Understanding why animals are healthy offers path to precision medicine

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Researchers at Duke University School of Medicine and Brigham and Women's Hospital, Harvard Medical School have identified a mechanism that explains why some mutations can be disease-causing in one genome but benign in another.

In a study appearing June 29, 2015, in the journal *Nature*, the researchers compared thousands of human disease-causing mutations with the analogous sequences of some 100 animal species. They discovered non-human genomes carrying mutations that cause severe disease in humans, yet were benign in the animals.

Although generally in line with earlier observations, the scale of the findings motivated geneticists to find the explanation for this apparent mystery.

"We found many examples in which an entire species should have a serious genetic ailment, but instead were healthy," said Nicholas Katsanis, Ph.D., director of the Center for Human Disease Modeling and professor cell biology and pediatrics at Duke. "So, if we can understand how animals escape illness from such severe genetic mutations, we might have a way to make humans better.

"What we considered is that for many mutations, there must be a buffering mechanism - another mutation that protects the animal from the detrimental affects of the disease-causing mutation," Katsanis said.

The researchers considered two possible explanations: Disease suppression might be the result of one or two additional substitutions on the same gene that buffer the harmful effect of the mutation; or suppression may be caused by numerous small substitutions throughout the genome that form an aggregate "shield."

"Evolutionary theory told us that such a shield must exist, we just did not know how if would work," Katsanis said. "Now we know at least part of the answer."

The team tracked changes in protein sequence that travelled with the disease-causing mutation and were candidates for offering protection. If a species lost the "traveler", it would also have to eliminate the mutation or become extinct.

The researches tested this notion using molecular tools to identify these sites. They first engineered mutant proteins that were defective, then added secondary sites and were able to completely restore protein function.

"In the end, it looks like you can shield mutations with a single change elsewhere in the same gene, creating a single champion." Katsanis added.

With the advent of genome engineering, scientists are now introducing hundreds of different human mutations in other species to study their effects and develop new drugs. Because the effect of mutations on protein function might be dependent on the broader context of the human sequence, this approach will also lead to serious false negative conclusions, Katsanis warns.

"We are really beginning to appreciate the fundamental complexity of the human genome and genomes in general," Katsanis said. "It used to be black-and-white: mutation, bad; no mutation, good. But it's far more

complex. We are now beginning to be able to compute the effect of mutations in the context of the rest of the genome. There is no question that this will improve our ability to interpret human genomes and inform clinical practice"

Co-author Shamil Sunyaev, Ph.D., professor of medicine at Brigham and Women's Hospital and Harvard Medical School, agrees that the results highlight the complexity of interpreting DNA sequences.

"Our study provides an example of the utility of comparative genomics and evolutionary models for medicine," Sunyaev said. "At the same time, it shows how data accumulated by medical geneticists can be used to better understand evolution. Beyond medicine and evolution, the logical next step would be to explain biochemical mechanisms underlying interactions between mutations."

More information: Identification of cis-suppression of human disease mutations by comparative genomics, DOI: 10.1038/nature14497

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