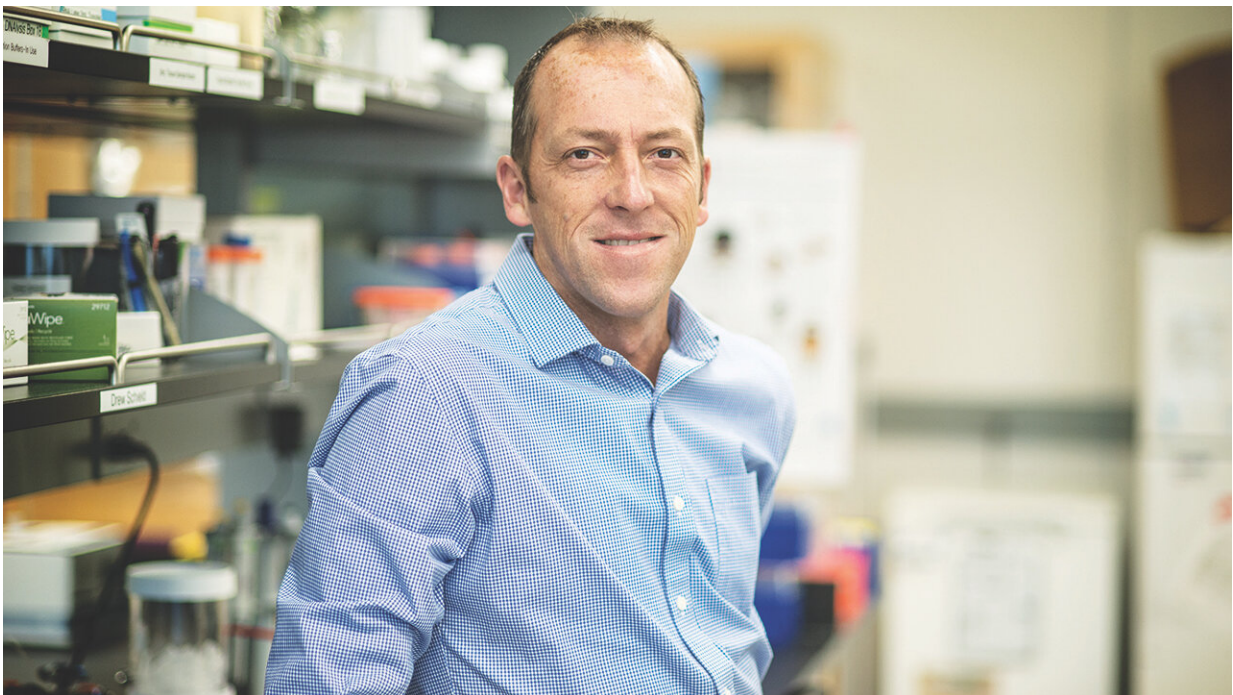


# Biologists show new insights into chromosome evolution, venom regulation in snakes

April 1 2019, by Herb Booth

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Todd Castoe. Credit: UT Arlington

How do snake genomes direct the production of deadly venom toxins and other key extreme features of snakes?

Snake genomes encode the secrets to their unique and often extreme

adaptations, but genome resources for snakes and other reptiles have lagged behind their mammal and bird counterparts.

In a new paper, a team of biologists led by Todd Castoe, associate professor of biology at The University of Texas at Arlington, addressed these questions by generating and analyzing the first most complete chromosome-level genome for a [snake](#)—the prairie rattlesnake (*Crotalus viridis*). Their work, "The origins and evolution of chromosomes, dosage compensation, and mechanisms underlying [venom](#) regulation in snakes," is published in the April issue of *Genome Research*, the scientific journal published by Cold Spring Harbor Laboratory.

UTA co-authors include Drew Schield, Daren Card, Nicole Hales, Blair Perry, Giulia Pasquesi, Richard Adams, and Andrew Corbin, all current or former members of Castoe's lab; doctoral student Balan Ramesh; biology Professor Esther Betrán; and biology Associate Professor Jeffery Demuth. Other co-authors include UTA doctoral graduates Heath Blackmon, Texas A&M University, and Jesse Meik, Tarleton State University.

The team analyzed the rattlesnake genome to investigate diverse features of vertebrate and snake biology, including the evolution of genome structure, how some chromosomes became sex chromosomes during snake evolution, and how multiple layers of genome organization drive the precise regulation of venom.

