How cats got their stripes: The mystery of color patterns in mammals

In 1902's *Just So Stories*, Rudyard Kipling famously explained how the leopard got his spots in what would today be deemed an extremely racist fable. Now Christopher Kaelin, Kelly McGowan, and Gregory Barsh, from the HudsonAlpha Institute for Biotechnology, have discovered how the tabby cat got its stripes: from a signal in the fetus. Their findings appear in *Nature Communications*
.

"The genes that control simple color variation, like albinism or melanism, are the same in all mammals for the most part. However, the biology underlying mammalian color pattern has long been a mystery, one in which we have now gained new insight using domestic cats," said Barsh, who is editor-in-chief of PLoS Genetics.

To trace the origins of the common striped coat pattern, the team analyzed gene expression in single skin cells from fetuses collected from feral cats in trap-neuter-release programs being spayed – half of such females are pregnant. The work revealed a novel mechanism behind the origin of stripes, like Jackie's in the photograph.

Alan Turing's idea

Color is easier to study in fish, in which individual pigment cells denote a specific color, and the organization of the cells forms patterns. It's a little like following the directions in a paint-by-numbers kit and watching an image emerge as small areas of color become confluent.

In mammals the situation is more complex. Local-acting hormones determine the output of pigments from cells called melanocytes, but the number of melanocytes tends to be the same in all individuals of a species. Humans of different skin colors have about the same number of melanocytes, but the cells produce differing amounts of the two variations of melanin pigment. The overall color reflects the proportions of black?brown eumelanin and red?yellow pheomelanin.

The colors of cats are more intricate than the hues of humanity, with striations and spots of light and dark creating the distinctive coat patterns of ocelots, jaguars, cheetahs, and of course the leopard's spots of fable fame. These are called periodic color patterns. A hypothesis explaining how this complex coloring may arise dates from the early 1950s from a seemingly unlikely source – Alan Turing of computer science fame.

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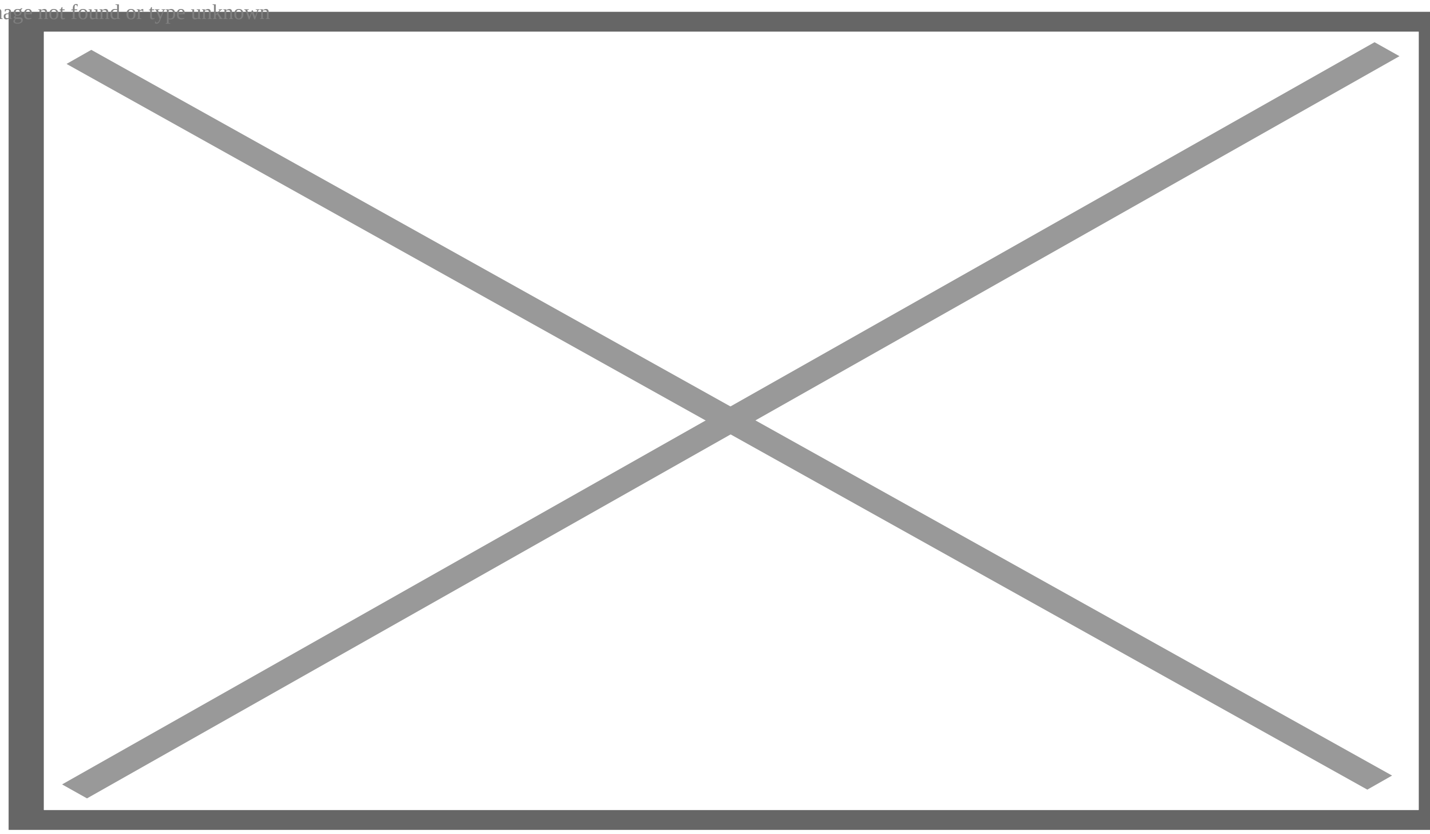


