Genetic discovery reveals who can benefit from preterm birth therapy

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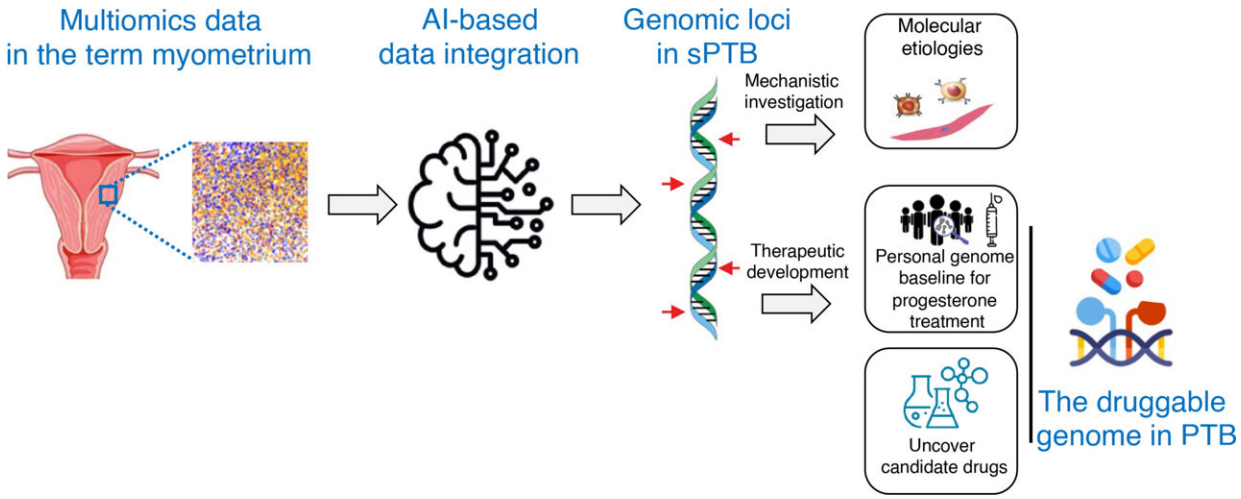

Study design shown in the flowchart. Credit: *Science Advances* (2024). DOI: 10.1126/sciadv.adk1057

A UC San Francisco-led study has for the first time identified genetic variants that predict whether patients will respond to treatment for preterm birth, a condition that affects one in 10 infants born in the United States.

The findings are critical because no medication is available in the U.S. to treat preterm birth. Last year, the Food and Drug Administration (FDA) pulled the only approved therapy to help prevent this condition, a synthetic form of progesterone sold under the brand name Makena, from

the market, citing ineffectiveness.

The new research found that pregnant individuals with high levels of mutations in certain genes—specifically those associated with involuntary muscle contraction—were less likely to respond to the treatment. Screening for the mutations could allow doctors to target the medication to those most likely to benefit, the authors suggest.

"This study calls for a precision framework for future drug development," said the study's senior author, Jingjing Li, Ph.D., associate professor in UCSF's Department of Neurology and the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research. "In addition to understanding drug effects based on population averages, we also need to take into account the drug response of each individual patient and ask why some respond and some don't."

The study, which was conducted in collaboration with Stanford University, appears in the journal *Science Advances*.

New genes associated with preterm birth

Preterm birth, or babies born alive prior to 37 weeks of gestation, is the leading cause of infant mortality and affects some 15 million pregnancies worldwide each year. Preterm birth also leads to a range of long-term health consequences including breathing problems, neurological impairments such as cerebral palsy, developmental disabilities, visual and hearing impairments, heart disease and other chronic illnesses.

To conduct the study, researchers developed a machine-learning framework to analyze genomes of 43,568 patients who had spontaneous preterm births. The approach uncovered genes that had not previously been known to be associated with preterm birth.

They then examined mutations in the genes among those who had received the progesterone treatment Makena. The FDA had approved the drug in 2011 after a single clinical trial but took it off the market last spring after concluding the drug didn't work.

The decision left doctors without an approved medication for preterm birth and frustrated those who had found it effective for a subset of their patients. This posed the question: Could there be a genetic reason why progesterone therapy worked for some, but not for others?

The researchers discovered that the patients in the group with low levels of mutations in the genes associated with muscle contractions were more likely to respond to Makena, but those with higher levels tended not to respond.

The finding indicates a personalized medicine approach that involves genetic screening could lead to successful results in patients without a high burden of those mutations.

"Progesterone therapy was the only treatment for recurrent preterm birth over the past decade, and its recent withdrawal by the FDA has left a void in the medication options available for preterm birth patients," said the study's first author, Cheng Wang, Ph.D., a postdoctoral scholar at UCSF.

"In previous clinical practice, we did see that many patients benefited from progesterone therapy," Wang said. "We probably should reevaluate its efficacy, if we can identify those who respond positively to the treatment."

The researchers included a cohort of African American patients in the study to determine whether the findings applied broadly across different races. Black women in the U.S. are almost twice as likely to give birth

prematurely than white women.

They found the genetic burden did not vary by race. This suggests the high rate of preterm birth among Black mothers may be due primarily to environmental factors such as elevated stress hormones, health care biases and lack of prenatal care.

A new type of precision medicine

The researchers then went beyond that finding to identify new targets and potential therapies to treat preterm birth. They screened more than 4,000 compounds and homed in on 10 that were predicted to interact with the genes associated with preterm birth.

Many of these therapeutic compounds are already being used to treat cancer and other diseases, which means that these drugs could possibly be repurposed to help prevent preterm labor.

A top candidate is the small molecule RKI-1447, a drug that is currently being used to treat cancer, glaucoma and fatty liver disease. Additional study of the potential of these molecules in treating preterm birth is needed.

More information: Cheng Wang et al, Integrative analysis of noncoding mutations identifies the druggable genome in preterm birth, *Science Advances* (2024). DOI: 10.1126/sciadv.adk1057

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