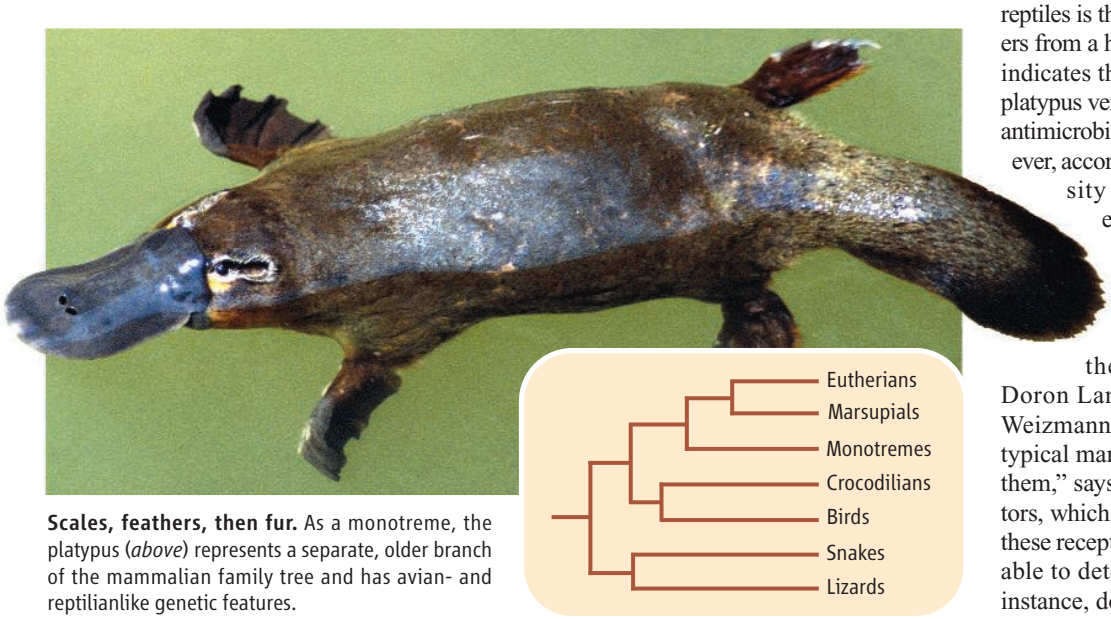
GENOMICS

Genome Speaks to Transitional Nature of Monotremes

Zoologists have always thought that the platypus was a missing link in the chain between reptiles and mammals. The furry beaverlike mammal lays small, round, leathery eggs from a reptilelike cloaca, and the hatchlings slurp milk from modified sweat glands off the mother's stomach. Now an analysis of the genome reveals how platypus DNA is also an amalgam of mammalian and reptilian features. Wes Warren of the Genome Sequencing Center at Washington University in St. Louis, Missouri, and 100 authors describe these features in the 8 May issue of *Nature*.

Mammals divide into three groups. Most—from whales to shrews—are eutherians with highly developed placentas. Some are marsupials, which, like kangaroos and opossums, give birth to and then provide milk for immature young outside the womb. The platypus and its cousins, the echidnas, are all that remains of the monotremes, which branched from the marsupials and eutherians some 166 million years ago. "If there is something between reptiles and mammals, it's monotremes," says Stephen O'Brien of the U.S. National Cancer Institute in Frederick, Maryland.



Scales, feathers, then fur. As a monotreme, the platypus (*above*) represents a separate, older branch of the mammalian family tree and has avian- and reptilianlike genetic features.

The new genome sequence confirms the ancient split between monotremes and other mammals. "It's a missing part of the big evolutionary genetics puzzle," O'Brien adds.

The clearest traces of the journey from reptile to mammal come from tracking the yolk and milk genes. Chickens have three vitellogenin egg yolk genes; the platypus has just one left. But the casein milk protein genes that mammals have but reptiles don't are all there. And just as in other mammals, in platypus, they are clustered next to the tooth enamel genes from which they are thought to have evolved, the researchers report.

