Scientists illuminate genetics underlying the mysterious powers of spider silks

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Golden orb-weaver spider (*Nephila clavipes*). Credit: Matjaz Kuntner, Slovenian Academy of Sciences and Arts

Spider silks, the stuff of spider webs, are a materials engineer's dream: they can be stronger than steel at a mere fraction of weight, and also can be tougher and more flexible. Spider silks also tend not to provoke the human immune system. Some even inhibit bacteria and fungi, making them potentially ideal for surgery and medical device applications. Exploitation of these natural marvels has been slow, due in part to the challenges involved in identifying and characterizing spider silk genes, but researchers from the Perelman School of Medicine at the University of Pennsylvania have now made a major advance with the largest-ever study of spider silk genes.

As they report today in an advance online paper in *Nature Genetics*, Penn scientists and their collaborators sequenced the full genome of the golden orb-weaver spider (Nephila clavipes), a prolific silk-spinner that turns out to produce 28 varieties of silk proteins. In addition to cataloguing new spider silk genes, the researchers discovered novel patterns within the genes that may help to explain the unique properties of different types of silk.

"There were so many surprises that emerged from our study: new silk genes, new DNA sequences that presumably confer strength, toughness, stretchiness and other properties to silk proteins; and even a silk protein made in venom glands rather than silk glands," said senior author Benjamin F. Voight, PhD, an associate professor in the departments of Genetics and Systems Pharmacology and Translational Therapeutics. "All this new information should greatly advance our efforts to capture the extraordinary properties of these silks in man-made materials."

Even though spider silks have been studied for more than 50 years, earlier foundational work had identified only a comparative handful of spider silk genes. Even recent work from species with smaller silk repertoires than the golden orb-weaver's were incomplete. To find all of the silk genes hidden across the golden orb-weaver's genome—the veritable "lab rat" of spider silk science—required the construction of the entire genome, a daunting task in itself.

In the new study, Voight and his colleagues began with the herculean task of sequencing and reassembling the genome of the golden orb-weaver: a task comparable to solving a multimillion-piece jigsaw puzzle, with few clues as to how these pieces fit together.

In the golden orb-weaver's genome—which turns out to be about as large as the human genome—the researchers identified more than 14,000 likely genes, including 28 that appear to encode spider silk proteins, known as spidroins.

Spidroins have been classified into seven categories according to their protein sequences and functions; these categories include aciniform silk for wrapping prey (and tying down partners for mating); and the super-strong major ampullate silk from which spiders (and Spider-Man) swing while at work. However, some of the newly discovered spidroins have sequences that do not fit neatly into any of these categories, suggesting that the encoded silk proteins may have novel functions, or that the existing categories need to be redefined.

An extensive computational analysis of the orb-weaver's spidroin genes revealed nearly 400 short sequences—many never before described—that appear repeatedly in these genes with small variations and in different combinations. These repetitive spidroin "motifs" are of great interest to biologists and engineers because they are likely to confer the key properties of a given spider silk, such as high-tensile strength, flexibility, or stickiness. The analysis also revealed novel, higher-order organizations of these motifs into groups of motifs ("cassettes") and groups of groups ("ensembles").

Voight's team also examined gene transcripts from different orb-weaver silk glands and in each case found transcripts belonging to more than one spidroin class, suggesting that these glands are not strictly specialized for producing one type of silk. "We found significantly more complexity in silk production than we expected," Voight said.

The biggest surprise was the discovery that one of the orb-weaver's spidroins—FLAG-b, a novel discovery by the group—appears to be produced primarily in the orb-weaver's venom gland rather than in any silk gland, hinting at intriguing new functions for silk connected to prey capture, immobilization, or preservation.

In their analyses of the genome data, Voight and colleagues also identified 649 likely genes that are not spidroin genes but are highly expressed in silk glands, and thus probably have roles in converting the liquid silk from spider cells into solid, spinnable threads—a tricky process that biotech engineers are just beginning to achieve outside of spiders.

Voight and his team are now following up with a genome-sequencing study of Darwin's bark spider, which makes the strongest known silks, and has been known to span rivers with them.

The scientists are also at work on technology for the rapid production of silks in the lab starting from their spidroin DNA sequences, to better understand how these sequences and their motifs encode silks' biological and physical properties.

"When I say that we'd like to build a 'web-shooter' like Spider-Man's in the lab, I'm only half joking" Voight said.

More information: The Nephila clavipes genome highlights the diversity of spider silk genes and their complex expression, *Nature Genetics* (2017). nature.com/articles/doi:10.1038/ng.3852

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