# Two genes help an embryo pick sides

The growing human embryo quickly learns to tell left from right. That's vital, since the outward bilateral symmetry of a human body isn't matched internally. The heart, stomach, and spleen reside on the left, while the liver prefers the right. Even paired organs such as the lungs exhibit some asymmetry; the right lung has three lobes, while the left has two.

To understand how this left-right axis arises, scientists have sought the mutated genes responsible for the rare cases in which the internal organs of people, or mice, are flipped left to right or positioned randomly on either side of the body. They've now found two such genes.

"These are the first demonstrations of single-gene defects that lead to naturally occurring left-right patterning abnormalities in human and mouse," writes Deepak Srivastava of the University of Texas Southwestern Medical Center at Dallas in the November NATURE GENETICS.

Brett Casey of the Baylor College of Medicine in Houston, who describes one of the new genes, grew fascinated with left-right asymmetry many years ago when he performed an autopsy on an infant whose internal organs, particularly the heart, were askew. At the autopsy, a colleague told Casey about a large family in which newborn boys frequently had similar problems.

After studying the family's history, Casey concluded that a mutated gene must exist on the X chromosome. In 1993, he narrowed its location to a small region of the chromosome. In the November NATURE GENETICS, Casey and his colleagues identify the gene and describe mutations found in the original family and in other people with left-right developmental anomalies.

The newfound gene encodes a protein called ZIC3, whose amino acid sequence suggests that it binds to DNA and regulates gene activity. The investigators do not yet know how ZIC3 contributes to formation of left-right asymmetry, but they think its gene acts early in the process.

The discovery of the gene may help unearth additional genes that create the bilateral axis. Mutations in ZIC3's gene account for only a small percentage of people with abnormal left-right asymmetry.

"There are obviously too many genes involved in this complicated cascade to think that any one will be the dominant player," says Casey.

By studying two strains of mice in which some animals are born normal, some with their internal organs inverted completely, and some with organs in random positions, researchers have found a second gene that seems to play a role in left-right asymmetry.

"We think this gene may be involved in the initial determination of left-right asymmetry," says Martina Brueckner of the Yale University School of Medicine.

The gene, described in the Oct. 30 NATURE, encodes a dynein, a protein that forms huge complexes which can serve as molecular motors. Dynein complexes usually interact with long intracellular rods called microtubules, transporting cargo along them or bending them.

Since microtubules have distinguishable ends and dyneins always move toward the same end, the microtubules may act as one-way streets that establish an original left-right asymmetry.

"You've got to have something asymmetric to create new asymmetry. You can't create it out of nothing," Brueckner notes. "We're assuming that the original asymmetric molecule is the microtubule and that the dynein takes that asymmetry and converts it into cellular asymmetry."

Determining how that conversion takes place is next on the agenda, she adds. *—J. Travis*

muscles connected to the ribs draw air into a network of sacs located in the abdomen—an extremely efficient system for supplying the oxygen needed during flight.

Ruben's team contends that the pubic bones of theropod fossils closely resemble those of crocodiles, providing evidence that dinosaurs had a piston-driven diaphragm.

They gleaned additional clues about the breathing mechanism of dinosaurs from a Chinese dinosaur called *Sinosauropteryx* (SN: 5/3/97, p. 271). One fossil of this animal preserves evidence of internal organs that normally don't show up in dinosaur remains. These soft-tissue impressions in the chest cavity of *Sinosauropteryx* match the shape and placement of the diaphragm in crocodiles, offering further hints that dinosaurs breathed like crocodiles, says Ruben.

He and his colleagues argue that birds could not have evolved from animals equipped with diaphragms because the two breathing systems work in incompatible ways.

That conclusion supports the findings of another study, published in the Oct. 24 SCIENCE, which focuses on the hand bones of birds and dinosaurs. All land-dwelling vertebrates—from swallows to snakes—descended from ancestors that had five digits on each limb. Most theropod dinosaurs lost two of the digits on their hands during evolution, a pattern broadly similar to the three digits in the wings of birds.

Ann C. Burke and Alan Feduccia of the University of North Carolina at Chapel Hill contend, however, that the resemblance between bird wings and dinosaur hands is superficial. The researchers studied the embryos of birds, turtles, and alligators to decipher how the digits of the hands grow.

They observed that the fourth digit develops first in all modern vertebrate embryos that have five digits. This finding enabled them to number the developing digits in bird embryos. They determined that birds lack the first and fifth digits of the hand. Dinosaurs, though, lacked the fourth and fifth digits.

"The implication is that it's virtually impossible to imagine how dinosaurs could have given rise to birds," says Feduccia.

Most paleontologists dismiss the impact of the new findings and argue that the evidence linking birds to dinosaurs is growing (SN: 8/23/97, p. 120).

Kevin Padian of the University of California, Berkeley criticizes the hand study. Burke and Feduccia's interpretation of bird hands rests on rules of development derived from modern animals, and Padian says that such assumptions cannot explain the pattern seen in dinosaurs. "The [hand study] neglects the fact that theropods clearly violate all the laws that they regard as inviolable. It's complete nonsense."

Ruben/SCIENCE

*The chest of a dinosaur called* Sinosauropteryx *may hold evidence of an internal diaphragm (arrows) used in breathing.*

Paleontologist Lawrence M. Witmer of Ohio University in Athens calls the lung study intriguing, but he questions the conclusions. Theropod dinosaurs walked on two feet and had an immobile pubic bone, whereas crocodiles walk on four feet and have a pubic bone that shifts during movement. "The pelvic structures of crocodiles and dinosaurs were quite different. I'm not sure how to interpret the similarities that we see."

Witmer also says that the *Sinosauropteryx* specimen is squashed, making it difficult to interpret the tissue preserved in its chest cavity. *—R. Monastersky*