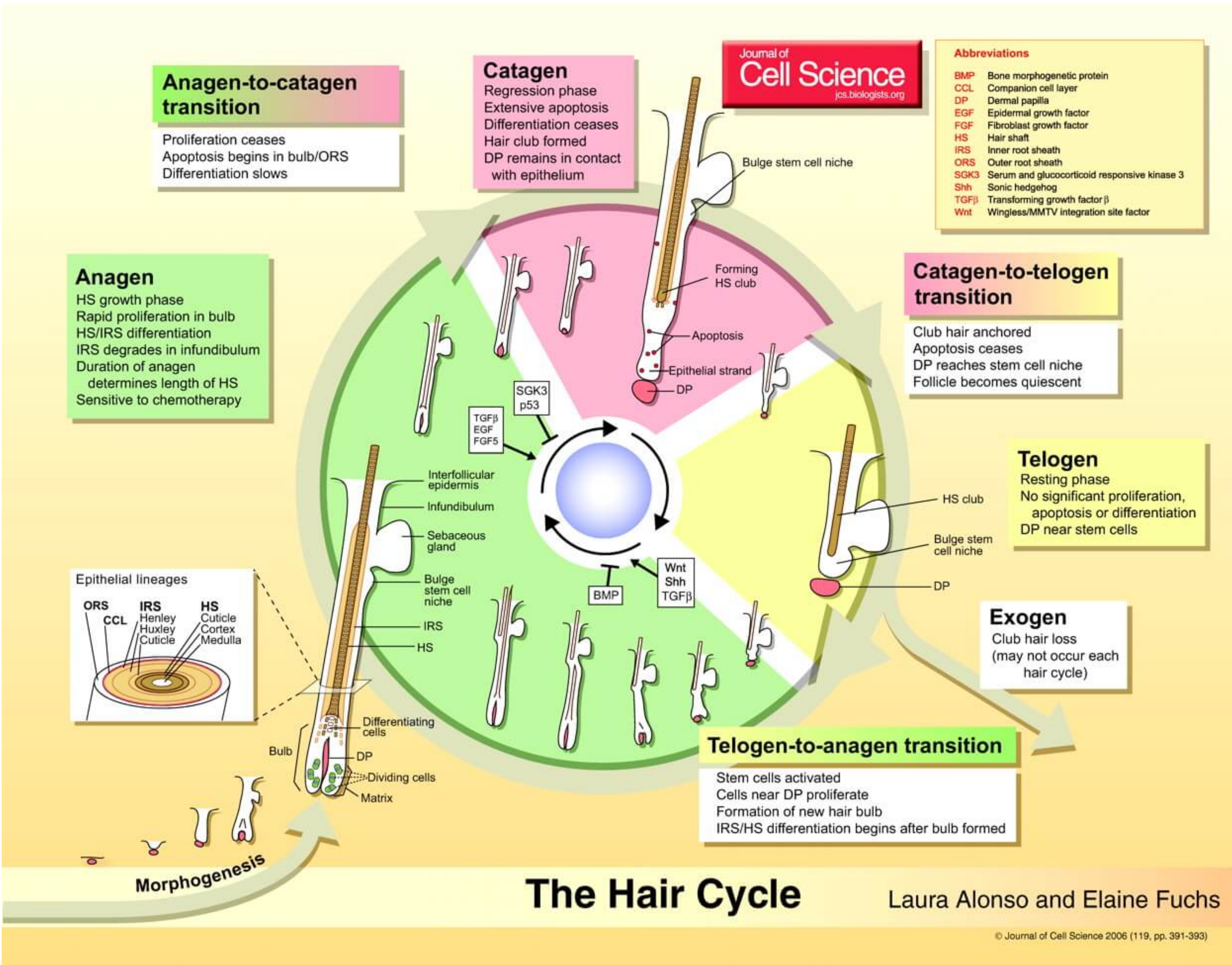
Alan Turing. Credit: History

Also a theoretical biologist, Turing posited that patterns such as the coat colors of large cats could arise from molecules that turn each other on and off as they move through a developing body’s tissues at different rates. His “reaction-diffusion mechanism” envisioned activator and inhibitor molecules overseeing deposition of pigments before birth templating coat color patterns. An activator coloring a cell triggers an inhibitor that diffuses away and suppresses pigment deposition in neighboring cells. From this molecular tango arose Jackie’s stripes.

How a signal sets the stage for stripes

A hair follicle arises from stem cells, which divide and are pushed upward as they specialize, accumulating keratin protein and melanin pigments. In a cat fetus, a follicle is developmentally destined to give rise to a hair that’s either light or dark, called its “pattern element identity.” Then a bath of local hormone signals sets the color hair-by-hair.

The color stamp persists even as the constituent cells divide, and in this way, the pattern of stripes on a kitten remains in the cat it becomes. A full grown cheetah has the same number of spots it did as a juvenile. Just like that, a dark hair falls out and is replaced with – a new dark hair. If I could replicate this process, I wouldn't need to periodically have my hair colored, some strands bleached blonder than others to create an overall effect. Cats don't have to go to the vet for a highlight touch-up to maintain their stripes.



Credit: Laura Alonso/Elaine Fuchs

The researchers sought the molecules behind cat stripes.

“Even before melanocytes enter the epidermis, the cells are predestined to signal a specific fur color. By understanding the developmental window and cell type in which color pattern establishment occurs, we were able to dive deeper and discover the molecules involved in pattern development,” said McGowan.

The details

The researchers analyzed the messenger RNAs produced in individual hair follicle cells of the cat fetuses. This commonly used technique, called single-cell RNA-seq, identifies the collection of mRNAs in a lone cell in a selected anatomical place and physiological time, that indicates, protein-by-protein, what’s going on. (I described RNA-seq in a COVID context recently here)

