Medical Xpress

Researchers find a link between genes and preeclampsia

July 14 2020

Preeclampsia is globally a leading cause of illness and deaths among mothers and their babies. This severe pregnancy disorder occurs in up to five percent of all pregnancies.

Preeclampsia is characterized by the elevated blood pressure of the mother, and the baby is often delivered preterm and smaller than usual.

Although preeclampsia is cured by the delivery of the placenta, the mechanism of the disease has still remained unclear.

"It is necessary for a successful pregnancy that the mother's immune system does not react too strongly and reject the fetus, even though half of its genes are from the father and thus foreign," says professor Juha Kere from Karolinska Institutet, Sweden.

Kere coordinated the research to uncover the role of the HLA-G gene in preeclampsia. This gene protects the placenta against mother's immune attack.

The results of the study have now been published in *EBiomedicine*, a journal published by *The Lancet*.

"The study reveals mechanisms of preeclampsia. In addition, we showed for the first time in any species that there is a gene directly influencing the balance of boys and girls born," says Dr. Satu Wedenoja, the lead author of the study, from University of Helsinki and Helsinki University

Hospital.

Fewer boys are born from preeclamptic pregnancies

The researchers studied 1.79 million births from the Finnish Birth Registry, a national preeclampsia cohort, and a group of stillborn babies. They found that fewer boys than girls were born from preeclamptic pregnancies, especially among babies delivered preterm and smaller than usual for the duration of pregnancy.

According to the results, certain alternative forms of the HLA-G gene are connected to the male-to-female ratio at birth, the survival of the fetuses, and preeclampsia.

The researchers pointed out that natural selection works even today on the HLA-G gene. The oldest forms of the HLA-G gene increase the risk of fetal death and preeclampsia, but might protect the fetus from infections during pregnancy, such as malaria. In placental samples collected from pre-eclamptic pregnancies, the gene expression of HLA-G was low, but in contrast, the expression was highly elevated for interferon-alpha-1, a gene involved in autoimmune disorders and tissue rejection.

"The results show that natural selection works through the fetal HLA-G gene influencing the pregnancy outcome and its complications. The results further strengthen earlier findings of the vulnerability of boys to mother's inflammation, late miscarriages, and preeclampsia," says Wedenoja.

Based on the results, the researchers propose that a well-known drug for autoimmune disorders might be tested to prevent or treat preeclampsia.

"The mother's immune system affects the survival of the fetus. This

generally safe drug can also be used during pregnancy and it modulates immune reactivity, thus potentially preventing preeclampsia," says Wedenoja.

More information: Satu Wedenoja et al. Fetal HLA-G mediated immune tolerance and interferon response in preeclampsia, *EBioMedicine* (2020). DOI: 10.1016/j.ebiom.2020.102872

Provided by University of Helsinki

Citation: Researchers find a link between genes and preeclampsia (2020, July 14) retrieved 19 April 2024 from https://medicalxpress.com/news/2020-07-link-genes-preeclampsia.html

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