Team proposes new model for snake venom evolution

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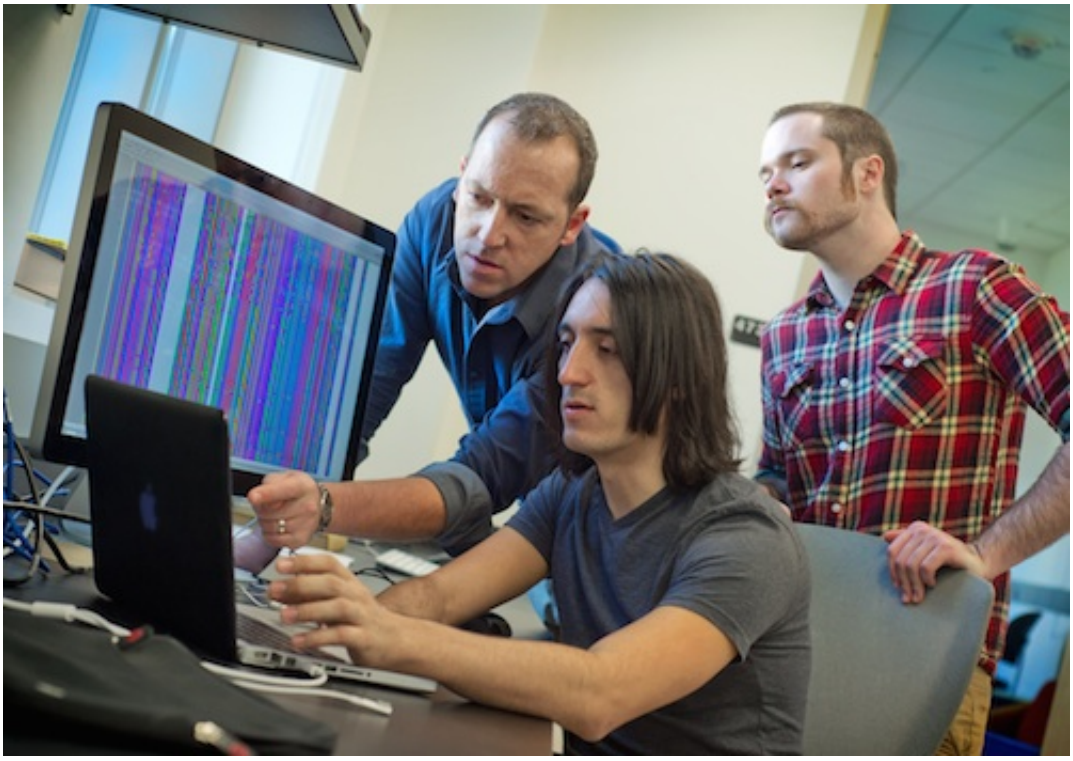

UT Arlington Assistant Professor of Biology Todd Castoe with graduate students Jacobo Reyes-Velasco and Drew Schield. Credit: UT Arlington

Technology that can map out the genes at work in a snake or lizard's mouth has, in many cases, changed the way scientists define an animal as venomous. If oral glands show expression of some of the 20 gene families associated with "venom toxins," that species gets the venomous label.

But, a new study from The University of Texas at Arlington challenges that practice, while also developing a new model for how snake venoms came to be. The work, which is being published in the journal *Molecular Biology and Evolution*, is based on a painstaking analysis comparing groups of related genes or "gene families" in tissue from different parts of the Burmese python, or Python molurus bivittatus.

A team led by assistant professor of biology Todd Castoe and including researchers from Colorado and the United Kingdom found similar levels of these so-called toxic gene families in python oral glands and in tissue from the python brain, liver, stomach and several other organs. Scientists say those findings demonstrate much about the functions of venom genes before they evolved into venoms. It also shows that just the expression of genes related to venom toxins in oral glands of snakes and lizards isn't enough information to close the book on whether something is venomous.

"Research on venom is widespread because of its obvious importance to treating and understanding snakebite, as well as the potential of venoms to be used as drugs, but, up until now, everything was focused in the venom gland, where venom is produced before it is injected," Castoe said. "There was no examination of what's happening in other parts of the snake's body. This is the first study to have used the genome to look at the rest of that picture."