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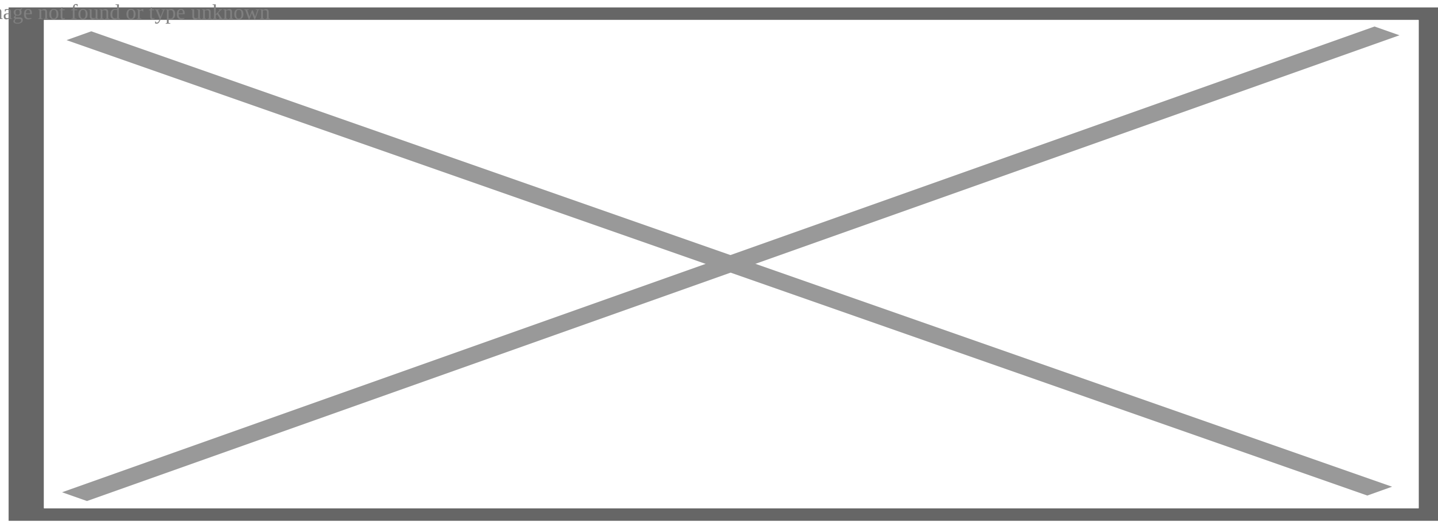

RNA is isolated (1), purified (2), sequenced (3), then analyzed (4). Credit: AllGenetics

Within the “gene expression pre-pattern” that the experiments revealed, the team discovered a strong signal from a well-studied gene in many vertebrates called Dickkopf 4 (“thick head” in German). In humans, the protein that the gene encodes inhibits liver cancer.

The first inkling of the coming feline phenotype is a pattern of raised stripes along the single cell layer that is the epidermis as a cat embryo hovers at the boundary of becoming a fetus, about the equivalent of a late-7-week human embryo. The two types of melanin will be laid down into the grooves, the first inklings of stripes. It’s a little like adding lines of chocolate to the vanilla batter of a developing marble cake before swirling.

The experiments showed that expression of 277 genes differs between fetal epidermal cells destined to be dark versus light, but the most influential is Dickkopf 4. As the days progress, Dickkopf 4 stimulates deposition of dark pigment in certain cells of the developing hair shaft. The gene encodes a protein that inhibits signaling of another protein called Wnt, which helps to set cell fates during prenatal growth and development.

A clue in Abyssinian cats

Geneticists like to make mutants to reveal and describe a gene’s normal function. That’s why I worked with flies that had legs growing out of their heads and mouths.

When Dickkopf 4 is mutant, the result is a cat with a “ticked” pattern – a uniform sandy or dull brown color that, on closer inspection, consist of hairs that are not dark or light, but have bands of color. This phenomenon is common among mammals and is called agouti. Plucked from a feline, an agouti hair would be white at the ends and grayish in the middle. A bit of yellow over the hair endows it with a sheen, which is how a cat preening in dappled sunlight can seem to have a different pattern if viewed from a different angle. It’s like the oily glop I put on my hair.

Two ticked cats are the familiar Abyssinian (aka an agouti tabby) and the exotic, domesticated wildcat the servaline (savannah pattern), which sells for $20,000 or thereabouts.