The paper provides the first chromosome-level assembly of a reptile genome, and provides new evidence that microchromosomes present in some vertebrates may functionally interact in the nucleus in unique and previously unknown ways.

"Despite extensive research on snake venom, very little is known about the genomic basis of this extreme adaptation and how venom has

evolved over time," Castoe said. "While venom is of major interest among snake biologists, the regions of snake genomes that harbor the genes to make venom have been among the most challenging regions of the genome to sequence and assemble accurately."

By leveraging cutting-edge genome sequencing methods, the team was for the first time able to generate well-assembled snake venom genes. This provided new genomic context for how venom genes have evolved through a process called tandem duplication, leading to discrete clusters of venom genes in the genomic landscape. They also discovered that many venom genes are found on microchromosomes, which are densely packed with genes and have other distinctive features.

The team also demonstrated that microchromosomes, which are absent in mammals but present in birds and many reptiles, have fundamentally distinct structure and function—providing evidence that the genomes of many vertebrates do not necessarily "work the same" as the genomes of mammals.

Researchers addressed how snakes are able to secrete venom via the regulation of venom genes exclusively in the venom gland, and not in other organs. They leveraged new cutting-edge sequencing approaches, called Hi-C sequencing, which captures information about interactions between different genomic regions in the nucleus, to analyze how genome organization directs this precise regulation of venom genes.

They found that venom gene regions are isolated within distinct chromosomal structures called TADs, or topologically associating domains, in venom-secreting cells. These TADs form loops in the genomic DNA to localize the gene regulation machinery specifically to the genes for making venom, leading to a highly precise pattern of gene expression only in the venom gland. This finding provides evidence of a previously unknown mechanism regulating [snake venom](#) secretion, and

exciting links between genome structure and function.

While humans and other mammals have X and Y sex chromosomes, the rattlesnake has Z and W sex chromosomes. In ZW systems, males have two Z chromosomes and females have one Z and one W chromosome. Rattlesnake sex chromosomes are highly differentiated and exhibit many distinct characteristics compared to non-sex chromosomes, called autosomes. Highly differentiated sex chromosomes often require mechanisms to equalize gene expression between genetic sexes to ensure proper genome function—these are called dosage compensation mechanisms.

Snakes are especially intriguing because, instead of evolving a mechanism to equalize gene expression across the whole chromosome, as humans do, they have evolved dosage compensation in particular regions and possibly even specific [genes](#) on the Z chromosome.

"One of the most exciting features of the rattlesnake genome assembly is that it includes the first complete sex chromosome for a snake," said Schield, lead author on the paper.

The researchers used the rattlesnake genome to trace the evolution of snake sex [chromosomes](#), and the origins of sex-specific patterns of gene expression on the Z chromosome. They also identified the first genetic mechanism that may underlie snake dosage compensation. These findings establish new genomic context for the evolution of sex determination in snakes and provide new insight into the diversity of sex determination systems in vertebrates.

Broadly, the findings of the paper focused on the rattlesnake genome highlight the tremendous biological value of quality genome resources for non-model species. The Castoe lab published the very first snake genome—the Burmese python genome—six years ago, and since then

several other snake genome resources have become available. Each snake genome has enabled new discoveries about snake and vertebrate biology.

With the rattlesnake genome, the caliber of snake genomes is now at the level of quality of many traditional model organisms. Having a diverse array of vertebrate genomes enables broad comparisons to understand fundamental aspects of genome biology. The rattlesnake genome adds to the growing list of species to allow for these comparisons, and also provides unprecedented potential to understand the unique features of snakes.

"Dr. Castoe and his colleagues have made an important advance in our knowledge of the snake genome at the chromosome level," said Clay Clark, professor and chair of the UTA Department of Biology. "Their findings about the genomic basis of venom evolution and snake [sex chromosomes](#) are exciting breakthroughs in snake genome research and confirms the Castoe lab's standing as one of the nation's leaders in snake [genome](#) research."

**More information:** Drew R. Schield et al. The origins and evolution of chromosomes, dosage compensation, and mechanisms underlying venom regulation in snakes, *Genome Research* (2019). [DOI: 10.1101/gr.240952.118](#)

Provided by University of Texas at Arlington

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