Genetic study explores how human pregnancy is unique

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Katelyn Mika. Credit: Cassie Scott

A new study delves into the evolutionary history of pregnancy, identifying hundreds of genes that evolved to be turned on or off in the uterus of humans during the early part of pregnancy, in contrast to a range of other animals.

The suite of genes identified includes ones that are thought to contribute to cell-to-cell communication, regulation of the immune response and inflammation, and the ability of the human placenta to burrow deeply into the uterine wall. Such functions are important to the health of a pregnancy, in which the mother must host and co-exist with a fetus containing foreign cells.

The findings help to illuminate what makes human pregnancy uniquely human—an intriguing question, as human pregnancy is quite unusual compared to pregnancy in many other animals, says Vincent Lynch, Ph.D., associate professor of biological sciences in the University at Buffalo College of Arts and Sciences, and the paper's senior author.

"Human pregnancy is different from pregnancy in other animals," he says. "Human pregnancy lasts longer than it should. Labor and delivery last way longer than it should. The human placenta is really, really invasive. It burrows into the wall of the uterus much more deeply than in other animals. And adverse pregnancy outcomes, such as preterm birth and preeclampsia, seem much more common in humans than other animals."

The study was published on Oct. 8 in *eLife*. The research was led by

biologists Katie Mika, Ph.D., and Mirna Marinić, Ph.D., at the University of Chicago; Manvendra Singh, Ph.D., at Cornell University; and Lynch at UB. Co-authors included Joanne Muter, Ph.D., and Jan Joris Brosens, Ph.D., at University Hospitals Coventry & Warwickshire and the University of Warwick.

Data from the project could lay the foundation for future studies that seek to understand, prevent and treat various adverse pregnancy outcomes, demonstrating the power of the emerging field of evolutionary medicine.

Spotlighting genes that help make human pregnancy unique

The research compared gene activity in the uterine lining of humans to that of other animals during pregnancy or while carrying eggs, including lizards, birds, monkeys and marsupials, and the platypus. The study identified hundreds of genes that gained or lost uterine expression in the human lineage, focusing on the first trimester of pregnancy.

As the study reports, the genes that evolved to be turned on and off in the human uterus are "enriched in immune functions, signaling processes and genes associated with adverse pregnancy outcomes such as infertility, recurrent spontaneous abortion, pre-eclampsia and preterm birth. Among these genes are those that may contribute to a previously unknown maternal-fetal communication system (HTR2B), augment maternal-fetal immunotolerance (PDCD1LG2, also known as PD-L2), and promote vascular remodeling and deep placental invasion (CORIN)."

"Our paper really highlights the useful role of evolutionary techniques in translational research," says Mika, postdoctoral scholar in the University

of Chicago Department of Human Genetics and Department of Organismal Biology and Anatomy. "The three genes we identified (HTR2B, PDCD1LG2 and CORIN) will advance work on signaling systems at the crucial maternal-fetal interface, which impacts the success and health of a pregnancy."

"I was particularly intrigued by our discovery that the recruited genes were enriched in a serotonin signaling pathway," says Marinić, postdoctoral scholar in the University of Chicago Department of Human Genetics and Department of Organismal Biology and Anatomy. "Other researchers have previously pointed to the potential role of serotonin and its derivatives at the onset of labor. I'd be curious to study further what is the exact molecular mechanism through which serotonin influences timing of the birth."

And though the paper shows how research on evolution can provide essential insights for medicine, Lynch says simple curiosity is one of his main motivations as a scientist: "We just want to know how evolution works. We're humans, so we want to know why humans are the way we are. Human pregnancy is really weird, so we want to understand what that weirdness is."

Singh, a postdoctoral researcher in molecular biology and genetics at Cornell University, also commented on the significance of the findings, noting that, "During human pregnancies, the regulation of immunotolerance remains an enigma, especially when the invasion of embryonic tissues is more profound than in the human's closest relatives. It was remarkable to notice that over 900 genes are uniquely expressed in human pregnancy. This observation suggests that re-wiring of regulatory sequences for these genes has modified the developmental processes and favored human pregnancy health.

"Upon digging further, we also found these genes have established

functions to regulate immune responses and hormonal controls; for example, a Serotonin receptor, mediators of interferon production, and more. As serotonin is produced and released from the brain, it is tantalizing to speculate that some of these genes may be involved in communicating with the brain during pregnancy. Overall, while this study is of great clinical relevance, it also opens multiple avenues to maternal-fetus interface research."

More information: Katelyn Mika et al, Evolutionary transcriptomics implicates new genes and pathways in human pregnancy and adverse pregnancy outcomes, *eLife* (2021). DOI: 10.7554/eLife.69584

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