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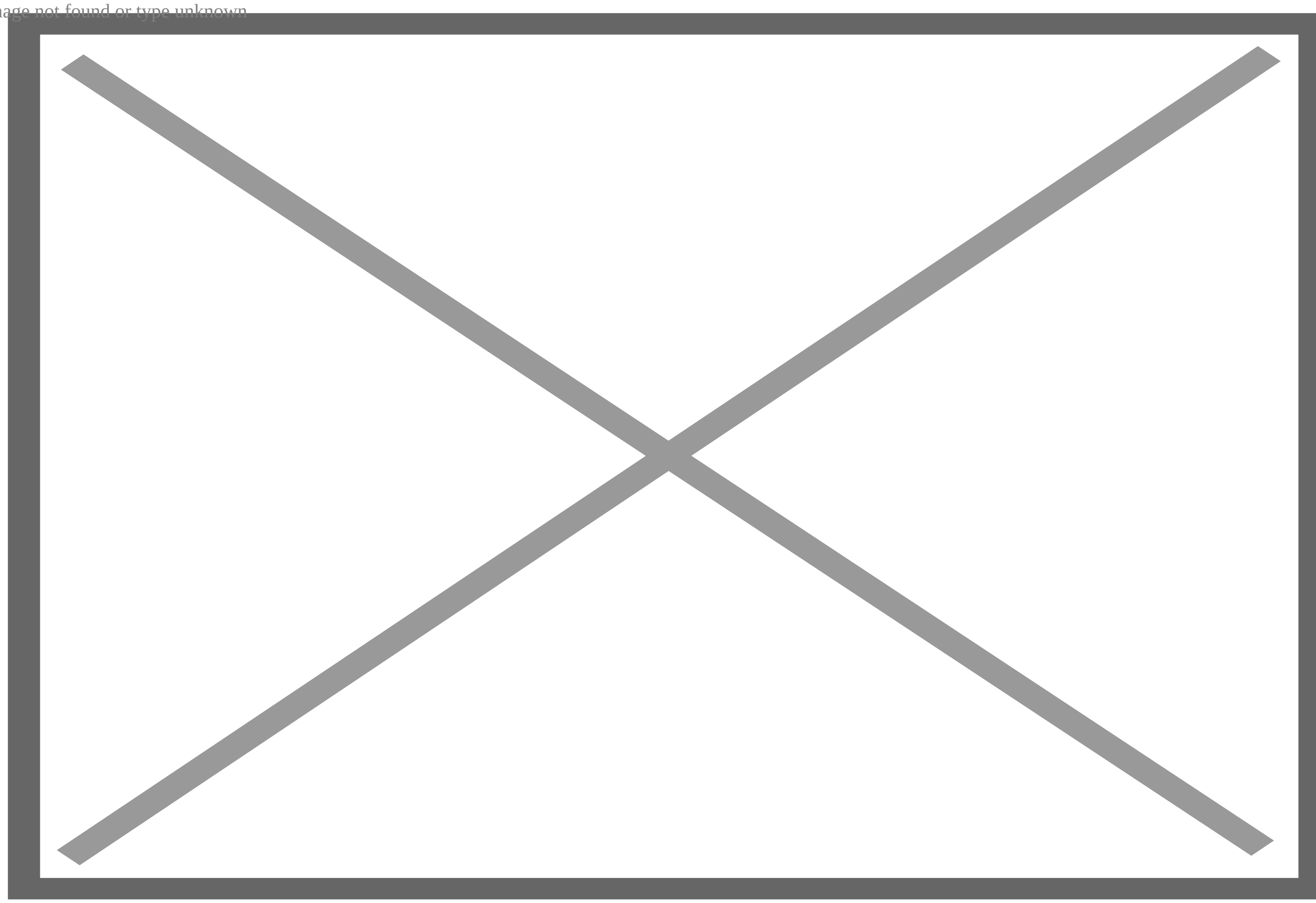

Abyssinian cat. Credit: ASPCA

Barsh explains. “In Abyssinian cats with the ticked phenotype, the consensus has been that there is an absence of the dark tabby markings. Based on our new findings, we propose that instead the typical tabby markings have increased in number and decreased in size to the extent that they are just not readily apparent.”

The mutations that disguise the tabby stripes in Abyssinians abolish the gene’s function. “Loss-of-function” has been a standard term in genetics for decades; it wasn’t invented to describe nefarious COVID research.

Summed up Kaelin, “Our analysis identifies a network of molecules involved in pattern formation. Several of the molecules function coordinately as activators and inhibitors, exactly as Alan Turing predicted 70 years ago.”

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