The story of the platypus' march away from the reptilian world is also told in the sex chromosomes. According to Jenny Graves of the Australian National University in Canberra, sex chromosome-wise, "they do it like a chicken." Typically, male mammals have X and Y sex chromosomes, with the Y chromosome carrying a male sex-determining gene called *SRY*. Male birds have two Z chromosomes, which carry a gene called *DMRT1* that is involved in male gender determination in fruit flies, humans (although it's not on the Y chromosome), and, most likely, birds. At first, cytologists thought the platypus was like the mammal: It had X and Y chromosomes, albeit five pairs of them, and it was thought that they were essentially humanlike. Then in 2004, Graves's lab discovered that one of these "X" chromosomes carried *DMRT1*. The genome sequence now shows that one of the platypus X chromosomes (X5) has more than just that one bird gene: It's almost entirely equivalent to the chicken Z chromosome. "We suspect *DMRT1* is involved in the platypus sex determination," says Frank Grützner, Graves's former postdoc, who now heads a lab at the University of Adelaide in Australia.

Gene regulation also seems to be more primitive, as platypus genes do not show parental imprinting. In marsupials and eutherians, imprinted genes are dialed to different settings and sometimes shut down altogether, depending on whether they originated from the male's sperm or the female's egg. According to Andrew Pask and Marilyn Renfree of the University of Melbourne, the distribution of repetitive DNA elements in this monotreme may explain the difference. As in other mammals, about 50% of the platypus genome is comprised of repetitive DNA. But although these repeats pepper imprinted genes in marsupials and man, they are largely absent from the equivalent genes in platypus. "Repetitive elements may have been useful for establishing imprinting in the other mammals," Pask suggests.

Another feature the platypus shares with reptiles is that it makes venom, which it delivers from a hind leg spur. The genome analysis indicates that, like snake and lizard venom, platypus venom appears to have evolved from antimicrobial genes known as defensins. However, according to Kathy Belov of the University of Sydney, the platypus genes evolved independently.

A big surprise is the platypus's large endowment of a particular class of vomeronasal receptor genes—about 1000 of them—based on the analysis by Doron Lancet and Tsviya Olender of the Weizmann Institute in Rehovot, Israel. "A typical mammal has a couple of hundred of them," says Lancet. Unlike olfactory receptors, which detect only airborne compounds, these receptors are more like nasal taste buds, able to detect nonvolatile compounds. For instance, dogs taste pheromones in urine by touching their tongue to the vomeronasal organ in their upper palate. Because the platypus spends 90% of its time in water, Lancet speculates that the platypus uses these receptors for detecting water-soluble odorants.

"Looking at the venom, egg, and milk genes is really interesting, but as with comparisons between opossum, mouse, and human genomes, the protein-coding sequences don't explain the interesting developmental transitions," notes John Mattick of the University of Queensland in Brisbane, Australia. Differences in gene regulation, most likely, provide the answer. And in this respect, the platypus researchers still have their work cut out for them, he adds: "[Gene regulation] information is there but is not yet understood."

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Published by AAAS

Monotremes are one of the three main groups of living mammals, along with placentals (Eutheria) and marsupials (Metatheria). The monotremes are typified by structural differences in their brains, jaws, digestive tract, reproductive tract, and other body parts compared to the more common mammalian types. In addition, they lay eggs rather than bearing live young, but, like all mammals, the female monotremes nurse their young with milk. This monotreme exhibits a fascinating combination of reptilian and mammalian characters. For example, platypuses have a coat of fur adapted to an aquatic lifestyle; platypus females lactate, yet lay eggs; and males are equipped with venom similar to that of reptiles. Analysis of the first monotreme genome aligned these features with genetic innovations. We find that reptile and platypus venom proteins have been co-opted independently from the same gene families; milk protein genes are conserved despite platypuses laying eggs; and immune gene family expansions are directly related to platypus biology. Expansions of protein, non-protein-coding RNA and microRNA families, as well as repeat elements, are identified. *Genome Technology Branch and â€ NISC, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892; Â§Clemson University Genomics Institute, Department of Genetics and Biochemistry and Life Science Studies, Clemson University, Clemson, SC 29634; Â¶Benaroya Research Institute at Virginia Mason, Seattle, WA 98101; and â^¥Arizona Genomics Institute, Department of Plant Sciences, University of Arizona, Tucson, AZ 85721.Â These ancient mammalian genomes are characterized by unusual architectural features with respect to G + C and repeat content, as well as compression relative to human.Â The unique genomic properties of marsupials and monotremes make their sequences of...