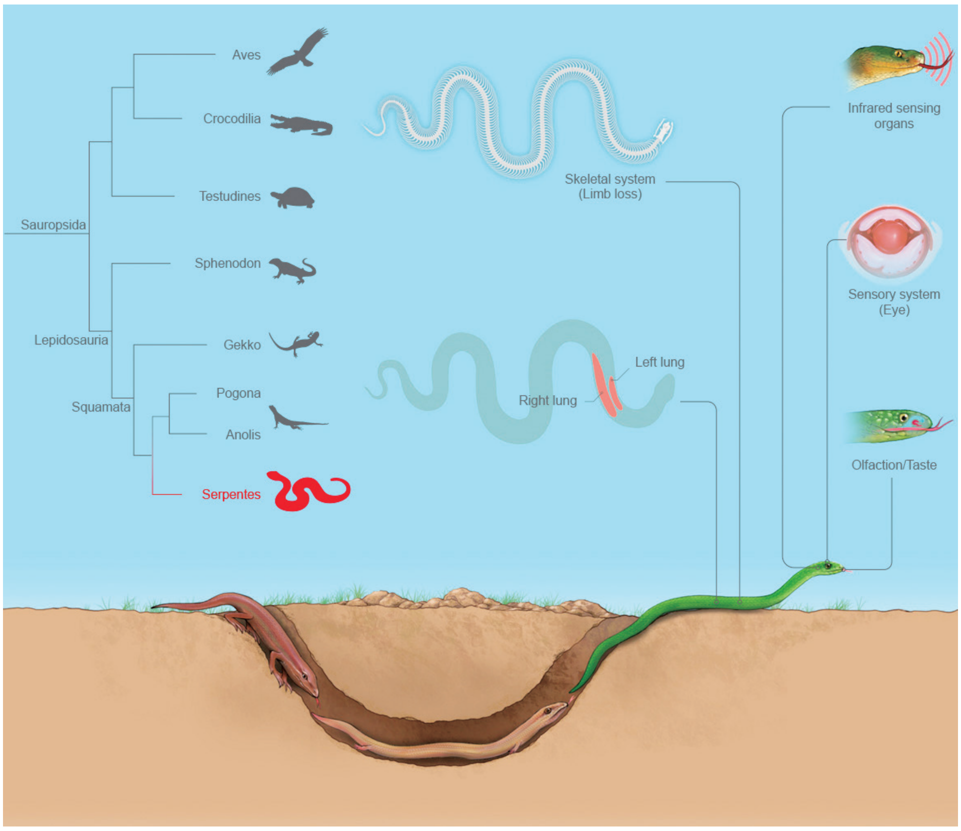
# New Snake Genome Study Sheds Light on Limb Loss and Sensory Superpowers

By YAN Fusheng (Staff Reporter)

A sweeping genomic study of snakes, published in *Cell*, has shed new light on the genetic basis of their unique traits and evolutionary adaptations. An international team, led by Dr. LI Jiatang from the CAS Chengdu Institute of Biology (CIB), analyzed the genomes of 25 snake species with a wide diversity, including blind snakes, pythons, and pit vipers. This extensive dataset allowed the researchers to track changes in the snake genome over 117 million years of evolution, and identify genetic modifications linked to limb loss, infrared sensing, asymmetrical lung development, and other distinctive snake features.




Snakes possess a remarkable morphological and sensory adaptations that aid their globally successful predatory lifestyles. These include limb loss and elongation of body plans to facilitate burrowing, enhanced infrared and vibration sensing for hunting, and swallowing of large prey relative to their body size. (Credit: C. Peng *et al.*/*Cell*)

Snakes have captivated humanity's imagination for centuries with their legless bodies, venomous bites, and hypnotizing movements. Yet much about their biology and evolution remains shrouded in mystery. Now, hissing out of the shadows comes a new genome study providing penetrating insights into snakes' ancient origins and genetic tricks behind their incredible adaptations.

An international team led by Dr. LI Jiatang at the Chengdu Institute of Biology (CIB) of the Chinese Academy of Sciences analyzed the genomes of 25 different snake species spanning the full diversity of serpents, including blind snakes, boas, pythons and vipers. This expansive genomic dataset allowed them to reconstruct how snakes evolved from their quadruped ancestors into limbless masters of stealth over 100 million years.

## Genomic Underpinnings of Limb Loss and Fit for Feasts

They found the forelimb development initiator gene *RDH10* was lost in all snakes studied. Mutations were also identified in the limb development genes *PTCH1* and *CPLANE1* across all snakes.

When the researchers introduced similar mutations into mice, the rodents' limbs showed stunted growth, confirming this gene's critical role. It's remarkable how tiny genetic tweaks can lead to massive transformations in anatomy over eons.

