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Morning sickness and hyperemesis gravidarum: Genetic and functional analysis of placenta and appetite genes GDF15 and IGFBP7 support causality

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Most women experience nausea and vomiting of pregnancy (NVP) and the most severe form, Hyperemesis Gravidarum (HG), occurs in 2% of pregnant women. HG is associated with weight loss, electrolyte imbalance, and ketonuria. It can cause brain, renal, and liver abnormalities, and esophageal rupture. HG is associated with a 4-fold increased risk of adverse fetal outcome including low birth weight, IUGR, preterm birth, fetal and neonatal death, and a 3-fold increased risk of neurodevelopmental delay. It is highly heritable.

Our recent GWAS identified the placenta and appetite genes GDF15 and IGFBP7 as the strongest genetic signals associated with NVP and HG https://www.nature.com/articles/s41467-018-03258-0. Both genes are believed to play important roles in implantation and placental development, and decrease prior to miscarriage. GDF15 and IGFBP7 serum levels are significantly higher in women with HG compared to controls at 12 weeks, but not at 24 weeks when symptoms typically decline. Whole-exome sequencing of 5 HG families revealed GDF15 risk variants segregate with disease. In addition, the GDF15 risk allele is significantly linked to recurrence.

GDF15 and IGFBP7 are also assocated with cachexia, a condition with similar symptoms to HG, that kills 20% of cancer patients. Lerner et al. blocked GDF15 in an animal model of cancer cachexia and restored body weight and appetite, making this a potential strategy for treating HG. Thus this work paves the way for a promising new area for research into the development of tools for prediction, diagnosis, and treatment for those suffering from NVP and HG

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