



GENOMICS

Bird genomes give new perches to old friends

Comparing genomes clarifies family relations and pinpoints genes for song learning

By Elizabeth Pennisi

With chicks that have claws on their wings and a digestive system that resembles a cow's, the pheasant-sized hoatzin that roams the Amazon has always puzzled those trying to place it within the avian family tree. But now researchers believe they have pinned down the odd bird's relatives—just one of the many findings revealed this week from a massive international project analyzing the sequenced genomes of 48 bird species representing nearly every order of bird. The fruits of this effort—eight papers this week in *Science* and more than 20 additional reports in several other journals—represent the biggest advance in avian biology in decades. “This has not been done for any other organism before,” says Per Ericson, an evolutionary biologist at the Swedish Museum of Natural History in Stockholm. “It's mind-blowing.”

The effort, involving 200 people from 80 labs and several months of supercomputer time, has yielded the most definitive avian family tree yet. It has also pinpointed gene networks underlying the traits that make birds birds, such as feathers and beaks instead of teeth. In one provocative finding, a team has identified

the gene network that underlies complex singing in birds—and found that the same network operates in humans, where it is presumably crucial to language.

Curiosity about vocal learning was what led Erich Jarvis to coordinate the project in the first place. Jarvis, who is a neurobiologist at Duke University in Durham, North Carolina, wanted to know how many times the ability to imitate sounds had evolved in birds. But he didn't trust the existing family trees, which were built on comparisons of less than a dozen genes or several thousand bases.

Jarvis began thinking that the solution was a tree based on whole genomes—which provide millions of bases for comparison. And at the same time, other researchers had begun an ambitious effort to sequence 10,000 vertebrate species, and China's sequencing giant, BGI, had agreed to kick that off by tackling 101 species, including 11 birds. In 2010, Jarvis and Tom Gilbert, a paleogenomicist at the University of Copenhagen, helped convince BGI and its collaborators to increase the number of bird species they did to 43. By the end of 2011, sequencing of 48 in total was done.

That proved the easy part. When the researchers tried to build the new avian family tree, “we were shocked to find we couldn't

With 48 bird genomes in hand, researchers discovered that hummingbirds (*top*), budgerigars (*right*), and zebra finches (*bottom*) sing using the same network of genes as humans talking.

get a solid answer,” Jarvis recalls. As the consortium developed more sophisticated bioinformatics tools to analyze the genome data, they discovered that protein-coding genes by themselves were not the most reliable for building good trees. The noncoding regions within or between genes, called introns, gave better answers. And although the group had access to supercomputers, they still had to come up with a way to allocate the analysis to the machines' many microprocessors. “It took 3 years to iron out the kinks,” Gilbert says.

The new avian tree, described on page 1320 by Jarvis's team, resembles one built in 2008 by others, based only on introns from 169 species. Some of the branches in that earlier tree were heretical at the time, but “a lot of the same relationships hold up even when you have access to entire genomes,” says Sushma Reddy, an evolutionary biologist at Loyola University Chicago in Illinois who took part in the earlier analysis. For example, the 2008 paper indicated that doves, sandgrouses, and flightless Madagascan

birds called mesites are all closely related and resemble the ancestors of so-called modern birds, which include all existing species except for chickens, ducks, and flightless birds such as the ostrich. Likewise, in 2008, few accepted a claim that flamingos and grebes are close relatives, but the new work confirms the link.

In contrast with the 2008 tree, the new analysis identifies the doves, sandgrouses, and mesites as close relatives of flamingos and grebes, creating a different view of the early modern birds. “That’s the key phylogenetic finding,” says co-author Joel Cracraft, an evolutionary biologist at the American Museum of Natural History in New York City. And it reveals that the hoatzin is not a relative of the cuckoos—which it faintly resembles—but instead belongs with cranes and plovers.

The results go beyond family relations, showing, for example, that song learning evolved three separate times: on the branches leading to songbirds, hummingbirds, and parrots. And on page 1311, Guojie Zhang of BGI in Shenzhen, China, and his colleagues confirm that bird genomes are smaller than other vertebrate genomes. They have less repetitive DNA and have also lost 7% of the

genes—58 million bases in total—found in a lizard cousin, the anole. Comparisons with other nonavian species revealed bird-specific genes, such as those for keratin proteins likely involved in feather development, Zhang says. “We can take an evolutionary view of the genome the way we have an evolutionary view of anatomy,” says Jarvis co-author Stephen O’Brien, a geneticist at St. Petersburg State University in Russia.