In addition, many snake-specific insertions and deletions of DNA segments were found in the regulatory regions of several other limb development genes. And the ZRS limb enhancer, a DNA enhancer that controls gene expression in the developing limb bud, showed a snake-specific deletion.

Together, these changes in both protein-coding genes and regulatory elements likely disrupted limb initiation and growth during snake embryonic development, leading to gradual limb reduction.

Since snakes have lost their forelimbs, they have evolved adaptations in their skull and digestive system to facilitate swallowing and digesting of large prey whole.

The researchers found that genes involved in lower jaw (mandible) and upper jaw (maxilla) morphogenesis, like *LIMK2* and *MMP14*, showed signs of positive selection in snakes, which facilitate the evolution of snakes' highly kinetic skulls and jaws. This would allow snakes to unhinge their jaws incredibly wide to swallow large prey whole. The transcription factor HOX7, which regulates tooth development, also evolved rapidly in snakes.

In the digestive system, snakes lost genes that stimulate appetite (*GHRL*) and suppress bile acid production (*MALI*). Meanwhile, complement genes *CFHs* are newly evolved in snakes, and the digestive enzymes GBA2 and TRYP2 showed positive selection.

Together, these changes suggest genetic adaptation in snakes in favor of infrequent large meals over small regular meals. The changes enhanced their ability to unhinge jaws, swallow prey whole, and efficiently digest large meals using newly evolved enzymes and regulators. Loss of appetite genes may allow snakes to endure long fasting periods.

Overall, alterations to both skull developmental genes and digestive genes gave snakes the unique ability to consume and digest proportionally massive prey relative to their body size.

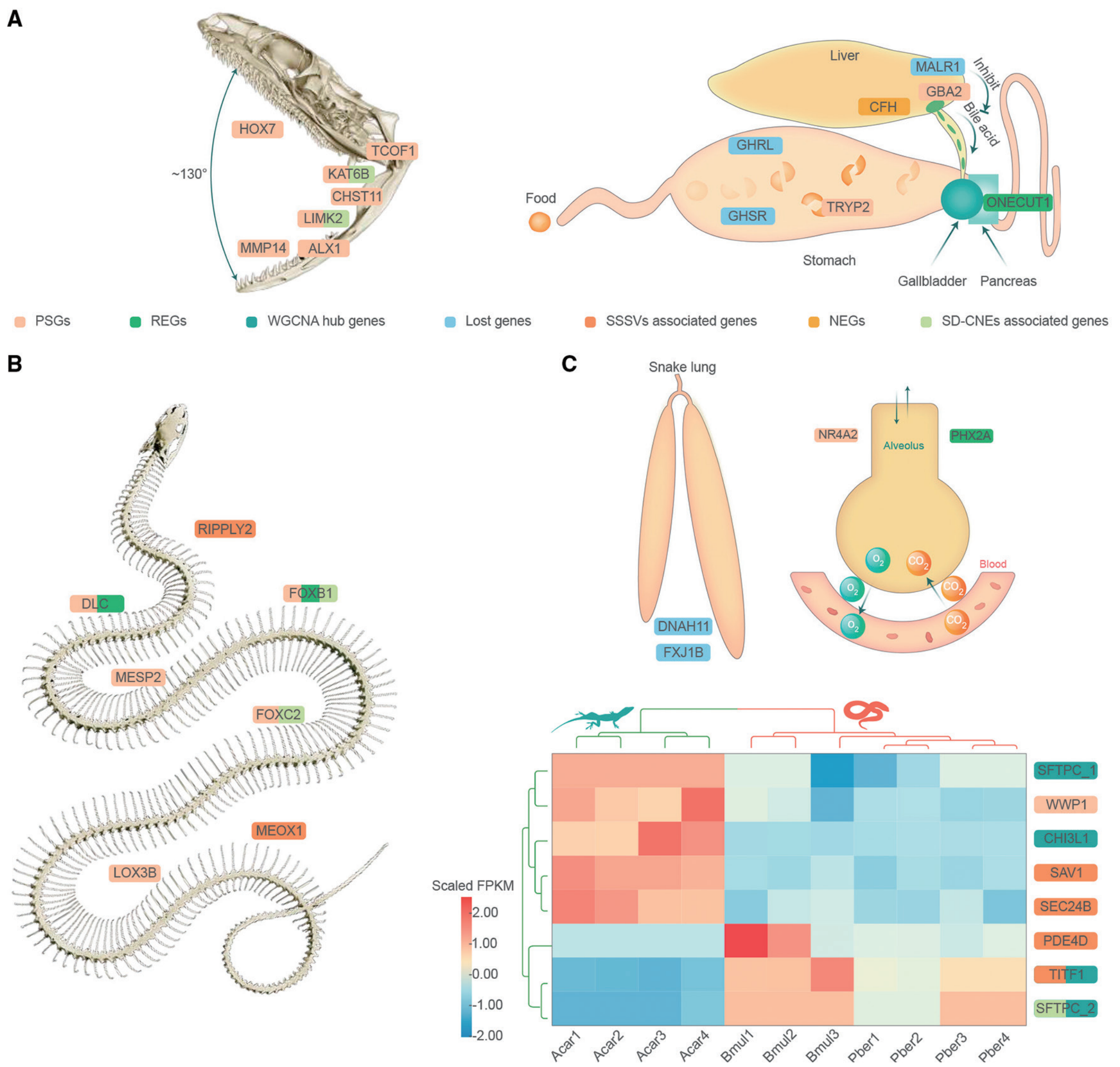
## Genomic Drivers of Snakes' Elongated Body and Asymmetrical Lungs

