Mapping the genome jungle: Unique animal traits could offer insight into human disease

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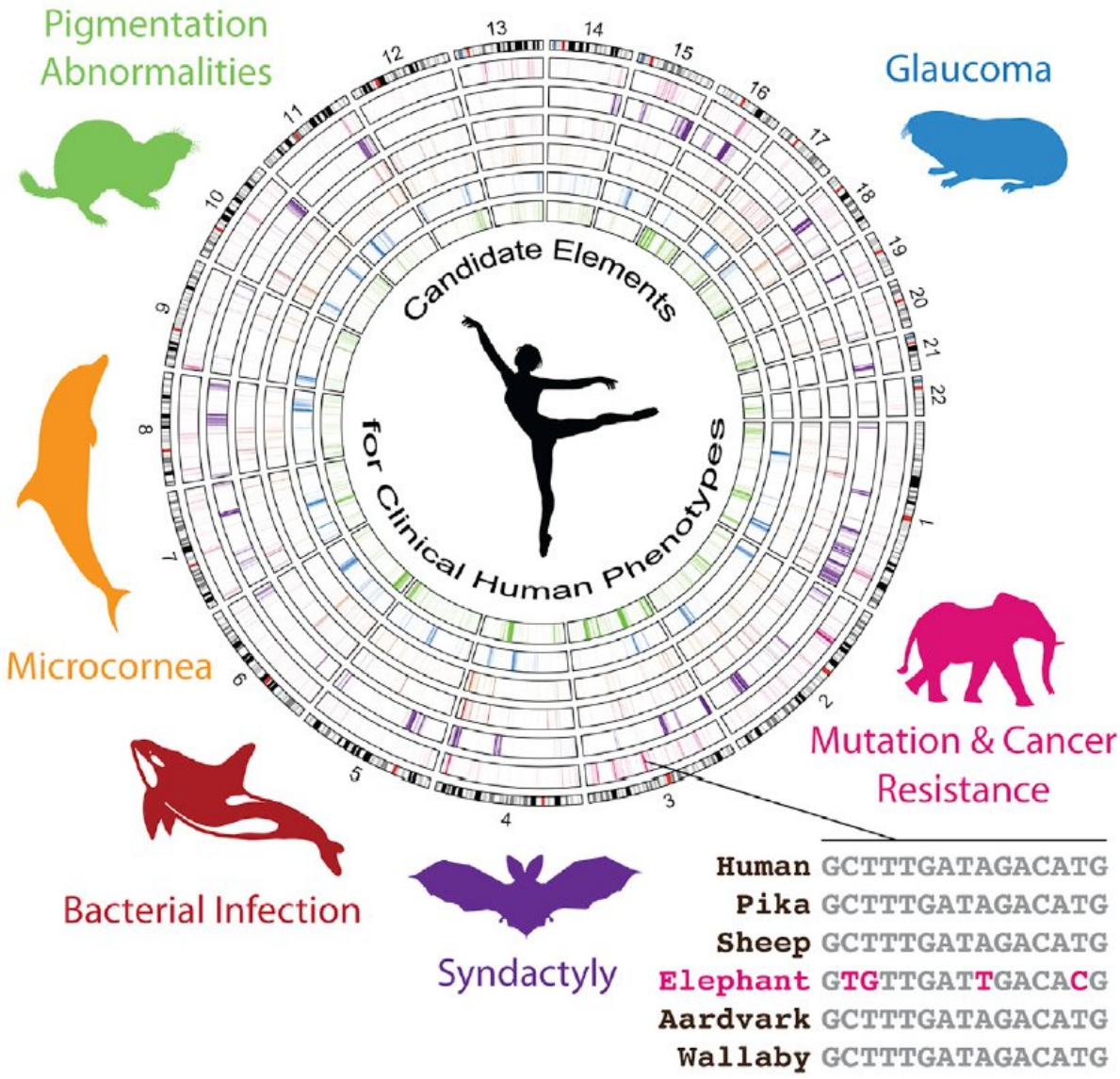

This visual abstract depicts the work of Ferris et al., who report an analysis of accelerated evolution in the elephant, little brown bat, big brown bat, orca, dolphin, naked mole rate, and thirteen-lined ground squirrel that reveals candidate functional genomic elements for shaping somatic mutation rate, cancer risk, digit development, immunity, glaucoma, pigmentation, and other clinical phenotypes. Credit: Ferris et al./*Cell Reports*

From a bat's wings to an elephant's cancer resistance, an interdisciplinary team of scientists at University of Utah Health are using animals' unique traits to pinpoint regions of the human genome that might affect health. The results of this project are available in the March 6 issue of the journal *Cell Reports*.

