "polygenic sex". But how robust are these examples?

In our recent paper we examine classic examples and recent claims for polygenic sex determination. We conclude the few systems that qualify represent abnormal and transient situations.

Multiple sex chromosomes need not mean multiple sex genes. In the platypus, all five Y chromosomes move together into sperm, and a single gene on the smallest Y directs male development. The African clawed toad solved the problem of its doubled genome by evolving a novel female-determining gene on a newly minted W chromosome.

In several systems, two sex genes are detected, but they control different steps of the same pathway that are regulated by a single master gene.

In some of the classic fish systems, like platyfish, the different variants all spring from the same chromosome, suggesting sex is controlled by different variants of the same gene. A Japanese frog has different sex chromosomes on different islands, but they are all variants of the same chromosome.

Other examples suggest systems in transition. Sea bass shows different frequencies of variants over its range. There are signs of a new system gradually replacing an old one in a European frog.

The zebrafish is particularly interesting. Strains bred independently in laboratories for 30 or 40 years have aberrant sex ratios and multiple sex genes.

But it turns out wild zebrafish have a regular ZW sex chromosome system. Lab stocks independently lost their W chromosome during lab breeding. All the lab fish are ZZ, and sex of the hatchlings is determined by weaker sex-differentiating genes that were lurking in the background.

Winning the war of the sex genes

Many "polygenic" systems turn out to be hybrids between two species. Species hybrids often have problems with reproduction, such as sterility or skewed sex ratios.

Their problem is incompatibility of different sex chromosomes and sex genes. If an XY male mates with a ZW female, offspring have all sorts of combinations of sex genes.

Incompatibilities can play out differently. For instance, two species of cichlid fish living side by side in Lake Malawi in Africa have unrelated XY and ZW systems. In their XYZW offspring, the W partially overrides the male determining effect of the Y, so XYZW fish have intersex traits. But, in another species combination, the W gene triumphs and XYZW fish are fertile females.

Species hybrids may reveal many genes with major and minor effects on sex determination. For instance, crossing two catfish speciess revealed seven male-associated and 17 female-associated genes on different chromosomes.

So there are certainly species where two or more genes act together or in opposition. However, in the long term there is strong selection for one or the other to gain the upper hand. This will turn an inefficient polygenic system into a single-gene system, delivering fertile males and females in a 1:1 ratio.

More information: Manfred Schartl et al, Polygenic sex determination in vertebrates—is there any such thing?, *Trends in Genetics* (2023). DOI: 10.1016/j.tig.2022.12.002

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