GENOMICS

Hotspots of evolution

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A new analysis of mammalian genomes has revealed rapidly evolving “hotspots” that may shed light on clinically important, non-coding DNA regions in humans. The work grows out of the fact that only about 2% of the human genome encodes genes, while the rest is largely mysterious. Previous researchers have tried various methods to pinpoint areas in the non-coding region that play important roles, such as regulating the production of proteins from specific genes, but the challenge remains daunting.

The team behind the new study, led by Christopher Gregg at the University of Utah, opted for an evolutionary strategy. “Our idea was to find regions of the human genome that are conserved across most mammals, and that immediately reduces the search space dramatically, to just 1% of the genome. Those are likely to be extremely important because they’re conserved. The next thing was to figure out which of those elements is likely to have an important role in a particular phenotype,” says Gregg.

The team compared conserved regions among humans and various animals with

interesting phenotypes, including bats (flight), elephants (cancer resistance), the naked mole rat (toxin metabolism, long lifespan, cancer resistance), hibernating squirrels (hibernation, diabetes resistance), and dolphins and orcas (endurance, breath-holding). “That menagerie of species covers diverse environments and different adaptations,” said Gregg.

Each animal revealed evolutionary hotspots that had changed more than would be expected based on chance alone, though it remains to be confirmed if the regions identified are functionally related to the clinically interesting traits.

In particular, researchers found regulatory elements in the mammalian genome that changed in elephants to potentially protect them from cancer. Decades ago, it was predicted that large animals with many cells and a long lifespan, like the elephant, should have higher rates of cancer than smaller, short-lived species, but in fact, the opposite appears to be true. This observation is called Peto’s paradox (*Br J Cancer* 32, 411–426; 1975) and suggests that

large species evolved unique mechanisms to avoid cancer and mutations in their cells. The elephant was a major focus of Gregg’s study, and the researchers found that the parts of the genome with the most elephant accelerated regions were close to a master regulator of DNA repair, called FANCL. FANCL is a part of the Fanconi anemia complex, which is critical for preventing mutations in human cells.

Gregg’s team is applying a similar strategy to other mammals with extraordinary traits. “There are at least one or two more stories coming,” he said. They are also using CRISPR in mice to modify the human and mouse versions of the control elements found in elephants. Those experiments in human and mouse cells should help determine their functional roles, particularly whether they influence mutation rates and cancer resistance.

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