MedicalXpress

How a gene called HAND2 may impact the timing of labor

February 22 2021, by Charlotte Hsu

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A new study illuminates how a gene called HAND2 may have a hand in the timing of human labor.

"We don't know why humans go into labor. It's a basic aspect of human biology that we just don't know the answer to, and it's kind of embarrassing that we don't," says senior author Vincent Lynch, an

evolutionary biologist at the University at Buffalo. "What happens in many other animals is that as gestation goes on, the level of progesterone keeps going up, and then a few hours before birth, progesterone levels drop to pre-pregnancy levels. Progesterone inhibits contractions, so once you lose it, the uterus starts contracting and the baby is born.

"But in humans, this isn't what happens—progesterone levels don't drop off. So we need to find another explanation for why labor begins."

The research was published on Feb. 1 in the journal *eLife*.

Lynch, Ph.D., assistant professor of biological sciences in the UB College of Arts and Sciences, led the study with first author Mirna Marinić, Ph.D., a postdoctoral researcher in the University of Chicago Department of Organismal Biology and Anatomy. Co-authors included Katelyn Mika and Sravanthi Chigurupati, both from the University of Chicago (Chigurupati is now at AbbVie).

The evolution of HAND2, placental mammals and pregnancy

Using new and existing datasets the team studied genes that were active in the uterine linings of different animals while pregnant or carrying eggs. Species researched included placental mammals (like humans and armadillos) and marsupials (like opossums and kangaroos), as well as egg-laying species like platypuses (an egg-laying mammal), birds, lizards and a frog.

A comparative analysis showed that the HAND2 gene evolved to be turned on in the uterine linings of placental mammals during pregnancy, but not in those of the other species studied.

"HAND2, which ancestrally plays a role in heart development, evolved to be turned on in the uterus during pregnancy, when things like maternal-fetal communication, maternal immune tolerance of the antigenically distinct fetus, and prolonged internal gestation are important," Lynch says. "Our research suggests that HAND2 may be involved in facilitating some of these processes."

HAND2 and questions about the timing of labor

In addition to tracing the evolutionary history of HAND2 in the context of pregnancy, scientists also investigated the changing levels of HAND2 during gestation.

The team concluded that in humans, the HAND2 gene becomes less active throughout pregnancy, reaching a low as labor nears. This is interesting because HAND2 has previously been shown to play a role in suppressing the activity of estrogen, a process that helps women stay pregnant.

The study also uncovered new details about the activity of HAND2 that suggest the gene may be involved in the timing of labor. As Lynch explains, "A region of the genome far, far away from HAND2 is associated with how long gestation lasts in humans, and we found that it acts as on/off switch for HAND2 in the uterus."

"Given the possibility that dynamic HAND2 expression over the course of pregnancy may be important in regulation of gestation length, it will be exciting to build upon our results further, especially in the context of researching preterm birth," Marinić says.

More information: Mirna Marinić et al. Evolutionary transcriptomics implicates HAND2 in the origins of implantation and regulation of gestation length, *eLife* (2021). DOI: 10.7554/eLife.61257

Provided by University at Buffalo