Learning more about venom evolution could help scientists develop better anti-venoms and contribute to knowledge about gene evolution in humans

Castoe said that with an uptick in genetic analysis capabilities, scientists are finding more evidence for a long-held theory. That theory says highly toxic venom proteins were evolutionarily "born" from non-toxic genes, which have other ordinary jobs around the body, such as

regulation of cellular functions or digestion of food.

"These results demonstrate that genes or transcripts which were previously interpreted as 'toxin genes' are instead most likely housekeeping genes, involved in the more mundane maintenance of normal metabolism of many tissues," said Stephen Mackessy, a co-author on the study and biology professor at the University of Northern Colorado. "Our results also suggest that instead of a single ancient origin, venom and venom-delivery systems most likely evolved independently in several distinct lineages of reptiles."

Castoe was lead author on a 2013 study that mapped the genome of the Burmese python. Pythons are not considered venomous even though they have some of the same genes that have evolved into very toxic venoms in other species. The difference is, in highly venomous snakes, such as rattlesnakes or cobras, the venom gene families have expanded to make many copies of those shared genes, and some of these copies have evolved into genes that produce highly toxic venom proteins.

"The non-venomous python diverged from the snake evolutionary tree prior to this massive expansion and re-working of venom gene families. Therefore, the python represents a window into what a snake looked like before venom evolved," Castoe said. "Studying it helps to paint a picture of how these gene families present in many vertebrates, including humans, evolved into deadly toxin encoding genes."

Jacobo Reyes-Velasco, a graduate student from Castoe's lab, is lead author on the new paper. In addition to Castoe and Mackessy, other co-authors are: Daren Card, Audra Andrew, Kyle Shaney, Richard Adams and Drew Schield, all from the UT Arlington Department of Biology; and Nicholas Casewell, of the Liverpool School of Tropical Medicine.

The paper is titled "Expression of Venom Gene Homologs in Diverse

Python Tissues Suggests a New Model for the Evolution of Snake Venom." It is available online here: http://www.ncbi.nlm.nih.gov/pubmed/25338510.

The research team looked at 24 gene families that are shared by pythons, cobras, rattlesnakes and Gila monsters, and associated with venom. The traditional view of venom evolution has been that a core venom system developed at one point in the evolution of snakes and lizards, referred to as the Toxicofera, and that the evolution of highly venomous snakes, known as caenophidian snakes, came afterward. But little explanation has been given for why evolution picked just 24 genes to make into highly toxic venom-encoding genes, from the 25,000 or so possible.

"We believe that this work will provide an important baseline for future studies by venom researchers to better understand the processes that resulted in the mixture of toxic molecules that we observe in venom, and to define which molecules are of greatest importance for killing prey and causing pathology in human snakebite victims," Casewell said.

When they looked at the python, the team found several common characteristics among the venom-related gene families that differed from other genes. Compared with other python gene families, venom gene families are "expressed at lower levels overall, expressed at moderate-high levels in fewer tissues and show among the highest variation in expression level across tissues," Castoe said.

"Evolution seems to have chosen what genes to evolve into venoms based on where they were expressed (or turned on), and at what levels they were expressed," Castoe said.

Based on their data, the new paper presents a model with three steps for venom evolution. First, these potentially venomous genes end up in the oral gland by default, because they are expressed in low but consistent

ways throughout the body. Then, because of natural selection on this expression in the oral gland being beneficial, tissues in the mouth begin expressing those genes in higher levels than in other parts of the body. Finally, as the venom evolves to become more toxic, the expression of those genes in other organs is decreased to limit potentially harmful effects of secreting such toxins in other body tissues.

The team calls its new model the Stepwise Intermediate Nearly Neutral Evolutionary Recruitment, or SINNER, model. They say differing venom levels in snakes and other animals could be traced to the variability of where different species, or different genes within a species, are along the continuum between the beginning and end of the SINNER model.

Castoe said the next step in the research would be to examine the genome of highly venomous snakes to see if the SINNER model bears out. For now, he and the rest of the team hope that their findings about the presence of venom-related genes in other parts of the python change some thinking on what species are labeled as venomous.

"What is a venom and what species are venomous will take a lot more evidence to convince people now," Castoe said. "It provides a brand new perspective on what we should think of when we look at those oral glands."

Provided by University of Texas at Arlington