Take Jarvis’s vocal learning question. For decades, researchers have known that human speech and avian song learning are similar behaviors. Jarvis and others have since shown that songbirds, parrots, hummingbirds, and humans use equivalent forebrain regions for these processes as well. One study even showed that both feathered and nonfeathered vocal learners rely on a gene called *FOXP2*. The new avian genomes have now enabled Jarvis, Andreas Pfenning of the Massachusetts Institute of Technology in Cambridge, and their colleagues to assess whether the same gene networks always underlie vocal learning.

Pfenning first compared patterns of gene activity in different parts of the brains of the parakeet, hummingbird, and zebra finch, which represent the three avian lineages in which imitative singing arose. They also studied two birds that lack vocal learning,

the ring dove and quail. The same pattern emerged in all three song-learning birds, but not in the quail and the dove.

The researchers went on to compare the song-related pattern with other researchers’ maps of gene activity in the brains of humans and of macaques—which don’t have vocal communication as complex as human speech. Similar genes were at work in the human brain regions associated with speech, they report on page 1333, while the pattern was missing in the macaque. “It really nicely matches the behavioral and anatomical convergences,” says Kelsey Martin, a neurobiologist at the University of California, Los Angeles (UCLA). To Martin, the gene network highlighted by the work resembles those that other animals use for spatial learning. “It suggests there’s a core pattern of gene expression for learning,” she says.

On page 1334, Jarvis’s lab, led by Osceola Whitney, offers a closer look at gene activity patterns in the brains of adult zebra finches

after they had been singing. The team identifies more than 2700 genes regulated by singing, with different sets of them active in each of the four song-related brain structures. “These two [papers] are both tours de force,” says Stephanie White, a UCLA

neuroscientist. With them, “the songbird may be getting its recognition for what it has to offer the speech and language community.”

Though the avian genome project was ambitious, Jarvis and his colleagues view it as just a first step. Pfenning and Whitney, for example, now plan to probe the functions of the genes newly tied to vocal learning. And the bird family tree still needs refining.

In total, six of the 46 nodes, or branch points, in the new tree remain uncertain, Cracraft notes. One reason for the ambiguity is that birds, like mammals, underwent rapid diversification 66 million years ago, when the disappearance of most dinosaurs opened up many niches for new species to fill. The swift pace of evolution resulted in genomes that are a patchwork of novel and shared regions, making them hard to analyze and leaving some questions still unanswered—where owls belong, for example.

It will take more bird genomes to solve many of the puzzles, says Shannon Hackett, an ornithologist at the Field Museum in Chicago and lead author of the 2008 bird tree. “We’re as close as we’ve ever been to the true phylogeny,” Ericson says. “[But] we are not there yet.” That may not take long: At BGI, the genomes of about 200 more birds are done and waiting to be analyzed, with thousands more planned. ■

“We’re as close as we’ve ever been to the true phylogeny.”

Per Ericson. Swedish Museum of Natural History

INFECTIOUS DISEASES

The genetics of resistant malaria

Studies confirm changes in suspected gene confer resistance to artemisinin

By Gretchen Vogel

The region around the Mekong River delta is infamous for its malaria parasites. Twice already—in the 1950s and the 1960s—they have developed resistance to key drugs, and the underlying mutations spread inexorably around the world, forcing public health officials to find new ways to fight the disease. Now it is happening again. Over the last decade, artemisinin, the most powerful drug available to cure malaria, has failed in more and more people in Cambodia, Myanmar, Vietnam, Laos, and border regions of Thailand. Researchers and public health experts worry that history will repeat itself and resistant parasites will go global. With any new drugs still years away from clinical use, that would be a disaster.

Money has poured into efforts to contain and eliminate the region’s resistant strains, so far without success (*Science*, 14 May 2010, p. 844). This week, two papers online in *Science* offer new insights into the genes behind the threat. One helps explain which genetic changes allow the parasites to survive the drug (<http://scim.ag/JStrainer>). The other details how the mutations protect the parasites: by slowing their development and ramping up their defenses against the kinds of protein damage that artemisinin seems to cause (<http://scim.ag/SMok>). Such insights should help scientists identify and track resistant parasites and perhaps find better ways to kill them. The studies are “extremely interesting and important,” says Pascal Ringwald, who coordinates the malaria drug resistance and containment program for the World Health Organization in Geneva, Switzerland.

Artemisinin is derived from sweet wormwood, a plant used for centuries in China to fight fevers. In the 1970s, Chinese researchers discovered that artemisinin made a powerful malaria drug. It, and several related derivatives, have since helped drive spectacular drops in the number of malaria deaths worldwide. The drug is easy to administer,