

New candidate genes for human male infertility found by analyzing gorillas' unusual reproductive system

May 14 2024, by Tom Dinki



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Despite their formidable bodies, male gorillas are lacking in one particular area of their anatomy.

They have the smallest penises and testes of all apes, and produce a low

amount of sperm that neither swims fast nor binds easily to eggs. In fact, their reproductive system may be functioning at the lowest level possible for a mammal.

With gorillas sharing a common ancestor and over 98% of their DNA with humans, the genetics behind their abnormal genitals and sperm might hold answers about infertility in men.

A University at Buffalo-led research team has found that, indeed, some of the same genes whose [mutations](#) gave rise to a low functioning male gorilla reproductive system may also be responsible for human male infertility.

In a [study](#) published May 9 in *eLife*, researchers identified 109 reproductive-related gorilla genes that are often mutated when present in [infertile men](#). There are likely even more yet to be identified.

"We have a set of genes that are involved in sperm biology and have the signatures of harmful mutations when in gorillas. We can then look at those same genes in infertile men and see if they have mutations," says the study's lead author, Vincent Lynch, Ph.D., associate professor of biological sciences in the UB College of Arts and Sciences.

"Here the gorilla genome essentially acts as a discovery tool for finding candidate genes for human male fertility that we previously wouldn't have been able to identify."

Gorillas lack sperm competition

Male gorillas' small genitals and low sperm count can be attributed to their polygynous mating system. The alpha male silverback's intimidating figure gives him near exclusive access to the females in his group, so his sperm doesn't compete with other males' sperm within the

female reproductive tract.

"There are two ways to compete for mates: You can either use your body or your sperm," Lynch says. "Most mammals use a combination of both. Gorillas use only their bodies."

This lack of [sperm competition](#) likely led to the evolution of small testicles with few sperm-producing cells, as well as structurally abnormal and immotile sperm. These kinds of harmful gene mutations would normally be deleted from a population through what's known as purifying selection, yet sometimes purifying selection is so relaxed that mutations become fixed within a species over time.

The UB-led research team wondered if identifying relaxed genes in gorillas could lead to identifying genes crucial to human fertility.

Infertility affects approximately 5%–7% of couples worldwide, yet the underlying genetics are not well understood. For one thing, there's roughly 22,000 genes in a single person. Even if a mutation is found in one of them, it's hard to know whether it's impacting the ability to reproduce.

"So rather than looking at all of a man's genes for rare mutations, you could look at only those genes whose gorilla counterparts cause abnormal sperm biology," says Jacob Bowman, Ph.D., a postdoctoral researcher in Lynch's lab and the study's first author.

'Relaxed' gorilla genes are often mutated in infertile men

First, researchers used models powered by UB's Center for Computational Research (CCR) to search for signatures of relaxed

purifying selection in a dataset of more than 13,000 genes across 261 mammals. Of these genes, 578, or 4.3%, showed such signatures in the gorilla lineage.

To determine which of these relaxed gorilla genes impact male fertility, the team deleted them in the fruit fly, *Drosophila melanogaster*.

"Most of the genes that are important for reproductive biology are conserved across many different species, including *Drosophila*, and you can do these loss-of-function experiments at scale in *Drosophila* in a way that you can't in other organisms," Lynch says.

Suppressing these genes in fruit flies confirmed that many of them are crucial to male reproductive function, including 41 genes not previously associated with male fertility.

Next, researchers compared the relaxed gorilla genes to a genomic database with 2,100 infertile men, from those with low sperm counts to no sperm. In total, they found 109 of the relaxed gorilla genes were significantly enriched for loss-of-function mutations in infertile men, indicating these genes are likely associated with human male infertility.

"Just a few years ago, there weren't enough sequenced genomes and computing power to conduct these kind of studies," Lynch says. "As science collects more genetic data, we'll have a better understanding of why infertility happens."

More information: Jacob D. Bowman et al, Pervasive relaxed selection on spermatogenesis genes coincident with the evolution of polygyny in gorillas, *eLife* (2024). [DOI: 10.7554/eLife.94563.1](https://doi.org/10.7554/eLife.94563.1)

Provided by University at Buffalo

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