Team develops computational method to explore evolution's influence on preterm birth

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Human pregnancy can easily be taken for granted as a natural and regularly occurring event, but it is the product of the complex, coordinated function of two bodies, mother and baby, that has evolved

side by side with other important human adaptations. For the first time, researchers have established how a complex disorder associated with pregnancy—spontaneous preterm birth (sPTB) – has been shaped by multiple evolutionary forces.

The article, "Accounting for diverse evolutionary forces reveals mosaic patterns of selection on human preterm birth loci" was published in the journal *Nature Communications* on July 24.

Preterm or premature birth, medically defined as labor starting at 37 weeks of gestation or earlier (instead of the usual 40 weeks), affects more than 15 million pregnancies each year and is the leading cause of infant mortality worldwide. Both the associated medical conditions of the mother which cause sPTB and the outcomes of sPTB on an infant's health have been well-defined. It is not well understood, however, how and why genetic factors influence sPTB and birth timing. A team of scientists led by Antonis Rokas, Cornelius Vanderbilt Chair in Biological Sciences and director of the Vanderbilt Evolutionary Studies Initiative and Tony Capra, associate professor of biological sciences, set out to demystify this element of pregnancy and human life.

The research, co-led by postdoctoral scholar Abigail LaBella and by M.D./Ph.D. candidate Abin Abraham, developed a computational approach to detect how evolution has shaped genomic regions associated with complex genetic traits, such as height or obesity. "Our approach integrates techniques developed in labs from all over the world to quantify how natural selection has influenced genomic regions involved with complex diseases," said Capra. "We hypothesized that parts of our genome involved in disease might experience contrasting evolutionary pressures due to their involvement in multiple and different traits."

This work was done in cooperation with Louis J. Muglia, co-director of the Perinatal Institute at Cincinnati Children's and president and CEO of

the Burroughs Wellcome Fund and Ge Zhang, associate professor at Cincinnati Children Hospital Medical Center and collaborator at the March of Dimes Prematurity Research Center-Ohio Collaborative. Zhang and Muglia recently completed the largest genome-wide association study (GWAS) on sPTB which identified multiple genomic regions associated with this complex disease. "Preterm birth is a global health concern, affecting ten percent of pregnancies in the United States. Understanding the evolution of genomic regions associated with spontaneous preterm birth is a major step forward in how we understand the foundations of human life and provide the best possible care to mother and child," said Muglia.

Using this GWAS, the researchers found that genomic regions associated with sPTB have experienced multiple types of natural selection. From this information researchers can hypothesize why these risk-related genomic regions remain in human populations and what their potential functions may be. "While we knew of a few examples of selection like negative selection acting on genes associated with spontaneous preterm birth, we uncovered that every type of selection we tested had acted on at least one genomic region. Our initial figures looked like a mosaic made up of all the different metrics we had tested," says Rokas.

The team's results suggest that genomic regions associated with sPTB have experienced diverse evolutionary pressures, such as population-specific selection, and provide insights into the biological functions some of these regions. "It is difficult to study pregnancy in humans and we lack good models for laboratory studies," LaBella explains. "We still have much to learn about the mechanisms through which human pregnancy is initiated." For example, the group uncovered differences in a region near the gene OPRL1, involved in both the relaxation of maternal tissues and pain perception during childbirth, that are specific to certain human populations. Population-specific differences in this region may contribute to the uneven risk of sPTB between human

populations. "This work is a part of a burgeoning field of evolutionary medicine, one of the types of interdisciplinary research that many of the investigators of the Vanderbilt Evolutionary Studies Initiative are engaged in," says Rokas.

Both Abraham and LaBella plan to continue to foster collaboration between medicine and evolution in their future research. "Having this pipeline at our disposal opens up a range of new, exciting questions such as asking whether diseases of pregnancy, which involve two genomes, that of mom and baby, experience different evolutionary pressures than other complex genetic diseases," says Abraham.

More information: Abigail L. LaBella et al. Accounting for diverse evolutionary forces reveals mosaic patterns of selection on human preterm birth loci, *Nature Communications* (2020). DOI: 10.1038/s41467-020-17258-6

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