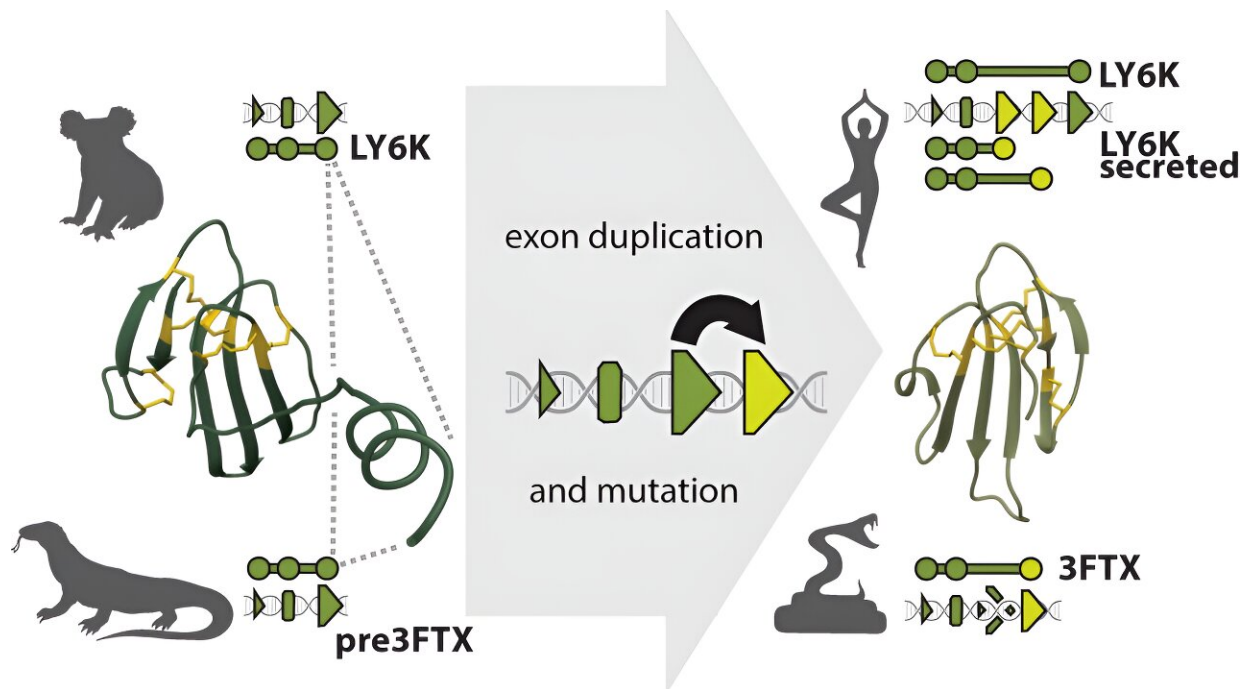


Evolutionary history of three-finger snake toxins decoded

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Proposed mechanism of parallel evolution of membrane-anchored forms into secreted forms of LY6 genes. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40550-0

Snakebites cause around 100,000 deaths worldwide every year. Researchers at the Technical University of Munich (TUM) have investigated how the toxin emerged between 50 and 120 million years ago through the modification of a gene that also occurs in mammals and

other reptiles. The results could help with the development of better snakebite treatments and lead to new knowledge for the treatment of illnesses such as type 2 diabetes and hypertension.

When venom passes into a snakebite victim, it binds onto receptors on nerve and [muscle cells](#) and interrupts communication pathways between them. This initially causes paralysis and, without an antidote, can cause death within a matter of minutes or hours. A team of researchers has studied how the protein structure of [snake](#) venoms known as three-finger toxins (3FTxs) has changed over the course of evolution.

Emergence of three-finger toxins

The team working with Burkhard Rost, a professor of bioinformatics, discovered that three-finger toxins developed over time from the Ly6 gene, which is also present in mammals and other reptiles. It is responsible for various metabolic functions such as the immune response of cells and neural regulation. The research is published in the journal *Nature Communications*.

Dr. Ivan Koludarov, a researcher at the Chair for Bioinformatics and a first author of the study says, "It is inferred from previous studies that snakes diverged from other lizards around 120 million years ago. Present-day [venomous snakes](#) and other snake species diverged around 50 million years ago and both already carry functional 3FTx [genes](#). That means that the Ly6 gene changed so much over the period from 50–120 million years ago that it now causes a strong toxic effect."

In the course of evolution the Ly6 gene, which generates the instructions for the toxin, doubled repeatedly. Consequently, venomous snakes carry multiple copies of the gene. On these copies, various segments have mutated. As a result, the function of the protein encoded by the gene changed so radically that it no longer performs its original function and

instead acts as a toxin.

Various forms of the venom

Tobias Senoner, a doctoral candidate at the Chair for Bioinformatics adds, "The gene has mutated in different ways in the various snake species. Based on the resulting protein structures, we can distinguish four forms of the 3FTx [toxin](#). Each one has specific structures and therefore acts differently on the snake's prey."

Prof. Burkhard Rost explains, "For [our study](#), we collected all available information from the UniProt database, which provides data on proteins of all living organisms and viruses. In addition, we accessed biomedical and [genetic information](#) from the National Center for Biotechnology Information. We analyzed these data through the lens of artificial intelligence."

The insights from the study will help to improve the treatment of snakebite victims and bring about progress in [drug development](#). The understanding of the toxins could help in the development of new treatment methods for type 2 diabetes or hypertension, for example, or better pain medications.

More information: Ivan Koludarov et al, Domain loss enabled evolution of novel functions in the snake three-finger toxin gene superfamily, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-40550-0](https://doi.org/10.1038/s41467-023-40550-0)

Provided by Technical University Munich

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