Snakes have evolved extremely elongated and slender bodies compared to their ancestors. The researchers found mutations in several genes involved in somite development and body segmentation that may contribute to this elongated body plan, including *DLC*, *FOXC2*, *LOXL3B*, and *MESP1*.

In addition, mutations in *HOX* genes, which regulate body patterning, were observed in snakes. This suggests changes to developmental pathways helped extend the number and size of body segments during snake evolution.

Along with body elongation, snakes evolved asymmetrical lungs, with the left lung absent or substantially reduced. The researchers found the left-right symmetry gene *DNAH11* was lost in all snakes studied.

Several other mutations and regulatory changes were identified in lung developmental genes that may alter airflow and capacity in snakes. This suggests




Genetic basis of skeletal system evolution and organ adaptation in snakes. Renewal of genomic elements contributing to snake skull development and digestion (A). Related genes are shown in their corresponding regions. The evolution of genomic elements has potentially facilitated the evolution of the elongated body (B) and asymmetrical lungs (C) in the snakes. (Credit: C. Peng *et al.*/*Cell*)

genetic divergence in pathways controlling lung symmetry allowed the elongation of one lung without impacting respiratory function.

## Evolution of Snake Sensory Systems

In addition to lost limbs and elongated body, the analyses revealed snakes bulked up genes involved in smell, fitting with their forked tongues and sharp scent-tracking skills.

The researchers also found extensive loss of photoreceptor genes in snakes compared to lizards and mammals, indicating visual regression. However, some photoreceptor maintenance genes were upregulated, suggesting adaptation to dim light conditions. Mutations in eye development genes like *CC2D2A* may also have contributed to morphological changes.

Snakes have reduced external and middle ear structures, but the connection between their jawbone and their inner ear improves their vibration sensing. Loss of genes like *OTOS*, which is important for hearing in mammals, suggests adaptations in the cochlea to enhance low-frequency vibration detection.

Newly evolved olfactory genes as well as selection on taste receptors indicates enhancements in snakes' chemical sensing abilities. The olfactory amplifier gene *UBR3* evolved rapidly in snakes. Overall, snakes retained functional taste receptors that align with their ability to evaluate and consume large prey items.

Some lineages of snakes have independently evolved infrared sensing abilities, including pythons, boas, and pit vipers. These three groups are not closely related, but they have each developed specialized heat-sensitive pit organs or receptors.

The researchers found evidence of convergent evolution in the genes related to infrared sensing in these three snake lineages. For example, the heat-sensing ion channel gene *TRPA1* showed similar patterns of amino acid changes in pythons, boas, and pit vipers compared to other snake species.

Another gene called *MAP2K7*, which is involved in temperature sensitivity, was found to have evolved rapidly along the lineages leading to pythons, boas, and pit vipers.

The convergent evolution of similar genetic changes related to infrared sensing in these three distantly related snake groups is likely due to the selective pressures of their environments. Detecting infrared radiation provides a strong advantage for hunting at night. So random mutations that enhanced infrared sensitivity were probably favored and became fixed independently in these lineages.

This expansive snake genome study sheds new light on the genomic basis of serpents' unique adaptations, from limb loss to infrared sensing. While linking specific genetic changes to phenotypic evolution remains challenging, the researchers reveal numerous genomic variants correlated with distinctive snake traits. Functional analyses of mutations in key genes like *PTCH1* confirm their role in anatomy shaping over time.

Though many evolutionary mysteries still hide beneath the surface, this foundational resource spotlights how snakes tweaked their developmental pathways to gain remarkable sensory powers and sleek, limbless mobility.

Moving forward, more comprehensive snake genome sequencing and editing will further unravel the winding genetic routes that spawned slithering serpents from lizard-like ancestors. For now, these insights highlight promising gene candidates for studying snake biology and affirm how subtle, yet impactful genetic changes can be.

**Reference**

Peng, C., Wu, D. D., Ren, J. L., Peng, Z. L., Ma, Z., Wu, W., . . . Li, J. T. (2023). Large-scale snake genome analyses provide insights into vertebrate development. *Cell, 186*(14), 2959-2976.e2922. doi:10.1016/j.cell.2023.05.030