# Snails and humans use same genes to tell right from left

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Right- and left-handed shells from the collections of the UC Berkeley Natural History Museums. Credit: Nipam Patel/UC Berkeley

(PhysOrg.com) -- Biologists have tracked down genes that control the handedness of snail shells, and they turn out to be similar to the genes used by humans to set up the left and right sides of the body.

The finding, reported online in advance of publication in *Nature* by University of California, Berkeley, researchers, indicates that the same genes have been responsible for establishing the left-right asymmetry of animals for 500-650 million years, originating in the last common ancestor of all animals with bilateral body organization, creatures that include everything from worms to humans.

"Previous studies indicated that the methods for breaking left-right

symmetry in animals seem to differ widely, so there was nothing suggesting that the common ancestor of humans, snails and other bilateral organisms had a common strategy for left-right asymmetry," said Nipam H. Patel, UC Berkeley professor of integrative biology and of molecular and cell biology, and an investigator of the Howard Hughes Medical Institute.

"Indeed, scientists thought that one of the genes that is critical for setting up left-right asymmetry in vertebrates was only present in vertebrates and related groups and not in any other animals," said UC Berkeley post-doctoral fellow Cristina Grande. "But we found that gene in snails, which has a lot of evolutionary implications. This cellular pathway was present already in the ancestors of most animals."

The finding, the researchers say, could help to track down the ultimate cause of symmetry-breaking in snails and other organisms, and the cascade of gene activation that leads to complex shapes, such as coiled shells.

Despite humans' superficial symmetry - our left and right sides appear to be mirror images - we are anything but symmetric. Most people's hearts are towards the left side of the body, which means the left lung is slightly smaller to make room for the heart, and our intestines are arranged in an asymmetric coil. This asymmetry is unrelated to being left- or right-handed, a preference determined in the brain.

While a small percentage of people have their insides flipped, their overall internal arrangement is a mirror image of the norm. Anyone with a random arrangement of internal organs would be dead, Patel said, because his or her organs wouldn't fit together properly.

Other vertebrates are the same. In fact, scientists have identified a gene called "nodal" that - in all vertebrates checked to date - is expressed on

the left side of the body and necessary to set up left-right asymmetry. If nodal doesn't work or is knocked out, internal organs are jumbled and the organism dies.

"In vertebrates, a set of genes tells the body it has to form a heart toward one side, and nodal is one of those genes," said Grande, who recently took a position at the Centro de Biología Molecular "Severo Ochoa" in Madrid, Spain.

"There are a lot of asymmetric molecules in the body, that is, molecules that are active on only one side of the body, but nodal is always expressed on the left side in all vertebrates, which is evidence of a conserved pathway," Patel said.

Genes similar to nodal have been found throughout the so-called deuterostomes, one of the three subgroups of bilateral animals that includes not only vertebrates, but also sea urchins and sea squirts.

But the most common lab animals, fruit flies and nematodes, apparently do not have a gene like nodal, despite their asymmetry. As a result, biologists have assumed that fruit flies and all other non-deuterostomes - snails included - use some other mechanism to establish right and left. Fruit flies and nematodes are in the clade Ecdysozoa, while snails and worms are members of the clade Lophotrochozoa.

Grande approached Patel four years ago to collaborate in a test of this assumption in snails, which have an obvious and easy-to-check handedness: Their shell either coils right, like a standard screw, or left. Patel, a biologist who focuses on the genetics and evolution of crustacean and insect development, such as the formation of segments and appendages in shrimps and crabs, invited Grande to join his lab, even though he had never before worked with snails.

Snail handedness becomes obvious very early in the embryo, Patel said. When the four-cell embryo divides to become eight cells, the new cells blossom from their predecessors in a clockwise spiral, in which case the snail ultimately forms a right-handed, or dextral, shell; or a counter-clockwise spiral, creating a left-handed, or sinistral, shell. Biologists had earlier shown that this decision is made by the mother snail, which dumps many proteins and RNA molecules into the egg to jump-start embryonic development and, in the process, imprints her offspring with specific characteristics.

"No one knows what that maternal gene is, and you can't track it down using the standard approach of looking for genetic markers because there are not yet enough markers in snails, so we looked for any molecular entry into the cause of asymmetry," Patel said.

That proved to be the genome of the marine limpet Lottia gigantea, a right-handed snail whose genome was sequenced recently by the Department of Energy's Joint Genome Institute (JGI) in Walnut Creek, Calif. Grande looked for genes in Lottia similar to nodal, and found one, as well as a gene analogous to the gene, Pitx, which is activated by nodal and also involved in setting up left-right asymmetry in vertebrates.

She used this information to look for and find similar genes in the left-handed snail Biomphalaria glabrata, the fresh-water host of the parasite that causes schistosomiasis. Experimental tests showed that nodal and Pitx were active or expressed on the right side of embryos in the right-handed snail Lottia, and on the left side in the left-handed snail Biomphalaria.

A key test of the critical nature of nodal involved treating the snails with a chemical known to inhibit the activity of nodal. While most treated snails died, some lost the asymmetric expression of Pitx and, most strikingly, developed a straight shell, Patel said.

Grande has since found analogs of nodal in the genome of the marine worm Capitella, which was sequenced by JGI, suggesting that nodal is active throughout the Lophotrochozoa.

"Everybody thought using nodal and Pitx for left-right asymmetry was an invention of this one group, the deuterostomes," Grande said. "The fact that we find them setting up asymmetry in snails and worms means that is not true; the ancestor of all bilaterians already used these genes to set up left-right asymmetry."

Because the ancestral snail was right-handed and thus, presumably, expressed nodal and Pitx on the right side of the body - similar to sea urchins, an early offshoot of the deuterostome branch leading to humans - the authors propose that the common ancestor of all bilateral animals had left-right asymmetry controlled by nodal and Pitx expressed on the right side of the body.

The discovery also could help Grande and Patel track down the maternal factors that ultimately determine handedness in snails.

Provided by University of California - Berkeley