Study on placenta membrane cells identifies genetic markers associated with preterm birth

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A new research study from the March of Dimes Prematurity Research Center led by investigators at the University of Chicago has identified

new genetic markers associated with gestational length, providing new insights into potential risk factors for preterm birth.

In a collaboration between multiple labs and funded through the March of Dimes Foundation, the investigators set out to map important gene regulatory regions and genetic markers relevant to preterm birth. Their first challenge was addressing the lack of functional genomics data in pregnancy-relevant tissue types.

"When you're studying a disease, there are typically a lot of genetic and tissue resources available in public databases," said co-senior author Carole Ober, Ph.D., Chair of Human Genetics at UChicago. "But pregnancy related conditions, like preterm birth, get much less attention or funding, and as a result pregnancy-relevant tissues are not well represented in those databases."

The paper, published on Dec. 2, 2020 in *Science Advances*, focused on decidualized cells derived from the endometrial cells attached to the placenta. Decidualized cells line the uterus during the latter half of the menstrual cycle, preparing it for implantation and supporting the growth and development of the placenta and fetus throughout pregnancy.

The investigators collected placental tissue donated by patients who had given birth and isolated the decidualized cells in the lab. Genetic analysis of these cells identified two new candidate preterm birth genes, HAND2 and GATA2.

"These genes are both important transcription factors that regulate the expression of several other genes," said co-first author Ivy Aneas, Ph.D., a research associate professor of human genetics at UChicago. "HAND2 mediates the effect of progesterone on the uterine epithelium while GATA2 is involved in stem cell maintenance."

Both of these processes and the genes that control them are known to be important for endometrial decidualization and embryo implantation.

"The fact that we identified a link between these two genes and the duration of gestation suggests that their roles in pregnancy may be more important than previously anticipated," said co-first author Noboru Sakabe, Ph.D., a staff scientist at UChicago.

Understanding how these genes contribute to the length of pregnancy could be a key to developing new preventions against preterm birth.

"Researchers have recognized a number of factors that can lead to preterm birth, ranging from environmental to infectious disease and beyond, but what is vexing is that we haven't been successful in preventing it," said co-senior author Marcelo Nobrega, MD, Ph.D., professor of human genetics at UChicago. "Our research took a look at the genetics and allowed us to pull out some links that might illuminate genetic pathways and signaling molecules involved in the decidualization process, which in turn might provide new targets for therapies."

The researchers were able to leverage combined expertise in human genetics, genomics and statistical analysis to combine data gathered from human endometrial cells in the lab with data from existing genome-wide association studies (GWAS) to zero in on key genetic variations that may be linked to preterm birth.

"Only six or seven genomic regions have been linked to preterm birth and gestational length," said co-senior author Xin He, Ph.D., assistant professor of human genetics at UChicago. "We don't know which genes are involved or how that influences cell function and risk of preterm birth. With our approach, we integrated genomics data generated from our center and integrated it with other databases to identify the underlying genetic interactions. This can lead us to genes that may be

involved in this condition, which gives us a hint to the underlying biology."

While genetic factors are thought to play only a small role in the risk of preterm birth, the investigators were glad to see such clear results in their study.

"Preterm birth is so common, and some people experience it repeatedly," said Ober. "If you have a preterm birth, it doesn't matter if it's genetic or not, you just don't want to experience one again. We can now use this information to better understand some of the genetic component and how it plays a role in the condition."

Future research will investigate other kinds of cells that may play key roles in pregnancy and preterm birth, such as the immune cells that reside at the maternal-fetal interface, and grow the "roadmap" of genomic variations in endometrial cells by examining the effects of varied environmental conditions on gene expression.

The study, "Transcriptome and regulatory maps of decidua-derived stromal cells inform gene discovery in preterm birth," was supported by the March of Dimes Foundation.

More information: "Transcriptome and regulatory maps of decidua-derived stromal cells inform gene discovery in preterm birth" *Science Advances* (2020). advances.sciencemag.org/lookup … .1126/sciadv.abc8696

Provided by University of Chicago Medical Center

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