Researchers decipher comprehensive black-legged tick genome

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A University of Maryland-led team of scientists has deciphered the first comprehensive, continuous genome for a parasite responsible for transmitting Lyme disease and other serious infections to hundreds of thousands of Americans yearly. With their newly described genome for the black-legged tick, or deer tick, the researchers identified thousands of novel genes and new protein functions, including proteins associated with tick immunity, disease transmission and developmental stages.

This work provides valuable information for developing interventions for various tick-borne diseases, far surpassing previous efforts to sequence the tick's genome, which resulted in partial genomes or fragments of genome with gaps and uncertainties.

The study was published January 19, 2023, in the journal *Nature Genetics* and was made possible by close collaborations between multiple academic institutions, industry and federal institutions.

"We are really excited to have this reference genome now, because there are so many unanswered questions about how these parasites evolved and transmit disease," said Utpal Pal, senior author of the study and a professor in the Virginia-Maryland College of Veterinary Medicine at College Park. "We believe there are genetic factors that contribute to why these ticks are so good as disease vectors, but we can't really understand it without a very good genome like this."

Black-legged ticks (*Ixodes scapularis*) or closely-related species are widespread throughout North America, Europe, North Africa and Asia. They are the primary vectors of a number of diseases, including Lyme disease, which infects nearly half a million Americans annually. Yet

many aspects of their biology remain unknown.

With a complete genome, scientists can begin to unravel the molecular mechanisms behind many aspects of the parasite's biology and its interactions with both hosts and the diseases it transmits.

A black-legged tick's genome is made up of more than 2 billion discrete pieces of DNA code (expressed as combinations of four nucleotides represented by the letters ATCG). Like letters that are bundled together to form words in a sentence, the DNA codes are bundled into genes that make up the genome.

Previous work to decipher the tick genome used many immature ticks or tick cells that had been grown in laboratories for multiple generations, which introduced errors, or combined samples from multiple individual ticks, resulting in fragmented bundles of code with many redundant snippets. Researchers had to reassemble the snippets, determining where each gene begins and ends and how they should be arranged.

To overcome these challenges, Pal and his colleagues combined two methods to sequence the genome of a single tick. One method deciphered the entire genome at once, creating a sequence that was complete, but a bit "fuzzy," meaning the code wasn't clear in many places. In the second method, the researchers used a common technique called Polymerase chain reaction or PCR to "amplify" small segments of the genome so it could be read more clearly. The team then combined the two results, which was a little like using a fuzzy, big picture image as a reference for assembling high-resolution puzzle pieces. Finally, the researchers used a technique called "Hi-C" to bridge small pieces of DNA into longer, contiguous threads.

The result is a high-quality, contiguous genome that is 98% complete. The new genome revealed that 40% of the annotations previously

described for the black-legged tick relied on older technology and needed updating.

Next, the researchers compared their complete genome to snippets of genomes sequenced from 51 wild-caught ticks, showing that the new work could be used as a reference for identifying segments of genetic material from other individuals. This also identified unrecognized genetic diversity among groups of ticks from different regions in the U.S.

Finally, the team analyzed their tick genome to identify thousands of new genes and proteins and describe new critical functions of those genes. For example, in one experiment, they found some proteins were only present during certain phases of a tick's life cycle or at specific stages during a tick's blood meal and digestion. By knocking out a gene that tells tick cells to make one of those proteins, they were able to disrupt the tick's feeding and digestion process.

Future work like this could help target gene-based therapies and vaccines that interrupt some part of the disease transmission cycle between ticks and humans.

An additional outcome of the study was that the researchers identified and described a more comprehensive genome for *Rickettsia buchneri*, the pathogenic bacteria that causes rickettsiosis.

The genomic resources described in the paper are publicly available through major databases and will be helpful in advancing tick research and preventive measures.

The co-first authors of the paper from the University of Maryland College of Agriculture and Natural Resources-Veterinary Medicine Program are Assistant Research Professors Sandip De and Chrysoula

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More information: Utpal Pal, A high-quality Ixodes scapularis genome advances tick science, *Nature Genetics* (2023). DOI: 10.1038/s41588-022-01275-w.
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