The research team is turning their attention to the noncoding region of the mammalian genome. Making up 98 percent of the genome, these regions do not code for proteins, but they contain 'switches' that like a conductor control when and where genes are expressed. The role of most noncoding regions in health and disease remains unclear.

"People used to call the noncoding regions junk DNA, but I see it as a jungle that has not been explored," said Christopher Gregg, Ph.D., assistant professor in Neurobiology and Anatomy at U of U Health. "We are exploring the noncoding regions to try to discover new parts of the genome that might control different diseases."

Setting Guideposts in the Genome

The research team scoured the 'junk' sections of five animal genomes—elephant, hibernating bat, orca and dolphin, naked mole rat and thirteen-lined ground squirrel—to identify regions that evolved rapidly.

The team identified thousands of accelerated regions in each animal genome. Some of these accelerated regions of evolution may impart the recognizable traits we attribute to each species, like the wings of a bat, the massive body size of the elephant and the unique coloring of the thirteen-lined ground squirrel.

"We leveraged the extreme traits in different species to uncover noncoding regions in the human genome that likely have important roles in shaping health and disease," said Elliott Ferris, first author on the paper and a bioinformatician and computer programmer in Gregg's lab.

The researchers identified elements in the:

- elephant genome linked to DNA repair that could help in the study of cancer resistance;
- bat genome linked to wing development that could help in the study of hand and feet abnormalities;
- dolphin and orca genome linked to eye development that could help in the study of cornea development, as well as elements linked to adaptation to high pressure environments that could help in understanding blood clotting disorders;
- thirteen-lined ground squirrel genome linked to coloration/pigmentation that could help in study of albinism and Leopard Syndrome; and
- naked mole rat genome linked to eye development that could help in the study of glaucoma.

"This method allows us to shine a light on nature's potential solutions to disease across the entire animal kingdom," said co-author Joshua Schiffman, M.D., a pediatric oncologist and professor of Pediatrics at U of U Health and investigator at Huntsman Cancer Institute (HCI). "Dr. Gregg and his team are building the sandbox that we can explore together in order to expand our library of potential therapeutic targets

for diseases like cancer."

Forget Memory, Elephants Rarely Get Cancer

Every time a cell duplicates, it opens the door for new mutations that could lead to cancer. Yet the massive elephant, which has 100-times more cells than a human and lives for 60 to 70 years, is rarely afflicted by this disease.

Schiffman studies elephants to understand the genetics behind their natural resistance to cancer. In a previous study, his team worked with other collaborators to identify the potential role of extra copies of the tumor suppressor gene (p53) that increase the elephant's ability to eliminate pre-cancerous cells with DNA damage.

Gregg and Ferris tested whether the accelerated regions in the elephant genome revealed additional candidate elements that shape resistance to mutations and cancer. They identified three genes (*FANCL, VRK2* and *BCL11A*) associated with large numbers of accelerated regions of evolution. These genes are involved in DNA repair that guards against mutations.

Schiffman and his team conducted another series of experiments in the laboratory on blood samples from adult African elephants to find how these genes respond to DNA damage in the elephant cells. The Gregg lab was able to use this data to show that many different genes that respond to DNA damage are enriched with elephant accelerated regions. The results uncovered an atlas of elements in the mammalian genome that could potentially promote cancer resistance.

"We identified candidate mechanisms beyond p53 in the elephant genome for evading cancer," said Gregg. "The elephant results revealed noncoding sequences in the human genome that we predict may control

gene activity and reduce the formation of mutations and cancer."

Gregg and Schiffman are teaming up to investigate how the genomic regions identified in this study can be applied to human medicine. Future functional studies are needed to test whether these accelerated regions control disease processes in people.

"We are staring at uncharted territory," Gregg said. "This method gives us a new way to explore the genome and potentially uncover new approaches to identify, diagnose and treat disease."

More information: *Cell Reports*, Ferris et al.: "Accelerated Evolution in Distinctive Species Reveals Candidate Elements for Clinically Relevant Traits, Including Mutation and Cancer Resistance" www.cell.com/cell-reports/full … 2211-1247(18)30176-1 , DOI: 10.1016/j.celrep.2018.02.008

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