Study finds genetic patterns in preeclampsia

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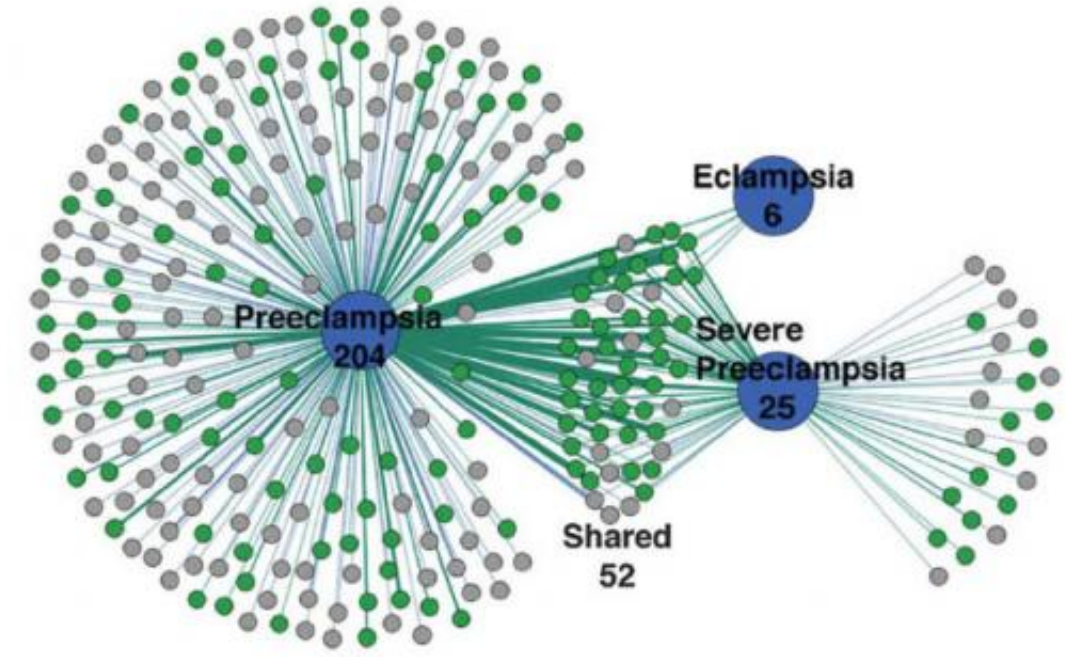

Among fetuses, 204 distinct genes are associated with preeclampsia, 25 are associated with the severe form, and 52, center group, are present in both forms. Green dots represent involved genes of both mother and fetus; gray dots are uniquely involved fetal genes. Credit: Triche lab/Brown University

Different manifestations of preeclampsia, such as early vs. late timing or typical vs. high severity, appear to have distinct genetic underpinnings, suggesting that they may need to be studied and treated differently. That and several other insights are described in a newly published comprehensive review of genetic studies of the condition, which

produces life-threatening complications such as high-blood pressure in as many as 8 percent of pregnancies in the United States.

"There are probably very different phenotypes of preeclampsia and it suggests that studies focused on very particular phenotypes may be necessary to really identify the genetic architecture of the disease," said co-lead author Elizabeth Triche, assistant professor of epidemiology in the Brown University School of Public Health.

The bioinformatics insights published in the journal *Obstetrics & Gynecology* provide a new resource for researchers and physicians who have been trying to produce a useful genetic understanding of preeclampsia, Triche said. Within about six months, the team plans to make all the data gathered in the review available in a free, searchable database on the Web so that others can generate their own findings.

"Bioinformatic tools are great assets to identify the genetic causes of complex diseases, such as preeclampsia," said Alper Uzun, a computational biologist and bioinformatician at Women & Infants Hospital and a co-lead author on the paper.

The data come from the team's use of advanced data mining techniques to identify about 2,300 studies with information about preeclampsia genetics. Over thousands of hours, the research team of six medical students, trained to curate the papers carefully, narrowed the list to 729 articles that documented 535 maternal and fetal genes with statistically significant associations with either preeclampsia or closely related conditions.

From there the team's bioinformatics analyses uncovered networks and clusters of association among the genes. The team was able to see whether certain genes were shared or unique between mother and fetus, whether they were differently correlated with specific manifestations of

preeclampsia or related disorders, and what the biological role of the key genes appeared to be.

They were also able to identify genes that were unique or shared in early- and late-onset preeclampsia. In another example, they found that 194 maternal genes are distinctly associated with preeclampsia, 39 genes are distinctly associated with severe preeclampsia, and 94 maternal genes are associated with both. Among fetuses, 204 distinct genes are associated with preeclampsia, 25 are associated with the severe form and 52 are shared between both.

In other words, the different clinical forms of the disease had distinct sets of genes involved both from the mother and the fetus.

"We were excited to see how much clustering there was [in different forms of the disease and] by maternal and fetal source," Triche said. "A lot of the research focuses typically on the mother because it's a maternal condition, but it does support the fact that the fetus plays an important role in the pathogenesis of preeclampsia."

Another key finding in the analysis was that the functions of implicated genes suggest specific biological contributions from mother and child to the development of the condition. Maternal genes that govern the response of the immune system were highly represented, while fetal genes pertaining to cell signaling, such as the molecular messages a developing baby passes to the mother via the placenta, were particularly common.

The new dataset and insights derived from it should help accelerate preeclampsia research by giving researchers a head start on the genetic combinations and biological processes at play in the different forms of the disease, Triche said.

"These more parsimonious sets of genes will allow comparison of gene-gene interactions or higher combinatorial effects with a greater degree of statistical power," she and her co-authors wrote.

The research method of compiling bioinformatics data from a systematic review of studies is a useful methodology for approaching other diseases, added co-author Dr. James Padbury, professor of pediatrics in the Warren Alpert Medical School of Brown University and pediatrician-in-chief at Women & Infants Hospital. In prior work he and Uzun amassed a similar database, for example, on preterm birth.

Provided by Brown University