Evolution of diverse sex-determining mechanisms in mammals

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Scientists historically have argued that evolution proceeds through gradual development of traits. But how can incremental changes apply to the binary switch between two sexes, male or female? Researchers at Case Western Reserve University's School of Medicine have found that a genetic process among the many species of rodents could have significant implications regarding our assumptions about sex determination and the pace of evolution.

"What we addressed is a long-standing puzzle in natural history: why different types of rodents can exhibit profound differences in how male sex is determined in the embryo," said Michael Weiss, MD, PhD, chairman of the Department of Biochemistry, the Cowan-Blum Professor of Cancer Research and a professor of biochemistry and medicine. "Some rodent populations have both XY males and XY females, and in other populations the Y chromosome has disappeared entirely."

In a study published in *Proceedings of the National Academy of Sciences*, Weiss and his research team analyzed the Sry gene, which is part of the Y chromosome. This mammalian gene, which steers differentiation in the embryonic gonad toward the development of testes, begins the process leading to the birth of males. For most mammals, including primates, Sry is a conserved feature of the Y chromosome, ultimately giving rise to male anatomy; females generally have two X chromosomes and no Y.

But within anomalous families of rodents, common in South America, activation of the Sry gene may have uncertain consequences. Some of these groups have both XY males and XY females as normal components of the population. Other related species have even lost their Y chromosomes altogether. Without the emergence of compensating ways of specifying sex, the species could not produce males—and would become extinct. For such rodents, therefore, evolution meant inventing entirely different methods of sex determination. These mammals have in essence evolved other ways to play nature's mating game.

The CWRU team attributed the rapid evolvability of sex determination in rodents to a novel protein domain added to the SRY protein. Scientists knew that this domain existed, but Weiss and his team wanted to understand more about its function in gene regulation and its role in evolution. The team determined that the new protein domain acts as a "genetic capacitor," providing a protective buffer to the Sry gene. This buffer allowed male development even when a mutation occurs elsewhere in the gene that might otherwise cause sex reversal—but the buffer is unstable over generations. Slippage of DNA during the production of sperm can lead to sudden changes in the length of the buffer and the degree of protection. By analogy to a capacitor in an electric circuit, the team suggested that this domain can "discharge" to accelerate the pace of evolutionary change. The idea of a genetic capacitor was pioneered by MIT Professor Susan Lindquist in studies of heat-shock proteins in fruit flies in (Nature, "Hsp90 as a capacitor for morphological evolution") and the present paper extended this idea to the pace of mammalian evolution.

How did the Sry buffer arise? "We discovered that a genetic accident 20 million years ago in an ancestral rodent holds the key to solving this puzzle. A simple DNA repeat sequence (called a 'micro-satellite') invaded the Y chromosome and was incorporated into the Sry gene. This invasion accelerated the evolvability of Sry and probably the Y

chromosome in general, enabling this subgroup of rodents to explore new molecular mechanisms of sex determination," Weiss said.

Weiss and his team will continue this research, but believe these initial results may have additional implications for our understanding of human evolution and genetics. Because rodents have higher mutation rates and shorter life spans, they also evolve more rapidly and so provide a natural laboratory for studies of mammalian evolution.

Research last year at MIT has shown that in humans and other primates the Y chromosome has been stable for at least the past 25 million years (*Nature*, Strict evolutionary conservation followed rapid gene loss on human and rhesus Y chromosomes), which Weiss suggests may reflect the absence of micro-satellite-related slippage in the Sry gene. Yet the transcriptional strengths of the murine and human Sry factors are similar. The research suggests that human SRY and its specification of male development has evolved to be just above a genetic threshold of activity, which may in turn enable human communities to benefit from a diversity of male characteristics and behaviors.

"A key lesson of this 20 million-year history is that maleness is a 'close call' as the Sry protein functions near the edge of ambiguity," Weiss explained. "We think that the 'genetic decision' in an embryo to create a testis (instead of an ovary) is tenuous in all social mammals, including us. The critical next question is why?"

More information: Microsatellite-encoded domain in rodent Sry functions as a genetic capacitor to enable the rapid evolution of biological novelty, www.pnas.org/cgi/doi/10.1073/pnas.1300860110

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