Human pregnancy is weird—new research adds to the mystery

21 April 2020, by Charlotte Hsu

Credit: CC0 Public Domain

From an evolutionary perspective, human pregnancy is quite strange, says University at Buffalo biologist Vincent Lynch.

"For example, we don't know why human women go into labor," Lynch says. "Human pregnancy tends to last longer than pregnancy in other mammals if you adjust for factors like body size. The actual process of labor tends to last longer than in other animals. And human pregnancy and labor are also much more dangerous."

With these oddities in mind, Lynch and colleague Mirna Marinic set out to investigate the evolution of a gene that helps women stay pregnant: the progesterone receptor gene.

But the results of the study only add to the mystery, says Lynch, Ph.D., an assistant professor of biological sciences in the UB College of Arts and Sciences.

Unexpected findings about a gene that's critical to pregnancy

Past research has shown that the progesterone receptor gene underwent rapid evolution in humans, and some scientists have suggested that these swift changes occurred because they improved the function of the gene. This is called positive selection.

But Lynch and Marinic's study—published online on April 17 in the journal *PLOS Genetics*—draws a different conclusion.

Their research finds that while the progesterone receptor gene evolved rapidly in humans, there's no evidence to support the idea that this happened because those changes were advantageous. In fact, the evolutionary force of selection was so weak that the gene accumulated many harmful mutations as it evolved in humans, Lynch says.

The results come from an analysis of the DNA of 115 mammalian species. These included a variety of primates, ranging from modern humans and extinct Neanderthals to monkeys, lemurs and lorises, along with non-primate mammalian species such as elephants, pandas, leopards, hippos, aardvarks, manatees and walruses.

The findings were a surprise, Lynch says.

"We expected something very different. It opens up this mystery that we didn't anticipate," he says. "I thought that the progesterone receptor gene would have evolved to respond better to progesterone, to be better at suppressing inflammation or contractions to keep us pregnant for longer. It looks like it's the reverse: In human pregnancy, there's just an incredible amount of progesterone around, and yet the gene is less good at doing its job. I wonder if this might predispose us to things like preterm birth, which is not that common in other animals."

"Pregnancy is such an everyday event—none of us would be here without it—and yet, so many aspects

of this process remain puzzling," says Marinic, Ph.D., a postdoctoral researcher in the University of Chicago Department of Organismal Biology and Anatomy. "This study focused on an essential ingredient, progesterone signaling via progesterone receptors, and our results add another step toward deeper understanding of specificities of human pregnancy."

Provided by University at Buffalo

The progesterone receptor gene is crucial to pregnancy because it provides cells with instructions for how to create tiny structures called progesterone receptors.

During human pregnancy, these receptors detect the presence of progesterone, an anti-inflammatory hormone that pregnant women and the placenta produce at various points in time. When progesterone is present, the receptors jump into action, triggering processes that help keep women pregnant in part by preventing the uterus from contracting, reducing uterine inflammation, and suppressing the maternal immune response to the fetus, Lynch says.

Evolution changed the function of progesterone receptors in humans

In addition to exploring the evolutionary history of the progesterone receptor gene, Lynch and Marinic conducted experiments to test whether mutations in the human version of the gene altered its function. The answer is yes.

As the scientists wrote in their paper, "We resurrected ancestral forms of the progesterone receptor and tested their ability to regulate a target gene. We found that the human progesterone receptor forms have changed in function, suggesting the actions regulated by progesterone may also be different in humans. Our results suggest caution in attempting to apply findings from animal models to progesterone biology of humans."

More information: Mirna Marini? et al, Relaxed constraint and functional divergence of the progesterone receptor (PGR) in the human stem-lineage, *PLOS Genetics* (2020). DOI: 10.1371/journal.pgen.1008666